Brachytherapy Treatment for Equine Ocular and/or Periocular Squamous Cell Carcinoma

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STATEMENT OF ORIGINALITY

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Yolanda Surjan

ACKNOWLEDGEMENT OF AUTHORSHIP

I hereby certify that this thesis is in the form of a series of published papers of which I am a joint author. I have included as part of the thesis a written statement from each co-author, endorsed by the Faculty Assistant Dean (Research Training), attesting to my contribution to the joint publications.

Yolanda Surjan

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Many a lesson is learnt by a PhD student, none the least than to be patient and resolute in reaching what at times seems impossible. I have reached the end but not without the support of many along the way. Foremost, Associate Professor Helen Warren-Forward in whose expertise and knowledge I have had complete confidence and who constantly reminded me to keep my priorities properly aligned; family first, all else after. Thank you Helen, for your calmness at times of crisis.

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Thesis Publications

Manuscripts published in peer reviewed journals;

1. **Surjan Y,** Milross C, Warren-Forward HM. Is there a role for radiation therapists within veterinary oncology? Radiography 2011; 17 (3):250-253
2. **Surjan Y,** Ostwald T, Donaldson D, Milross C, Warren-Forward HM. A review of current treatment options in the treatment of ocular and/or periocular squamous cell carcinoma in horses: is there a definitive 'best' practice? Journal of Equine Veterinary Science 2014; 34(9): 1037-1050
3. **Surjan Y,** Ostwald T, Milross C, Warren-Forward HM. Radiation safety considerations and compliance within equine veterinary clinics: results of an Australian survey. Radiography 2014; 21(3): 224-230

Invited manuscripts published in peer reviewed journals;

4. **Surjan Y**, Donaldson D, Ostwald, T, Warren-forward, H. Ocular and periocular squamous cell carcinoma in horses: a short communication of the potential use of brachytherapy. The Australian Equine Veterinarian, 2015; 34(1): 47-49.

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Yolanda Surjan contributed to the conception and design of the study, conducted data collection, analysed data and drafted the manuscript. Helen Warren-Forward, Trish Ostwald and Chris Milross contributed to the conception and design of the study and the preparation and critical review of the manuscript within the capacity of their role as PhD supervisors.

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Peer Reviewed Conference Presentations

1. **Surjan Y,** Milross C, Ostwald, Donaldson D, Warren-Forward HM. Brachytherapy treatment of ocular/periocular squamous cell carcinoma in the horse: treatment results in 74 Cases (1999-2007). Proceedings of the Italian Society for Equine Veterinary (SIVE), Milan Italy, February 2014.
2. **Surjan Y,** Milross C, Ostwald, Donaldson D, Warren-Forward HM. Brachytherapy treatment of periocular squamous cell carcinoma in the horse: treatment results and recurrence in 42 cases (1999-2007). Proceedings of the European Society for Radiotherapy and Oncology (ESTRO) Geneva Switzerland, April 2013.
3. Donaldson D, **Surjan Y**, Milross C, Ostwald, Warren-Forward HM. Brachytherapy Treatment of periocular squamous cell carcinoma in the horse: treatment results and recurrence in 42 cases (1999-2007). Proceedings of the 2013 American College of Veterinary Ophthalmologists (ACVO), Puerto Rico, November 4-9, 2013.
4. **Surjan Y,** Milross C, Ostwald T, Donaldson D, Warren-Forward HM. Radiation protection in veterinary clinics, analysis of current practice: an Australian National Survey.' Proceedings of the European Society for Radiotherapy and Oncology (ESTRO-31) 2012, Barcelona Spain, May 9-13, 2012.
5. **Surjan Y,** Milross C, Ostwald T, Warren-Forward HM. Current use of brachytherapy treatment in periocular squamous cell carcinoma: results of an Australian survey. Proceedings of the 9th Annual Scientific Meeting of Medical Imaging and Radiation Therapy (ASMMIRT) Sydney Australia, April 20-22, 2012.
6. **Surjan Y,** Milross C, Ostwald T, Warren-Forward HM. Brachytherapy treatment of periocular squamous cell carcinoma in horses: the potential for the application of radiation therapy in the veterinary sphere - results of an Australian national survey.' Proceedings of the UK Radiological Congress, Manchester United Kingdom, June 6-8, 2011.
7. **Surjan Y,** Milross C, Ostwald T, Warren-Forward HM. Is there a role for radiation therapists within veterinary oncology? Proceedings of the 16th ISRRT World Congress Scientific Program, Gold Coast Australia, 2010.

Invited Presentations and Awards Resulting from Research

Invited Presentation

The Upper Hunter Branch of the Australian Veterinary Association Annual Meeting and Continuing Professional Development Seminar, 2015. Hunter Valley Equine Research Centre, Scone Australia.

Poster Award

Best Research Poster Award - $500

Surjan Y, Milross C, Ostwald T, Warren-Forward HM. Current use of brachytherapy treatment in periocular squamous cell carcinoma: results of an Australian survey. Proceedings of the 9th Annual Scientific Meeting of Medical Imaging and Radiation Therapy (ASMMIRT) Sydney Australia, April 20-22, 2012.

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^{103}Pd	Palladium-103
^{125}I	Iodine-125
^{137}Cs	Cesium-137
^{192}Ir	Iridium-192
^{198}Au	Gold-198
5-FU	5-Fluorouracil
^{60}Co	Cobalt-60
AEVA	Australian Equine Veterinary Association
ALARA	As Low As Reasonably Achievable
ARPANSA	Australian Radiation Protection and Nuclear Safety Agency
AVA	Australian Veterinary Association
BCC	Basal Cell Carcinoma
Bq	Becquerel
BVSc(Hons)	Bachelor Veterinary Medicine (Honours)
CIS	Carcinoma in Situ
CRT	Conformal Radiation Therapy
CT	Computed Tomography
DNA	Deoxyribonucleic Acid
DXR	Orthovoltage Radiation Therapy
EBRT	External Beam Radiation Therapy
Gy	Gray
HDR	High Dose Rate
ICR	International Congress of Radiology
ICRP	International Commission on Radiation Protection
ICRU	International Commission on Radiation Units and Measurements
LDR	Low Dose Rate
LET	Linear Energy Transfer
MBq	Megabecquerel
MDR	Medium Dose Rate
MeV	Mega Electron Volts
mGy	milliGray
MMC	Mitomycin
MRI	Magnetic Resonance Imaging
mSv	milliSievert
Mv	Mega Volts
NCRP	National Council on Radiation Protection and Measurements
OAR	Organs at Risk
OPG	Orthopantogram
OSCC	Ocular Squamous Cell Carcinoma
PDR	Pulsed Dose Rate
PDT	Photodynamic Therapy
POSCC	Periocular Squamous Cell Carcinoma
R	Roentgen
RBE	Relative Biologic Effectiveness

RO	Radiation Oncology/Radiation Oncologist
RPS	Radiation Protection Series
RT	Radiation Therapy/Radiation Therapist
SCC	Squamous Cell Carcinoma
SI	International System of Units
Sv	Sievert
SXT	Superficial Radiation Therapy
TD	Tumour Dose
TV	Tumour Volume
UK	United Kingdom
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
USA	United States of America
UV	Ultra Violet

ABSTRACT

Squamous Cell Carcinoma (SCC) is the most common tumour of the eye and adnexa in horses representing up to 75% of tumours. The management of equine ocular squamous cell carcinoma (OSCC) and/or periocular squamous cell carcinoma (POSCC) remains a challenge despite its high prevalence among horses. Literature suggests a number of treatment modalities currently exist; surgery, photodynamic therapy, cryotherapy, carbon dioxide (CO_2) laser ablation, radiofrequency hyperthermia, topical or intratumoral chemotherapy, and radiation therapy (RT), predominantly in the form of brachytherapy (implantation of sealed radioactive sources). Whilst no technique can conclusively be identified as the best approach to the treatment of OSCC/POSCC, successful treatment commonly involves one of the above therapies combined with cytoreductive surgery. Furthermore, the value of combining radiation therapy with surgery or using radiation therapy alone has been identified in relation to benefits in decreasing cosmetic and functional defects.

The research presented in this thesis originated following an initial anecdotal source of enquiry suggesting a standardised treatment technique for OSCCC/POSCC in horses was non-existent. Simultaneously, a request from a veterinary practitioner for RT expertise input into the development of future RT protocols in veterinary medicine reinforced the value in conducting the research enquiry.

The thesis presents a series of five studies demonstrating transition from the initial anecdotal source to the development of a Treatment Protocol. The interconnected research studies include; three literature reviews, a retrospective study (treatment modelling) and two surveys and concludes with the development of a Treatment Protocol and a supporting summary of the Code of Practice for Radiation Protection in Veterinary Medicine in the form of a flow-chart.

The literature reviews identified the need for radiation therapy/radiation oncology expertise in the field of veterinary oncology and upon investigation of current and past treatment options nationally and internationally, concluded that a consistently favoured treatment option for OSCC/POSCC does not currently exist. An invited

review was published in the Australian Equine Veterinarian Journal to coincide with the launch of the 2015 national survey.

The retrospective study was performed on data collected from medical records from an Australian Equine Clinic. Retrospective treatment modelling was conducted on 75 horse cases treated with brachytherapy implants with radioactive Gold-198 wire between 1999 and 2007. All cases were replicated using Varian BrachyVision™ radiation therapy treatment planning software. Results demonstrated treatments delivered between 1999-2007 were improved in most cases with the advantage of computerised optimisation. However, further analysis of previous treatments demonstrated a lack of consistency in reporting, radiation safety compliance and the absence of a standardised formal protocol.

Surveys conducted with Australian veterinarians explored current and past treatment options for OSCC/POSCC and assessed knowledge and general compliance with radiation safety protection principles and treatment protocol use. This research identified standardised treatment protocols for OSCC/POSCC are clearly non-existent, and that radiation safety compliance and practice is deficient.

In response to the findings of the retrospective modelling and the national surveys, a standardised Treatment Protocol in the form of a process flow-chart and a summarised version (visual-aid) of the Code of Practice for Radiation Protection in Veterinary Medicine were developed. The implementation of these resources will help translate an evidence based treatment approach using brachytherapy to a common neoplasm as well as minimise any unnecessary occupational irradiation.

CHAPTER 1: INTRODUCTION

1.1 THESIS OVERVIEW

This thesis by publication describes the development of a Treatment Protocol and a supporting summarised version of the Code of Practice for Radiation Protection in Veterinary Medicine in the form of a flow-chart which will assist veterinary medicine practitioners in the safe and effective application of brachytherapy for the treatment of OSCC/POSCC in horses.

The research firstly investigated the literature for relevant studies in the field of ocular and/or periocular squamous cell carcinoma treatment within veterinary practice. The perceived need for radiation therapy expertise was also investigated in the literature. This was followed by a retrospective analysis on 75 horse cases treated with brachytherapy between 1999 and 2007 in an Australian veterinary clinic. Treatment modelling was performed on the cases using Varian BrachyVision™ radiation therapy (RT) treatment planning software and data collection and analyses included RT specific dose distribution parameters; Maximum and Minimum doses, Total Dose (Minimum Target Dose) and dose to organs at risk (OARs). Two surveys were conducted to establish current use and perceptions of brachytherapy and radiation safety awareness and compliance by veterinary practitioners across Australia.

The results of the retrospective analysis and surveys identified the need for; a standardised treatment protocol for the treatment of OSCC/POSCC in horses in accordance with human brachytherapy principles and for the specific use of veterinary practitioners; and an increase in education and/or awareness in radiation protection compliance.

This thesis comprises (Figure 1.1); five journal articles; a retrospective analysis of 75 treatment cases (modelling); a Treatment Protocol; a series of comparative radiation therapy treatment plans (n=9) and a summarised version (visual-aid) of the Code of Practice for Radiation Protection in Veterinary Medicine. Full details of the published papers are given in Table 1.1.

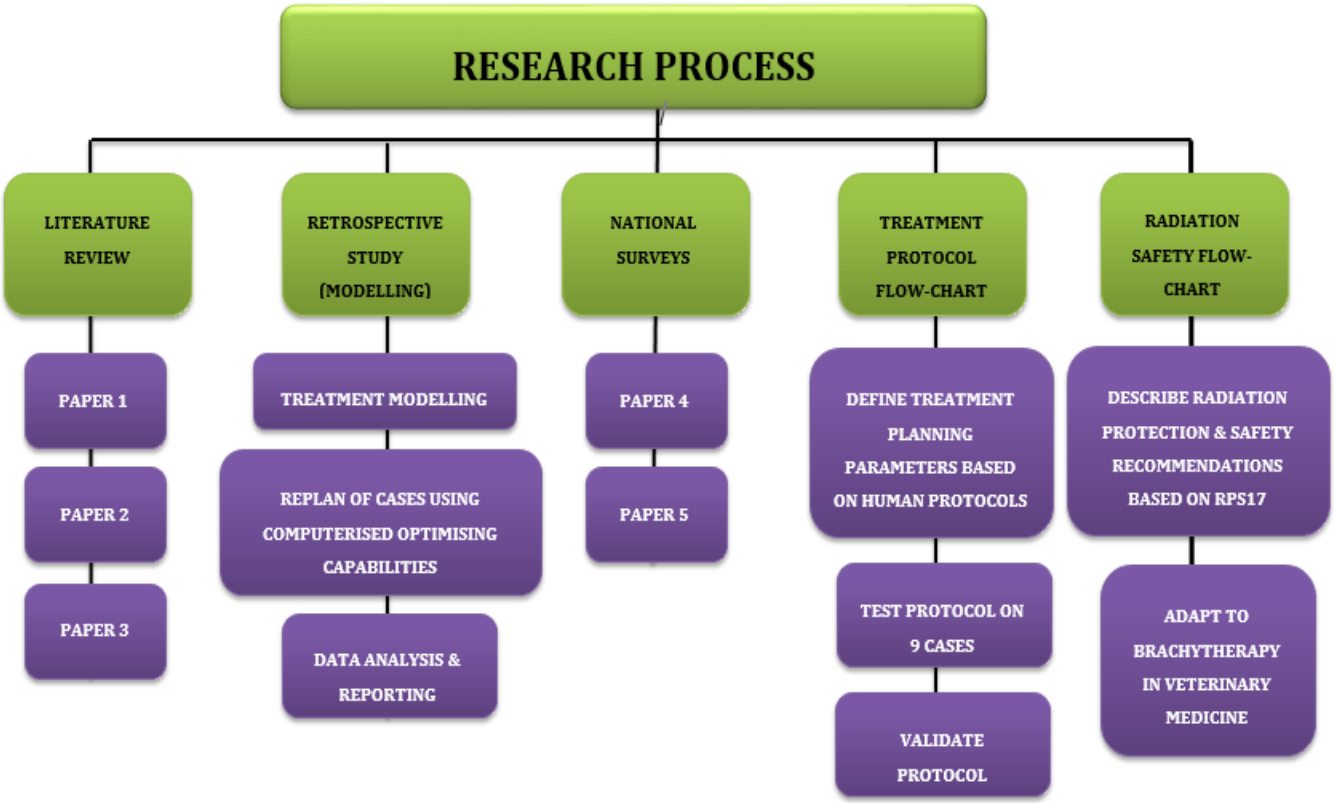

Figure 1.1: Research Process

Table 1.1: Published/Submitted Peer Reviewed Articles

Paper	Author	Title
1	**Surjan, Y. Milross, C. Warren-Forward, H.**	Is there a role for Radiation Therapists within veterinary oncology? *Radiography. 2011,* 17 (3); 250-253.
2	**Surjan, Y. Ostwald, T. Milross, C. Donaldson, D. Warren-Forward, H.**	A Review of current treatment options in the treatment of ocular and/or periocular squamous cell carcinoma in horses: Is there a definitive 'best' practice? *Journal of Equine Veterinary Science* 2014; 34(9): 1037-1050.
3	**Surjan, Y. Ostwald, T. Milross, C. Donaldson, D. Warren-Forward, H.**	Ocular and periocular squamous cell carcinoma in horses: A short communication of the potential use of brachytherapy. *The Australian Equine Veterinarian*, 2015, Vol 34(1): 47-49.
4	**Surjan, Y. Ostwald, T. Milross, C. Donaldson, D. Warren-Forward, H.**	Treatment approaches to ocular and/or periocular squamous cell carcinoma in horses: results of an Australian survey. *(Submitted: Australian Equine Veterinarian, 2015)*
5	**Surjan, Y. Ostwald, T. Milross, C. Warren-Forward, H.**	Radiation Safety Considerations and Compliance within Equine Veterinary Clinics; Results of an Australian survey. *Radiography*, 2014; 21(3): 224-230

1.2 THESIS OUTLINE

This thesis is presented as a series of four published and one submitted research paper. Additionally, the thesis comprises a comprehensive retrospective study analysis on 75 brachytherapy horse cases. The retrospective study analysis has not been submitted for publication. The data analysis and discussion resulting from the retrospective study was lengthy and not suitable for journal publication however provides critical supporting evidence for the progression of the thesis and final outcomes.

The background, methods, results and discussion for each individual research study is embedded within the research papers. A more detailed discussion of the research methodology is available in the Appendices which includes the surveys along with additional data pertaining to design and methodology of surveys. The final chapter, provides an overall discussion and summary of the findings of the research together with an indication of future work.

1.2.1 CHAPTER 1

This chapter provides the background and rationale for the research project. The aims and objectives of the research are outlined, along with the significance of the project, its limitations and assumptions including any biases and their possible effects on the research findings. Ethics approvals for the research will be detailed.

1.2.2 CHAPTER 2

This chapter reviews the literature and provides historical overview of brachytherapy followed by the physics behind its effective application. It also includes an overview of ionising radiation and relevant radiation safety principles, the biological effects of ionising radiation, national and international regulations and recommendations as related to the use of radiation. A description of horse eye anatomy and the characteristics of OSCC/POSCC are also included.

Discussion of current treatment options for OSCC/POSCC and the outcomes of these are investigated as a comparative means of justifying the use of brachytherapy. The need for radiation therapist input is investigated also. This review is supported by three papers (Papers 1, 2 & 3).

1.2.3 CHAPTER 3

This chapter presents the findings from the brachytherapy treatment modelling (retrospective study) and forms justification for the research and a foundation for the development of the standardised Treatment Protocol (process flow-chart) (Chapter 5). This chapter is supported by a comprehensive data analysis and discussion. The results have not been published in view of the length of discussion required to fully describe the method and analysis of the data.

1.2.4 CHAPTER 4

This chapter describes the results of the Australian equine veterinarian surveys (radiation safety and veterinary use in Australia). The outcomes of the surveys aided in determining current practice and future developments as well as providing a foundation for the development of the supporting summary of the Code of Practice for Radiation Protection in Veterinary Medicine in the form of a flow-chart presented in Chapter 6. This chapter is supported by 1 published and 1 submitted research paper.

1.2.5 CHAPTER 5

This chapter describes the development of the Protocol for the treatment of OSCC and/or POSCC in horses. It also contains a series (n=9) of replanned retrospective treatments to test the Protocol and validate its use.

1.2.6 CHAPTER 6

The developed supporting summary of the Code of Practice for Radiation Protection in Veterinary Medicine in the form of a flowchart is presented in this chapter.

1.2.7 CHAPTER 7

The final chapter contains a summary of the research and is presented along with a discussion of its impact, conclusions and proposed future directions.

1.2.8 APPENDICES

The appendices contain additional information including:

- APPENDIX A:
  - Surveys
  - Participant Information Sheets
  - Consent Forms
- APPENDIX B:
  - Conference Presentations
  - Invited Presentation

1.3 BACKGROUND

1.3.1 OCULAR AND/OR PERIOCULAR EQUINE SQUAMOUS CELL CARCINOMA

Squamous cell carcinomas (SCC) are grouped in the non-melanocytic neoplastic lesion spectrum of conditions. [1] The cause of these tumours may be related to extended exposure to the ultraviolet (UV) component of solar radiation, the degree of pigmentation or a genetic predisposition to carcinogenesis. Ocular and periocular SCCs are generally locally invasive and detected within their early stages due to their visible locations in and around the eye. [2] SCC is the most common tumour of the eye and adnexa in horses. [2-4] The prevalence of equine ocular/periocular SCC increases with the age of the horse and whilst most tumours are slow growing and invade locally, metastases (secondary spread) may occur in 10% to 15% of horses. [2] The neoplastic mass can originate from a spectrum of tissues including the cornea, limbus, nictitating membrane, conjuctiva, sclera, orbit and eyelid and third eyelid. [4] The lesions develop through progressive pathologic conditions before the carcinoma is identified. The

progress begins with a plaque (a thickened epithelium) followed by papillomas. A persistent papilloma may progress into carcinoma in situ; the stage before neoplastic cells have penetrated the lamina propria underlying the epithelium (Figure 1.2). [4]

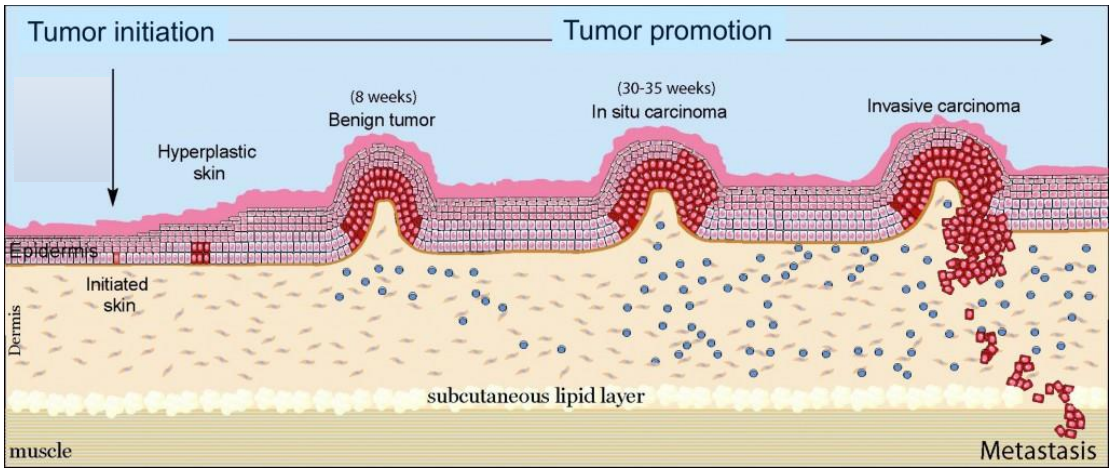

Figure 1.2: Tumour Progression [5]

Ocular SCC (OSCC) is defined as any lesion located in the cornea, limbus or bulbar conjunctiva region, periocular SCC (POSCC) includes the eyelids and third eyelid (Figure 1.3).

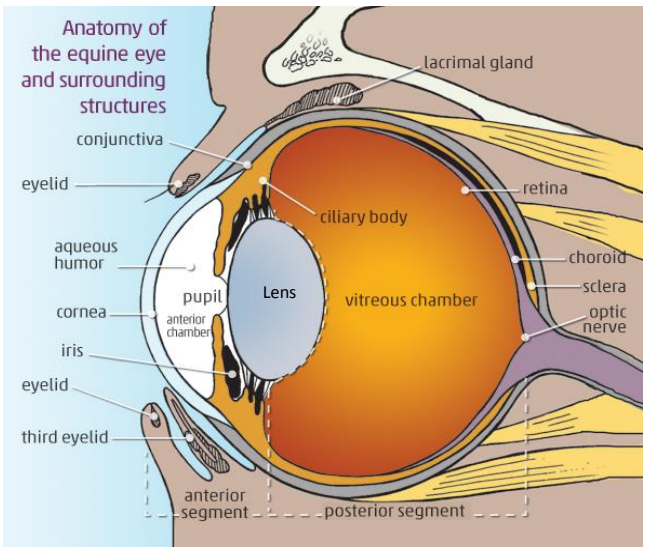

Figure 1.3: Equine Eye Anatomy [6]

1.3.2 CURRENT TREATMENT OPTIONS IN HORSES

The management of OSCC/POSCC remains a challenge regardless of its high prevalence among horses. Whilst the published evidence base is large, the quality of reporting is generally poor and lacks conformity, making the ability to make cross-study comparisons problematic. Adding to the complexity of identifying a 'best practice treatment' is the overall tendency toward global reporting without details of relevance such as exact tumour location, size or previous treatment.

There are a broad range of treatment options currently available for OSCC/POSCC in horses. Treatment options reported in the literature include; photodynamic therapy (PDT), carbon dioxide CO_2 laser ablation, radiofrequency hyperthermia, cryotherapy, topical or intratumoral chemotherapy and radiation therapy (these are further discussed in Chapter 2). [7] Treatment decisions in human cancer treatment are driven by 'best practice' protocols including evidence regarding efficacy of treatment, tumour location, type of tumour, size and depth of infiltration along with previous treatment history. In the absence of best practice evidence-based protocols in veterinary medicine for OSCC/POSCC, treatment type is guided by treatment availability (equipment/facilities), clinician experience based on anecdotal information, available expertise, preference and cost and owner willingness to bear the cost.

The weaknesses in reporting on treatment approaches and outcomes within the veterinary literature make it impossible to ascertain a definitive best practice approach however some notable consistencies can be documented in terms of recurrence rates. Low success rate in surgical approaches is notable in a large number of studies when used as a sole treatment approach however, [3, 8-12] when combined with other modalities, such as those noted above, recurrence rates are notably lowered and long-term control improved significantly. [3, 8-10, 12, 13]

Site-specific data reveals that for third eyelid lesions, total excision is potentially curative however in the case where a complete excision is not possible, adjunctive brachytherapy provides non-recurrence rates of 80%-100%. In the case of limbal SCC, non-recurrence

rates of 75%-100% are observed when using surgery in combination with carbon dioxide CO_2 laser ablation, topical chemotherapy or brachytherapy.

Whilst current overseas use of brachytherapy within veterinary oncology is showing good results in the form of local control and decreased recurrence, the evidence is circumspect considering it is reported with a non-stringent, clinical approach. Furthermore, the initial diagnosis of ocular and/or periocular SCC in horses is generally deduced based on a visual inspection as opposed to a histopathological biopsy. [9]

1.3.3 CURRENT TREATMENT OPTIONS IN HUMANS

Human patients with skin SCC have various treatment options available to them. These include surgery (excisional or Moh's surgery), cryosurgery, 5-Fluorouracil (5-FU) as an applicable cream or radiation therapy. The location and size of the lesion, previous treatment, depth of invasion and the risk of recurrence indicates the treatment type chosen. [14, 15] When SCCs are located in places of cosmetic significance; the lips, nose, face ears and eyes, radiation therapy is generally the treatment of choice. Equally, in locations where surgical removal is problematic, radiation therapy in one of its forms (External Beam Radiation Therapy (EBRT) or brachytherapy) is the treatment of choice.

Due to the superficial location of skin tumours, highly penetrative X-rays (megavoltage) are rarely used. This leaves electrons, kilovoltage X-rays and brachytherapy as treatment options. Good curative and cosmetic results have been recorded for temporary brachytherapy implants and molds using iridium-192 (^{192}Ir) or cesium-137 (^{137}Cs) as well as permanent implants with gold-198 (^{198}Au). [14]

1.3.4 INTRODUCTION TO BRACHYTHERAPY

Brachytherapy is a term used to describe treatment of cancer with sealed radioactive sources implanted directly into or onto a cancer, or within a body cavity, and referred to as interstitial, surface, and intracavitary applications respectively. The dose is delivered continuously, either over a short period of time (temporary implants) or as a one-time implantation procedure (permanent implants). In the latter case, the implant remains in place over the lifetime of the source to a complete decay. [16] Brachytherapy allows the delivery of a high radiation dose to a localised affected area (cancer) and relatively spares

surrounding normal tissue as a result of the rapid fall-off of radiation away from the source. [16] Interstitial radioactive sources are pre-fabricated and supplied by manufacturers in the form of radioactive needles, wires or seeds. [16]

The most frequently used gamma-emitting nuclides in interstitial and intracavitary brachytherapy are iridium-192 (^{192}Ir), cesium-137 (^{137}Cs), cobalt-60 (^{60}Co) and iodine-125 (^{125}I), although gold-198 (^{198}Au) has been used in the past. Beta-emitting sources are used to irradiate very superficial lesions, their use is therefore less frequent than gamma-emitting sources; the two most commonly used beta-emitting nuclides are strontium-90 (^{90}Sr) and ruthenium-106 (^{106}Ru). [17] Many other nuclides are available and are described at length in Chapter 2.

1.3.5 BRACHYTHERAPY USE IN AUSTRALIA AND INTERNATIONALLY

There has been a substantial growth over the past decade internationally in the use of radiation oncology as a specialty within veterinary oncology. [18] Veterinary oncology has paralleled the human entity in the United States of America (USA) with the establishment of veterinary radiation facilities. These facilities have historically used low energy orthovoltage units with a subsequent shift to cobalt-60 and linear accelerators as the staple treatment technique. [18]

A survey of veterinary radiation facilities in the USA in 2001 was conducted under the sponsorship of the Veterinary Radiation Therapy Oncology Group. A total of 42 facilities were identified to be providing EBRT, with 40% of these being academic facilities and 60% private institutions. Furthermore, some of these facilities used human centres for the treatment of their animal patients. [18]

RT treatment of equine OSCC and/or POSCC in Australia is not routinely performed with the authors being aware of only a small number of facilities to provide radiation therapy (linear accelerators, brachytherapy equipment in the form of strontium plaque) for veterinary patients. This information was sourced by searching online and making telephone enquiries to veterinarians advertising RT as a treatment option offered by their clinics. Investigations into the current availability and use of radiation therapy in Australia were carried out prior to the distribution of the surveys and in light of the

anecdotal information provided by currently practicing veterinarians. The search for centres currently in keeping of radiation therapy equipment of any description and actively treating animals with radiation in Australia equate to less than ten (anecdotally). These use in-house linear accelerators, superficial machines (SXT) or orthovoltage (DXR) machines. There are also a non-descript number of centres who gain access to human linear accelerators in hospitals after-hours for animal treatments and some who may use plaque therapy (strontium-90). The use of interstitial brachytherapy (^{198}Au) wires, was also identified as having been active in years past in a small number of Australian clinics. The high cost of the use of radiation therapy for small or large animals, accessibility to radionuclides, cost and expertise, pose a hurdle for veterinary surgeons interested in utilising this technology. Furthermore, the implications of radiation safety add to the complexities of the treatment.

Whilst historically, veterinary medicine has based their radiation treatment applications on human experience, a concerted effort to standardise protocols or procedures explicitly for the purposes of veterinary practice, is not evident. This has resulted in a lack of consistency with respect to RT administration and hindered collection and analyses of reportable outcomes. [19]

This current research identified a number of barriers (anecdotally) to the use of brachytherapy in Australia in horses, propelling further research in the current veterinary situation to; establish legitimate barriers to treatment use; investigate the possibility of reversing the current situation and remove obstacles to re-introduce the treatment technique to Australia.

1.4 AUTHORITIES ON RADIATION MEASUREMENTS AND PROTECTION

1.4.1 INTERNATIONAL COMMISSION ON RADIATION UNITS AND MEASUREMENTS (ICRU)

The ICRU (originally known as the International X-Ray Unit Committee and later as the International Committee for Radiological Units) was initiated at the First International Congress of Radiology (ICR) in 1925 (London) and became active in 1928 following the ICR-2 in Stockholm. [20] The objective of the Committee was the development and promulgation of internationally accepted recommendations on radiation quantities and

units, terminology, measurement guidelines and reference data in medical use. A universally accepted dose-specification and reporting system now exists. The latest ICRU recommendations were updated in 2010. Specific reports/recommendations for the various medical professions and techniques are available, one of which is directly related to brachytherapy (ICRU-58). [21]

1.4.2 INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION (ICRP)

The International Commission on Radiological Protection (ICRP) system of radiation protection is based on three principles; justification, optimisation and dose limitation. The work of the ICRP aids in preventing cancer and other effects and diseases related to ionising radiation exposure. ICRP, since 1928, has developed the basis for radiological protection standards, legislation, guidelines, programs and practice, now used world-wide. [22]

1.4.3 UNITED NATIONS SCIENTIFIC COMMITTEE ON THE EFFECTS OF ATOMIC RADIATION (UNSCEAR)

UNSCEAR was established by the General Assembly of the United Nations in 1955. The purpose of the Committee was to assess and report levels and effects of exposure to ionising radiation. Scientific reports on the effects of exposure to ionising radiation are published by UNSCEAR and used by other international organisations such as ICRP (International Commission on Radiological Protection) as a basis for establishing radiation protection recommendations. [23]

1.4.4 AUSTRALIAN RADIATION PROTECTION AND NUCLEAR SAFETY AGENCY (ARPANSA)

The Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) is the Australian Government's principal authority on radiation protection and nuclear safety. ARPANSA regulates Commonwealth bodies using radiation with the objective of protecting people and the environment from the harmful effects of radiation. ARPANSA promotes national uniformity, and the implementation of international best-practice across all radiation professions. [24]

1.5 RATIONALE FOR STUDY

SCC is the most common tumour of the eye and adnexa in horses [2-4] however current treatment options vary in their application and outcomes. Literature demonstrates very little conformity in the benefits of any one treatment type in veterinary medicine. In contrast, RT for the treatment of skin SCC in humans is highly effective and long-term studies and data are available to support its use. [7, 14, 15]

In the absence of a standardised treatment option, veterinarians often develop treatment practices based on the experiences of other practitioners, preferences and anecdotal information. Discussion (informal) with veterinary practitioners prior to the commencement of this research provided anecdotal evidence to suggest a range of approaches were being used to treat SCC ophthalmic lesions, with brachytherapy being one of the approaches in past times. The varied techniques result in a lack of consistently reportable treatment outcome data, hampering the potential for the development of a 'best practice' treatment option. Furthermore, the inconsistencies posed by the varied treatment options may lead to tumour recurrence, excessive side-effects and/or overall treatment failure. In Australia, discontinuation of brachytherapy is associated with difficulties in attaining radioactive sources, a lack of training in the specialty and an overall reluctance to be involved with a technique that may pose radiation safety implications

Veterinary practice of brachytherapy within Australia has been based on 'personal communication' as opposed to evidenced based practice. Surgeons have passed down their experience and knowledge to colleagues based solely on visible clinical outcomes over the period of their practice. In contrast, the efficacy of (human) radiation therapy (external or interstitial) is based on the evidence-based paradigm. The preparation of human RT treatment is complex and requires patient imaging followed by computer optimisation to establish source placement among other parameters and requires evaluation and approval by appropriately qualified practitioners prior to treatment commencement. In comparison, the configuration of sources during implantation within veterinary oncology is a random process by today's current human practice resulting in possibly uneven isotope distribution and uneven dosimetry. [25] Once the sources have

been implanted the factors of uneven dose distribution and dosimetry are impossible to correct. As a result, neoplastic cells may be forced into the vascular and lymphatic system surrounding the tumour further reducing the possibility of local control. [26] Accurate dosing of tumours is reliant on properly calibrated radioactive sources and the accurate measurements of the mass in order to accurately plot the isodose curves. [27] Currently there is no provision for this type of dosimetry within the veterinary sphere in Australia, and brachytherapy treatments appear to have been previously applied in a haphazard fashion.

A combination of veterinary skills and knowledge, radiation therapy expertise (in the form of application of planning and treatment) and radiation oncology expertise forms the basis of this research project. The outcome of this research in the form of two process flow-charts (Protocol and Radiation Safety Summary) constitute the initial phase in the development of highly adaptable and feasible treatment guidelines to be used within Australia for the brachytherapy treatment of OSCC/POSCC.

1.6 AIMS

The aims of the research are to:

1. Investigate treatment practice in horses in Australia for OSCC/POSCC. Practice is defined as the methods applied currently and in the past by veterinary surgeons and is inclusive of Protocol.
2. Contribute to the evidence base by providing veterinary medicine with a brachytherapy Protocol in view of its known treatment benefits in human SCC.

1.7 OBJECTIVES

The key objectives of this research are to:

i. Undertake a comprehensive literature search to understand what research had previously been done in the area and to conduct gap analysis.
ii. Seek out veterinary experience to support the progress of the research.
iii. Obtain ethics approval for the research.
iv. Source horse head CT imaging data for planning purposes.

v. Complete plan modelling for retrospective data to support the development of the Protocol.
vi. Formulate surveys and distribute to seek information from Australian veterinarians on radiation safety compliance, current and past treatment approaches for OSCC/POSCC.
vii. Complete plan comparisons using Protocol to validate its use.
viii. Develop radiation safety resource for veterinarians.

1.8 RESEARCH ETHICS

Ethics applications and variations for all phases of the research were approved by the University of Newcastle Human Research Ethics Committee (approval number H-2009-0136). Further details including Participant Information Statements, Consent Forms and email invitations can be found in the Appendix A.

1.9 SCOPE OF RESEARCH

The research was conducted over a five year period, which is within the typical timeframe and funding limitations of a part-time doctoral study (seven years). This thesis initially seeks to determine current and past treatment options used for OSCC/POSCC in horses within Australia. For the purposes of informing the research completely, treatment techniques used internationally and their relevant outcomes were also investigated.

During the initial period when the literature review was being conducted, it became evident that veterinary expert input was essential in ensuring data interpretation was accurate. As a result, Doctor David Donaldson BVSc (Hons) DipECVO MRCVS, an European Equine Ophthalmology Expert from the United Kingdom (UK) was contacted and agreed to collaborate in the research. The search for an expert in the field was broad and included Australian-based specialists however it was concluded that Dr Donaldson would be an asset to our research in view of his direct involvement with brachytherapy (High Dose Rate) in his clinic of employment in the UK (Equine Ophthalmology Unit, Animal Health Trust, Lanwades Park Kentford, Suffolk) and his well-known, world-wide expertise in ophthalmology in horses.

Retrospective clinical data (data volunteered for the purposes of analysing treatment practice and outcomes) for use in modelling brachytherapy treatments was collected in 2009 from an Australian veterinary equine clinic site (anonymity maintained) in which the treatments were recorded manually and without a standardised approach. The data was processed and as much as possible, a replica of each treatment plan developed (modelled) with the use of Varian BrachyVision™ radiation therapy treatment planning software. The purchase of the Brachyvision™ computer software licence and the corresponding remote test box was made possible following a successful application for a University of Newcastle Equity Grant. The test box was located at an external site (Chris O'Brien Lifehouse, Radiation Oncology Department) where one of the PhD supervisors is located (Associate Professor Chris Milross, Director Radiation Oncology Department, Chris O'Brien Lifehouse Camperdown, Sydney, Australia), and used to evaluate individual plan outcomes.

Two surveys were developed, the survey participants in the research were Australian equine veterinary practitioners. Recruitment of participants was conducted through postal and online methods through the Australian Veterinary Association Newsletter. The first of the surveys (2011), used to collect veterinary current practice and radiation safety compliance data was completed by 86 participants. The second of the surveys aimed only at collecting data on veterinary current practice and perceptions and was completed by 24 participants (2015).

1.10 LIMITATIONS AND ASSUMPTIONS

A major limitation within this study is that this research is limited to Australia and therefore generalised to Australian equine veterinarians and their practices. It cannot be guaranteed that all equine veterinarians were included within the initial invitation to participate due to the logistics of survey distribution therefore all veterinarians with relevant expert knowledge may not have had the opportunity to contribute to the research. It may be possible that those that completed the survey may not have had expert knowledge in the relevant fields however there may have been others within the clinic who had but did not contribute to the answers.

The retrospective data proves to highlight most of the limitations foreseen in this research. The raw data provided by the clinic was a compilation of written notes and not-to-scale schematic diagrams depicting radioactive wire arrangements and locations. Additionally, dosing parameters were not available and hence assumptions on reasonable prescriptions were made. The specific anatomical site of treatment (specific location within the eye and adnexa) was not always identified and assumptions were made based on the locations noted in the schematic diagrams based on known equine eye anatomy. The distances between each wire were equally based on assumptions made by the researchers following discussions with the veterinary surgeon regarding his treatment approach. Additionally, the results of the retrospective data originate from an individual equine clinic, hence are not a true representation of all Australian clinics. However, what it did evidence was the lack of adequate documentation on treatment approaches and outcomes.

1.11 SIGNIFICANCE

This research has identified that current and past practice for the treatment of OSCC/POSCC in Australia was varied and non-standardised. In relation to brachytherapy for OSCC/POSCC, the research also revealed variations in its application, outcomes and a lack of association with recommended guidelines for the application of human brachytherapy (ICRU, ARPANSA). [21, 28]

The treatment of OSCC/POSCC in horses using brachytherapy appears to have been a random practice within Australia. Whilst there may be a small number of clinics using strontium-90 (plaque application) and linear accelerators in some cases, interstitial brachytherapy appears to be no longer in use (since 2007). Whilst internationally the long term local control and recurrence for ocular and/or periocular SCC in horses is clearly favourable as a result of brachytherapy treatments in conjunction with surgery, the process by which these treatments were routinely performed lacked consistent guidelines and standardised protocols. Veterinary surgeons, whilst equipped with the manual skills to implant radioactive sources and, in past times, the ability to source and purchase these, lack the background required in radiation oncology that ensures the

treatment delivery is optimum and that the dosimetry applied is biologically appropriate and delivered homogenously.

The inconsistencies highlighted the need for a standardised approach to treating OSCC/POSCC. A Treatment Protocol for OSCC/POSCC in horses and a set of radiation safety guidelines (summary) have been developed to provide veterinarians with a standardised approach to treatment should they opt for brachytherapy as the treatment of choice. The Protocol and the Radiation Safety Resource will assist veterinarians in meeting ICRU, ARPANSA [21, 28] recommendations and guidelines, and will ensure treatments are comparative, standardised and delivered with a view to ensuring undue occupational irradiation is avoided.

Overall, the use of the standardised approach as prescribed by the developed Protocol supported by the Radiation Safety Resource should ensure better and measureable treatment outcomes in the treatment of OSCC and/or POSCC in horses in the future.

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CHAPTER 2: LITERATURE REVIEW

2.1 CHAPTER OVERVIEW

Squamous cell carcinoma of the eye and adnexa is the most common non-melanocytic tumour in horses. [1-3] Various treatment approaches are available however a standardised treatment approach is non-existent. Furthermore, whilst there is abundant literature on the various approaches used by individual practitioners [4-16], reporting of outcomes are diverse and non-standard, making it difficult to conclude on the efficacy of the various options. Without an evidence-based approach established on conclusive outcomes supported by guidelines, recommendations and reporting parameters, the treatment methods for OSCC and/or POSCC have become individualised and based on little else than anecdotal information.

In contrast, treatment for SCC in human counterparts is an established and successful therapy, with various possible options including excisional surgery (or Moh's surgery) alone or in combination with cryotherapy or RT. In view of the researcher's expertise in the field of RT and the known efficacy of RT in the treatment of human SCC, this literature review focusses not only on current and past literature on the treatment options available and implemented for OSCCS/POSCC in horses, but also investigates the literature to determine if radiation therapy expertise would be beneficial in veterinary clinics where brachytherapy techniques have been used as a treatment option. This chapter also provides information on brachytherapy background, principles and equipment and radiation protection principles.

Chapter 2 includes three embedded published articles: a narrative literature review on the 'best practice' treatment approach for OSCC/POSCC; and a narrative review discussing the potential for radiation therapy expertise input in veterinary medicine. Additionally a short communication/review paper (invited manuscript – Australian Equine Veterinarian Journal) written to coincide with the launch of the second survey (2015), has been included.

2.2 BRACHYTHERAPY IN VETERINARY MEDICINE

There has been considerable growth internationally over the past decade in the use of radiation oncology within veterinary medicine. [17] Veterinary oncology in the United States of America (USA) has progressed in the field with the founding of veterinary radiation services. These services have conventionally used low energy orthovoltage units with a successive shift to cobalt-60 and linear accelerators as the principal treatment method. [17]

A survey of veterinary radiation facilities in the USA in 2001 was conducted under the sponsorship of the Veterinary Radiation Therapy Oncology Group. Of the facilities identified to be providing EBRT (n=42), 40% were academic facilities and 60% private institutions. [17] Brachytherapy treatment of equine SCC in Australia has been practiced in the past, however, the current provision of radiation therapy treatment facilities and capability within practices (linear accelerators, brachytherapy equipment) for veterinary patients is insignificant in comparison to international practice.

Whilst historically, veterinary medicine has based their radiation treatment applications on human experience, a resolute standardisation of protocols or procedures explicitly for the purposes of veterinary practice have not been evidenced to allow for consistency in not only treatment application but for the purposes of collecting and analysing reportable outcomes. [18]

2.3 SQUAMOUS CELL CARCINOMA (SCC)

Squamous cell carcinoma is a neoplasm stemming from keratinizing cells with malignant characteristics. These include; anaplasia, local invasion, rapid growth and the potential for metastases if left untreated. [19] Factors initiating SCC include exposure to UV light or chemicals, alterations in immune response and mutations in tumour suppressor genes. There are three types of SCC; SCC in situ, superficial SCC and infiltrating SCC. [20] In-situ SCC is skin cancer in its earliest form, the cells of these cancers are still only in the epidermis (the upper layer of the skin) and have not invaded deeper into the dermis. Superficial SCC is cancer that has progressed into the dermis layer and infiltrating SCC refers to cancer that has progressed beyond the dermis. [21]

2.4 OCULAR AND/OR PERIOCULAR SQUAMOUS CELL CARCINOMA IN HORSES (OSCC/POSCC)

Squamous cell carcinoma is one of the most common neoplasms of the eye and adnexa in horses. Although SCC may be found in any breed of horse, Appaloosas, Haflingers, Draft horse and the American Paint Horse breeds are seemingly predisposed to SCC along with Thoroughbreds. [16, 22] Literature suggests prevalence increases with the age of the horse and it has been found to be more common in geldings than mares. [1, 3, 14, 23] As with human skin SCC, increased exposure to UV light is believed to be a risk factor for the development of SCC, especially in those with non-pigmented skin surfaces and in light coloured horses. [14]

2.5 EYE ANATOMY IN HORSES

The equine eye is considered to be a very sensitive organ; even the slightest injury could result in blindness. Vision limited to one eye within a horse restricts the athletic potential and work ability of the horse. [24] The eye and the adjoining adnexa are prevalent to UV exposure and as a result, to the potential of resulting SCCs.

The horse has a particularly large and protruding globe (eyeball). The equine eyeball is situated on each side of the head enclosed within a complete orbital rim with a large opening. [25] The orbit consists of a series of bones including; frontal, zygomatic, lacrimal, temporal and sphenoid. The approximate dimensions of the orbit are 6.0-6.2 cm (width) x 6.0-6.6 cm (height) and 8.5-8.9 cm in depth. [25] The anatomy of the equine eye is described below (Figures 2.1 & 2.2).

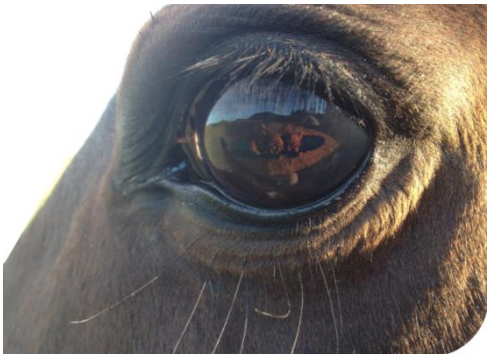

Figure 2.1: Equine Eye [26]

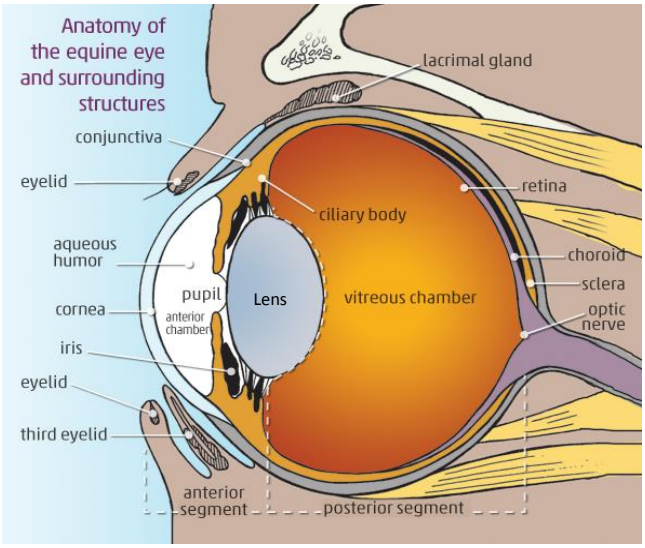

Figure 2.2: Anatomy of the Equine Eye [27]

2.5.1 ORBIT

The bony opening that houses the eyeball or globe is referred to as the socket. It also contains surrounding nerves, blood vessels, fat, connective tissue and muscle. It is protected by a complete orbital bony rim. [24]

2.5.2 EYELIDS

The eyelids protect the eyes, help control the amount of light that enters the eye and control tear distribution. The eyelids are divided into the skin and the inner lining of palpebral conjunctiva. [24]

2.5.3 NICTITANS (THIRD EYELID)

The nictitans or the third eyelid is located medially. It contains the third eyelid gland (tear production). Its movements are horizontal and it provides protection for the cornea. The third eyelid conjunctiva in horses is sometimes pink or darkly pigmented. [24]

2.5.4 CONJUNCTIVA

The conjunctiva is a transparent, mucous membrane that covers the inner eyelids, third eyelid and sclera and is important to the immune system of the eye. [24]

2.5.5 CORNEA, LIMBUS AND SCLERA

The anterior part of the eye is the cornea. It is a prominent, transparent tissue that supplies a large part of the eye's power to bend light. It is also a highly sensitive tissue. The limbus forms the zone between the cornea and the sclera (connected to the cornea) and is located at the peripheral edge of the cornea. The sclera makes up the major portion of the outer eyeball layer. [24]

2.5.6 LENS

The lens is a flexible transparent and avascular structure enclosed in a transparent capsule and situated posterior to the iris. It changes its shape to focus light onto the retina. [24]

2.5.7 RETINA

The retina is the most metabolically active tissue in the body. It is a layered structure lining the inner surface of the eye. It receives light that has been focused by the lens and converts it to neural signals, these are then sent to the brain for visual recognition. [24]

2.6 PREFACE – PAPERS ONE, TWO AND THREE

The literature review which follows was published in three separate articles. The first paper **(Paper One)** was intended for an audience of veterinarians and published in an international journal in the USA (*Journal of Equine Veterinary Science*). The paper provides a comprehensive outline of currently and previously used treatment techniques for OSCC and/or POSCC which form the basis of the PhD research. The article also introduces the concept of the potential of brachytherapy as an effective treatment technique but one still in its infancy within the world of veterinary medicine.

Paper Two is intended for an audience of radiation therapists, and was published in an international journal in the United Kingdom (*Radiography*). The paper provides the results of an enquiry into the potential for improvement in current radiation oncology practice within veterinary medicine through the active involvement of radiation therapists.

Paper Three intended to raise awareness of different treatment options including brachytherapy to Australian veterinarians and was published in the *Australian Equine Veterinarian Journal* to coincide with the launch of the 2015 national survey. As a result of this article and the interest it fostered among equine veterinarians, an invitation to speak on the research at the **Upper Hunter Branch of the Australian Veterinary Association Annual Meeting and Continuing Professional Development Seminar**, ensued in August 12th, 2015.

2.7 A REVIEW OF CURRENT TREATMENT OPTIONS IN THE TREATMENT OF OCULAR AND/OR PERIOCULAR SQUAMOUS CELL CARCINOMA IN HORSES: IS THERE A DEFINITIVE 'BEST' PRACTICE? (PAPER ONE)

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Review Article

A Review of Current Treatment Options in the Treatment of Ocular and/or Periocular Squamous Cell Carcinoma in Horses: Is There a Definitive "Best" Practice?

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ABSTRACT

This review examines the most commonly reported treatment options for ocular squamous cell carcinoma (OSCC) and periocular squamous cell carcinoma (POSCC) in horses and proposes to conclude on the most viable method based on available published studies in terms of treatment outcome, known side effects, advantages, disadvantages, and reliability of available evidence. After a literature search for peer-reviewed published articles, seven most commonly reported on treatments for OSCC and/or POSCC were identified: surgery, photodynamic therapy, carbon dioxide (CO_2) laser ablation, radiofrequency hyperthermia, cryotherapy, chemotherapy, and radiation therapy. Combination therapies were supported as a most successful recommendation; however, when considering site-specific outcomes, the following conclusions may be drawn: limbal squamous cell carcinoma (SCC) was most effectively treated with surgery and adjunctive therapy including CO_2 laser ablation, mitomycin C, and brachytherapy; third eyelid SCC reported good outcomes when treated with surgery alone (clear margins) and in combination with brachytherapy for unclear margins; eyelid SCC, surgical resection was usually limited and most reports supported the use of adjunctive brachytherapy, although photodynamic therapy appeared to be a promising new treatment. It was deemed unreasonable to conclude on the best treatment for cornea, conjunctivae (palpebral and bulbar), and medial canthi in isolation because of lack of evidence. A consistently favored treatment for OSCC and/or POSCC in horses does not currently exist. The presentation of data in the literature and its lack of consistency make it impossible to statistically analyze and make comparative conclusions on treatment outcomes. This review provides a basis for further research to establish a best-practice protocol.

1. Introduction

Globally, squamous cell carcinoma (SCC) is the most commonly found tumor involving the equine eye and adnexa. In spite of a significant body of research concerning the treatment of equine ocular SCC (OSCC) and/or periocular SCC (POSCC), its management remains a major challenge.

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In current clinical practice, the location of the SCC (OSCC vs. POSCC) often affects the type of treatment used [1]. Ocular SCC (cornea, sclera, limbus, and bulbar conjunctiva) are typically treated with excision and adjunctive therapy including β-irradiation, topical chemotherapy, or cryotherapy [2–4]. Periocular SCC (eyelids and third eyelid) are typically treated with excision and adjunctive therapy using cryotherapy, intralesional and/or intratumoral chemotherapy, immunotherapy, brachytherapy, or photodynamic therapy (PDT) [3,5–8]. The treatment types used currently are not universally accepted or indeed supported by evidence based on clinical practice and include a wide range of techniques, many of which are poorly documented or one-off applications. Furthermore and adding particular complexity to the analyses within this review is the lack of data relating to the specific anatomical location of tumors and the tendency for global reporting for OSCC and/or POSCC.

The present review aims to summarize current evidence regarding treatment of equine OSCC and/or POSCC with a view to inform future treatment guidelines within veterinary oncology.

The researchers have examined the literature to answer four research questions (RQs):

RQ1: What are the most commonly reported treatment options for OSCC and/or POSCC in horses?
RQ2: How are the clinical outcomes of these treatments reported on in the literature?
RQ3: What are the reported advantages and disadvantages of each treatment?
RQ4: What treatment may be defined as “best practice”?

2. Methodology

2.1. Criteria for Selection of Studies

Only peer-reviewed articles were included, limits were not set on the date of publishing or the type of study designs. Articles were excluded if they reported on only one case. Studies were included if they objectively measured treatment outcomes in relation to recurrence, cure rate, and/or local control. Studies were included in the analyses if the follow-up after treatment was at least 2 months, and a diagnosis of OSCC and/or POSCC was recorded. Any type of diagnostic technique (histology, cytology, and clinical diagnosis) was included within the review. All articles underwent screening, verification, and quality assessment against the criteria in Table 1.

2.2. Literature Review

The databases used included EMBASE, CINAHL, ScienceDirect, and Scopus. Keywords searched initially included OSCC and POSCC, equine and veterinary oncology, along with combinations of these words, and various permutations of treatment terms: surgery, PDT, carbon dioxide (CO_2) laser ablation, radiofrequency hyperthermia, cryotherapy, chemotherapy, and radiation therapy (RT).

Table 1
Inclusion criteria

Criteria 1	Published in English
Criteria 2	Population: Horses
Criteria 3	Sample size: $n > 1$
Criteria 4	Study reports on treatment outcomes in a format consistent with any one of the descriptors below (site specific and/or treatment specific only, global reporting excluded): • Recurrence rates • Cure rates • Progression-free survival, or • Local control
Criteria 5	Studies must be published after peer review
Criteria 6	A diagnosis of OSCC and/or POSCC
Criteria 7	Follow-up of at least 2 months

OSCC, ocular squamous cell carcinoma; POSCC, periocular squamous cell carcinoma.

2.3. Limitations

The review identified a number of significant weaknesses found within the literature. Definitions of OSCC and POSCC were somewhat unclear and lacked conformity. The overall tendency toward global reporting without exact tumor location limited the ability to compare studies and/or treatment protocols and draw conclusions regarding best practice. Furthermore, tumor grade and stage was underreported or poorly reported in most studies, hindering interpretation of the efficacy of different treatments. Tumor diagnosis methods were varied and included histology and cytology, as well as clinical diagnosis, thereby introducing the potential for erroneous diagnosis in some cases.

Some studies, which may be considered key research in this field [2,3,6], have been exempt from this review as a result of their propensity for global reporting on recurrence rates (all lesion locations and treatment types). Studies that did not report recurrence rate as related to specific locations or specific treatment types did not meet the initial criteria for inclusion.

2.4. Results

The outcomes of the studies have been tabulated (Table 2) and described using a narrative summary to include the type of therapy used, a description of the therapy, the number of cases investigated, the follow-up period, and the percentage recurrence in each case. In the case that a study represented findings for treatment of lesions in addition to OSCC and/or POSCC, only data relevant to OSCC and/or POSCC were extracted.

3. RQ1: What are the most commonly reported treatment options for OSCC and/or POSCC in horses?

There are a wide range of currently available treatment options for equine OSCC and/or POSCC [5,6,9–12]. The selection of literature included a total of 156 articles initially, with 23 articles (37 individual studies in total) comprising all inclusion criteria; most of the studies investigated a combination of treatment modalities and

Table 2
Literature Review of Treatment for Ocular and/or Periocular Squamous Cell Carcinoma in Horses

Type of Therapy	Protocol	No. of SCC cases	Location of lesions (No.)	Period follow-up & lost to follow-up (LTF) (where available)	% Recurrence: Overall (all OSCC/POSCC) & location specific where available
Medical Therapy					
Photodynamic Therapy [5] Study description: Photodynamic Therapy + Surgery	1mg/cm^2 of HPPH* in tumour bed + 665nm waveguide diode laser with incident light dose of 100J/cm^2 & dose rate 100mW/cm^2 (25-40 mins)	10	Eyelid (8) Temporal canthus (1) Nasal canthus (upper & lower) (1)	Av. 45 months Range: 25-68 months 0 LTF	Overall - 22% Eyelid - 12.5% Nasal canthus (upper & lower) - 100%
Chemotherapy [13] Study description: Cisplatin + Surgery	1mg/cm^2 q for 2 weeks for 4 treatments injected into tumor	3	Eyelid (2) Cornea (1)	Av. 15.24 months Range: 10 days-101.32 months 2 LTF	Overall - 100%
Chemotherapy [26] Study description: Mitomycin C (MMC) + CO_2 Laser Ablation	MMC: 0.4mg/mL applied for 1 to 5 minutes following CO_2 laser (6W & 9MHz interrupted pulse)	18	Bulbar conjunctiva (sclera) (7) Limbus (lateral corneoscleral margin) (5) Cornea (5) Third eyelid (1)	Range: 2-24 months 0 LTF	Overall - 27.8% Medial sclera - 14% Cornea - 60% Lateral corneoscleral margin - 20%
Chemotherapy [14] Study description: Mitomycin C (MMC) + Surgery (9) Mitomycin C (MMC) only (8)	Sole Therapy (MMC): 0.2mL of 0.04% solution of MMC instilled into conjunctiva every 6 hours for 7 days Surgery + MMC: As above, commenced 48 hours post-surgery	17	Third Eyelid (6) Sclera (2) Cornea (2) Sclera + cornea (3) Third Eyelid + cornea (1) Eyelid + conjunctiva (1) Conjunctiva+sclera + cornea (1) Third Eyelid + conjunctiva + sclera (1)	Av 22.5 months Range: 13-32 months 0 LTF	MMC alone overall - 25% MMC + surgery overall - 22% Sclera + cornea - 33% Eyelid + conjunctiva - 100% Conjunctiva + sclera + cornea - 100% Third eyelid + conjunctiva + sclera - 100%
Chemotherapy [28] Study description: Cisplatin in Oily Emulsion	4 intratumoral cisplatin chemotherapy sessions @ 2 week intervals (oily emulsion of 1mg of cisplatin/cm^3 of tumour)	3	Periocular (1) Inferior palpebra (1) Inferior palpebra + med canthus (1)	Range: 5-24 months 0 LTF No outcome reported for POSCC in this study	Overall - 66.7% Inferior palpebra - 100% Inferior palpebra + med canthus - 100%
Surgical Therapy					
Surgery [13] Study description: Excision	Nil provided	81	Eyelid (22) Cornea (11) Limbus or bulbar conjunctiva (12) Third eyelid (35) Palpebral conjunctiva (1)	Av. 15.24 months Range: 10 days-101.32 months 18 LTF Eyelid (4LTF) Cornea (3LTF) Third eyelid (11LTF)	Overall - 61.7% Eyelid - 68.2% Cornea - 63.6% Limbus or bulbar conjunctiva - 83.3% Third eyelid - 51.4% Palpebral conjunctiva - 0%
Surgery [4] Study description: Excision	Nil provided	18	Third eyelid (14) Limbus (3) Bulbar conjunctiva (1)	Av. 48 months Range: 4-132 months 0 LTF	Overall - 44.4% Third eyelid - 42% Limbus - 66.7%
Surgery [11] Study description: Excision/Lamellar Keratectomy	Nil provided	2	Cornea (1) Third eyelid (1)	Cornea (1) 6 month follow-up Third eyelid (1) 18 month follow up 0 LTF	Overall - 0%

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Table 2 (*continued*)

Type of Therapy	Protocol	No. of SCC cases	Location of lesions (No.)	Period follow-up & lost to follow-up (LTF) (where available)	% Recurrence: Overall (all OSCC/POSCC) & location specific where available
Surgery [25] Study description: En Bloc Resection	Complete removal of third eyelid	19	Third eyelid (19)	Av. 41 months Range: 3-87 months 0 LTF	Overall - 0%
CO_2 Laser Ablation [15] Study description: CO_2 Laser Ablation with Lamellar Superficial Keratectomy (2) or alone (2)	CO_2 laser - continuous mode (3-8W)	4	Limbal (4)	Range: 1-20 months	Overall - 25%
CO_2 Laser Ablation (MMC) [16] Study description: CO_2 laser + Surgical Resection (10) MMC + Surgical Resection (17)	MMC 0.4% solution applied directly to the wound for 5 minutes (intraoperatively) or MMC 0.04% through catheter (7 days on, 7 days off) (1-3 cycles) postoperatively CO_2 laser - continuous mode (2-3W)	27	Corneolimbal (27)	Mean. 19.5 (±10.2) months Range: 1-35.5 months (MMC) 47.4 (±20.8) months Range: 1-75.5 months (CO_2) 0 LTF	MMC Overall - 16.6% CO_2 Overall - 13.3%
CO_2 Laser Ablation [17] Study description: CO_2 laser + Superficial Lamellar Keratectomy + Bulbar Conjunctivectomy	Superficial lamellar keratectomy and conjunctivectomy + CO_2 laser - continuous mode (2-3W)	24	Corneolimbal (24)	Av. 40.3 (±24.6) months Range: 14-99 months 1 LTF (beyond 8 months)	Overall - 16.7%
CO_2 Laser Ablation [29] Study description: CO_2 laser alone	1993-1995: CO_2 laser - continuous mode (10-25W) 1995 onwards: CO_2 laser - continuous mode (32W)	3	Periocular Adnexa (3)	Variable follow-up, minimum 6 months 2 LTF	Overall - 33.3% no data available for 2/3
Radiofrequency Hyperthermia [30] Study description: Radiofrequency Hyperthermia alone	Electrodes (piercing probes) maximal power output 2.2W with 3 000-ohm load and 10W with 300-ohm load 30 seconds at 50°C	8	Ocular SCC (8)	Range: 2-10 months 0 LTF	Overall - 25% (at 2-10 months)
Cryotherapy [4] Study description: Cryotherapy + Surgery	Nil provided	6	Limbal (2) Eyelid (2) Third eyelid (2)	Av. 31.5 months Range: 3-60 months 0 LTF	Overall - 50% Metastases - 16.7% (n=1) Third eyelid - 50% Limbus - 50% Eyelid - 100%
Cryotherapy [27] Study description: Cryotherapy alone	Cryogen: liquid nitrogen Application: Closed probe, 1 freeze-thaw cycle: -20°C for 35 seconds. Repeated cryotherapy application for all cases (1 week, 4 weeks, 8 months)	4	Third eyelid (4)	Range: 1 week-8 months 0 LTF	Overall - 25%

Cryotherapy [11] Study description: Cryotherapy + Keratectomy (1) Cryotherapy + Excision (1) Cryotherapy only (1)	Cryogen: liquid nitrogen Application: spray, 3 freeze-thaw cycles either alone (1) + keratectomy (1) + excision (1)	3	Third eyelid (2) Cornea + bulbar conjunctiva (1)	Third eyelid (1) follow up at 24 months Third eyelid (1) follow up at 30 months Cornea + bulbar conjunctiva (1) follow up at 21 months 0 LTF	Overall - 33.3% Cornea + bulbar conjunctiva - 100% (treated with excision & cryotherapy)
Cryotherapy [18] Study description: Cryotherapy + Keratectomy	Cryogen: liquid nitrogen Application: closed probe, 2 freeze thaw cycles + keratectomy	11	Limbal (9) Limbal + third eyelid (2)	Mean. 57.6 months Range: 12-96 months 0 LTF	Overall - 45% Limbal - 44% Limbal + nictitating membrane - 50%
Cryotherapy [19] Study description: Cryotherapy + Keratectomy	Cryogen: liquid nitrogen Application: closed probe, 2 freeze thaw cycles + keratectomy	4	Limbal (2) Corneal extending into bulbar conjunctiva (2)	Range: 21-36 months 0 LTF	Overall - 0%
Cryotherapy [13] Study description: Cryotherapy + Surgery	Cryogen: not specified Application: 2 freeze thaw cycles + surgery	75	Eyelid (25) Cornea (14) Limbus or bulbar conjunctiva (20) Third eyelid (9) Palpebral conjunctiva (7)	Av. 15.24 months Range: 10 days-101.32 months 29 LTF Eyelid (9LTF) Cornea (6LTF) Limbus or bulbar conjunctiva (8LTF) Third eyelid (4LTF) Palpebral conjunctiva (2LTF)	Overall - 30.7% Eyelid - 40% Cornea - 28.6% Limbus or bulbar conjunctiva - 35% Third eyelid - 0% Palpebral conjunctiva - 28.6%
Radiation Therapy					
Strontium-90 [13] Study description: ^{90}Sr + Surgery	Radionuclide: ^{90}Sr Application: Surface applicator Dose: single 80- 100Gy (cornea); 100- 120Gy (conjunctiva); 120- 200Gy (eyelid) + cytoreductive surgery	33	Eyelid (3) Cornea (9) Limbus or bulbar conjunctiva (13) Third eyelid (8)	Av. 14.4 months Range: 10 days-101.32 months 20 LTF Eyelid (3) Cornea (5) Limbus or bulbar conjunctiva (6) Third eyelid (6)	Overall - 15.1% Eyelid - 0% Cornea - 0% Limbus or bulbar conjunctiva - 30.8% Third eyelid - 12.5%
Strontium-90 [20] Study description: ^{90}Sr + Keratectomy	Radionuclide: ^{90}Sr Application: Surface applicator Dose: single 200Gy + Keratectomy	25	Corneolimbal (25)	Av. 24 months Range: 12-168 months 9 LTF	8% Recurred before 12 months 13% Recurred at 24 months
Strontium-90 [21] Study description: ^{90}Sr + Surgery	Radionuclide: ^{90}Sr Application: Surface applicator Dose: single 100Gy + cytoreductive surgery	8	Limbus (5) Third eyelid (2) Eyelid + conjunctiva (1)	24 months (complete remission) 0 LTF	Overall - 12.5% Eyelid + conjunctiva - 12.5%
Strontium-90 [13] Study description: ^{90}Sr + Surgery + Cryotherapy	Radionuclide: ^{90}Sr Application: Surface applicator Dose: single 120- 200Gy (eyelid); 100- 120Gy (palpebral conjunctiva) + cytoreductive surgery + cryosurgery	5	Eyelid (3) Palpebral conjunctiva (2)	Av. 14.4 months Range: 10 days-101.32 months 4 LTF Eyelid (2LTF) Palpebral conjunctiva (2LTF)	Overall - 0%

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Table 2 (*continued*)

Type of Therapy	Protocol	No. of SCC cases	Location of lesions (No.)	Period follow-up & lost to follow-up (LTF) (where available)	% Recurrence: Overall (all OSCC/POSCC) & location specific where available
Strontium-90 [22] Study description: ^{90}Sr + Keratectomy	Radionuclide: ^{90}Sr Application: Surface applicator Dose: single 80- 100Gy + Keratectomy	24	Cornea (24)	Range: 12-108 months 1 LTF	Overall - 16.67%
Strontium-90 [23] Study description: Permanent AM transplantation or BC graft + Keratectomy or permanent AM transplantation or BC graft + Keratectomy + ^{90}Sr	Radionuclide: ^{90}Sr Application: Surface applicator Dose: 20 Gy per site x 4 sites + AM + Keractectomy (7) 20 Gy per site x 4 sites + BC graft + Keractectomy (2) Other treatment protocols: Keratectomy + AM (2) Cryotherapy + Keratectomy + BC graft (1)	12	Corneolimbal (12)	Mean. 226 ± 218 days Range: 21 days-25.58 months	Overall - 0%
Iridium-192 [13] Study description: ^{192}Ir + Surgery	Radionuclide: ^{192}Ir Application: Interstitial implants (placed for 5- 13 days) Dose: 58- 65Gy + cytoreductive surgery	19	Eyelid (12) Third eyelid (6) Palpebral conjunctiva (1)	Av. 14.4 months Range: 10 days-101.32 months 12 LTF Eyelid (9LTF) Third eyelid (3LTF)	Overall - 10.5% Third eyelid - 16.7% Palpebral conjunctiva - 100%
Iridium-192, Radon-222, Iodine-125 [21] Study description: ^{192}Ir, ^{222}Rn or ^{125}I + Surgery	Radionuclide: ^{192}Ir, ^{222}Rn or ^{125}I Application: Interstitial implants Dose: 36-100Gy + cytoreductive surgery	10	Third eyelid (8) Eyelid (2)	24 months (complete remission) 0 LTF	Overall - 40% Third eyelid - 25% Eyelid - 100%
Cobalt-60 [13] Study description: ^{60}Co + Surgery	Radionuclide: ^{60}Co Application: Teletherapy Dose: 32 - 36Gy (divided into 4 weekly treatments) + cytoreductive surgery	2	Eyelid (1) Third eyelid (1)	Av. 14.4 months Range: 10 days-101.32 months 0 LTF	Overall - 0%
Radon-222 [24] Study description: ^{222}Rn + Surgery	Radionuclide: ^{222}Rn Application: Interstitial implants (needles) Dose: 6000 roentgens (approx. 52.17Gy) + cytoreductive surgery	8	Eyelid (5) + upper and lower eyelid (1) Cornea & sclera (1) Eyelid & sclera (1)	Range: 6 weeks-18 months 0 LTF	Overall - 25% Cornea + sclera - 100% Eyelid + sclera - 100%
Gold-198 [31] Study description: ^{198}Au	Radionuclide: ^{198}Au Application: Interstitial implants (needles or seeds) Dose: 70Gy	4	Eyelid (4)	Range: 4-24 months 0 LTF	Overall - 0%

AM, Amniotic membrane; BC, Bulbar conjunctiva; CO_2, Carbon dioxide laser ablation; HPPH, 2-[1-hexyloxyethyl]-2 Devinyl Pyropheophorbide-a; LTF, Lost to follow-up; MMC, Mitomycin C; SCC, Squamous cell carcinoma

reportable outcomes (Table 2). Twenty-five studies included surgery in combination with the modalities being investigated [4,5,11,13–24]. Four studies reported on the use of surgery alone [4,11,13,25]. Eight studies reported on the use of a modality not in combination with surgery [14,15,26–31].

There was a notable concentration of articles in the field of RT particularly focusing on brachytherapy. Although a total of 36 articles reported on brachytherapy, only 11 of these met all inclusion criteria. Of the 11 articles (13 studies), 12 studies investigated combinations of brachytherapy treatments including Strontium-90 (^{90}Sr) with surgery or surgery and cryotherapy, and cytoreductive surgery with Iridium-192 (^{192}Ir), Radium-222 (^{222}Rn), or Iodine-125 (^{125}I) [13,20–24,31].

There were six chemotherapy studies (four articles) in total with five studies meeting all inclusion criteria. The cytotoxic drugs used included cisplatin and mitomycin (MMC) in combination with other therapies in the form of surgery or CO_2 laser ablation [13,14,16,26] and intratumoral cisplatin as the sole treatment in one study [28]. There were seven studies (six articles) investigating cryotherapy, one as a sole therapy and the remaining six in combination with surgery [4,11,13,18,19,27]. Radiofrequency hyperthermia was reported in a number of studies; however, only one met all necessary criteria [30]. There were 5 studies (four articles) reporting on the use of CO_2 laser ablation, either alone or in combination with surgery [15–17, 29]. A single study that met all inclusion criteria on PDT was identified [5].

The seven most commonly reported modalities were: surgery; PDT; CO_2 laser ablation; radiofrequency hyperthermia; cryotherapy; topical or intratumoral chemotherapy; and RT.

4. RQ2: How Are the Clinical Outcomes of These Treatments Reported on in the Literature?

All 23 articles (37 studies) reported on the recurrence or nonrecurrence rates of the treatment, with or without average disease-free intervals and local control. The time at which recurrence or nonrecurrence was measured differed substantially between studies (2 months–168 months).

5. RQ3: What Are the Reported Advantages and Disadvantages of Each Treatment?

5.1. Surgery

Literature confirms that surgical resection alone of equine SCC may be adequate as long as the tumors are small or identified as carcinomas in situ (CIS), and the margins are consistently clear [32]. Reports of tumor recurrence as a result of inadequate surgical excision are common [32,33]. Attempts at complete surgical excision followed by reconstructive blepharoplasty procedures for equine POSCC are limited in horses because of the need to preserve functional eyelid and the lack of skin which can be mobilized around the eye in this species. The equine skin is firmly attached to the underlying connective tissue and has poor superficial blood supply, and therefore the mobilization of adequate skin to be used in blepharoplasty procedures is limited [34]. In cases where the tumor margins are extensive, enucleation or exenteration is often necessary [35].

Surgical excision of OSCC and/or POSCC when used alone has a relatively low success rate. Studies investigating the efficacy of surgery as a sole treatment for OSCC and/or POSCC agree that tumor recurrence is significantly higher without the use of a combination of treatments [3,4,13]. A study investigating the effects of treatment with and without adjuvant RT for OSCC and/or POSCC in 157 horses identified surgery alone to have had the highest recurrence rate (61.7%) at all anatomic locations apart from the third eyelid [13].

The third eyelid is a form of POSCC in which a good prognosis is often given in practice as long as grossly clear surgical margins can be achieved [12]. This is supported by a single study by Payne et al [25], in which 19 horses diagnosed with third eyelid SCC (16 were histologically confirmed and three based on clinical diagnosis) were treated by complete en bloc resection excision of the third eyelid in all cases. Median follow-up was 41 months at which point no recurrences were detected in any of the 19 cases. Furthermore, there were no reportable complications in any of the cases as a result of the third eyelid excision. This is in contrast to Mosunic et al [13] who reported a recurrence rate of 51.4% when surgery alone was used in the management of third eyelid SCC. This discrepancy may relate to the varied extent and grade of the third eyelid SCC and whether grossly clear surgical margins were obtained – neither of which were reported in this paper.

5.2. Surgery as a Combination Therapy

Beyond occasions where extensive local spread of an equine OSCC and/or POSCC requires enucleation or exenteration to eradicate the malignancy, treatment usually involves surgical excision combined with adjunctive therapy including cryotherapy, intralesional and/or intratumoral chemotherapy, hyperthermia, CO_2 laser ablation, PDT, or brachytherapy [3,4,6,13,27,32]. Numerous studies have shown strong association with combination therapies and lower recurrence rates and long-term local control when compared with surgery alone [5,9,13,20,33,36,37]. Combining surgery with an adjunctive therapy improves the efficacy and reduces the morbidity of treatment [38]. The application of conservative surgery in combination with RT has been consistently shown to be as effective as radical surgery alone with the additional benefit of fewer cosmetic and functional defects [38].

5.3. Photodynamic Therapy

Photodynamic therapy uses light of a specific frequency and light-sensitive compounds (photosensitizers) in an oxygen-rich environment to cause localized tissue necrosis [8]. In a recent study by Giuliano et al [5], nine horses (n = 10 POSCC) were treated with a combination approach of surgery followed by PDT; locations included the eyelid (n = 7) and nasal canthus (n = 3). The results demonstrated an

average disease-free survival of 45 months. A recurrence rate of 22% (n = 2 of nine horses) was reported with 25–68 months of follow-up. The two cases with recurrence (eyelid and nasal canthus) had previously been treated with surgical resection and ancillary cryotherapy before PDT. Recorded short-term side effects after surgery and/or PDT included considerable swelling and a dark red to purplish discoloration of the eyelids. In two of the cases, epiphora resulted due to extensive surgical resection, which interfered with the nasolacrimal puncta [5].

5.4. CO_2 Laser Ablation

Carbon dioxide laser ablation involves a CO_2 laser operated in the continuous mode with an average output of 3–8 W. The laser provides "ablation" of the lesion as opposed to conventional surgical cutting [32]. English et al [15] treated four horses (n = 4 OSCC; limbal SCC) using CO_2 laser ablation either as a sole treatment or after a lamellar superficial keratectomy. The limbal SCC ranged in size from 1.5 to 5 cm with the largest tumor extending 3 cm into the cornea. Two of the cases were treated with lamellar superficial keratectomy in combination with CO_2 laser ablation; for both of these cases, there was no recurrence recorded at 7 months (the largest mass with 3-cm extension into cornea) and 14 months, respectively. One of the two cases receiving CO_2 laser ablation alone resulted in a recurrence 4 months postoperatively, which was retreated with CO_2 laser ablation. At 12 months follow-up, no recurrence was noted. The fourth case receiving CO_2 laser ablation alone was recurrence free at 20 months postoperatively. Minimal or no observable postoperative pain was reported in this study. Although the authors concluded that CO_2 laser ablation represents a promising new treatment option for OSCC, the small number of cases (n=4) limited the conclusions which could be drawn from the study.

A more recent retrospective study by Clode et al [16] investigated the complications and nonrecurrence rates following CO_2 laser ablation versus topical MMC therapy in 25 horses (n = 27 OSCC; corneolimbal SCC). Tumor sizes ranged from 11.2 to 11.5 mm (±4.7–7.4 standard deviation [SD]). All cases had surgical resection (superficial keratectomy and bulbar conjunctivectomy if involved) before the application of the adjunctive therapy with either MMC or CO_2 laser ablation. Of the 27 OSCC, 17 received MMC and 10 received CO_2 laser ablation. There was no significant difference between tumor nonrecurrence rates between the MMC versus CO_2 laser ablation therapy groups (83.4% and 86.7%, respectively) [16]. The follow-up in the MMC and CO_2 groups ranged from 1 to 35.5 months and 7 to 75.5 months, respectively. Complications were defined as major if they required a halt in treatment or enucleation of the affected eye. All other complications were considered minor. Minor complications were recorded in six of 17 (35%) of MMC-treated eyes and four of 10 (40%) CO_2 laser ablation–treated eyes and included granulation tissue, blepharospasm, and conjunctival necrosis. Major complications occurred in six of 17 of the MMC treatment group but in none of the CO_2 laser ablation–treated eyes.

Michau et al [17] retrospectively analyzed data to determine the complications and nonrecurrence rates after superficial lamellar keratectomy combined with bulbar conjunctivectomy and CO_2 laser ablation for equine OSCC. The treatment protocol was administered to 24 horses (n = 24 OSCC; limbal SCC); 23 were available for follow-up for periods ranging from 14 to 99 months (one case was enucleated at 8 months). The lesions were located along the limbus, more specifically in the lateral limbus (n = 17), medial limbus (n = 3), medial–ventral limbus (n = 2), ventral (n = 1), and lateral–ventral limbus (n = 1). The size of the lesions were measured to be between 5 × 6 mm and 20 × 20 mm with n = 17 of the cases measured to be ≥10 mm in diameter. Of the cases treated (n = 24 limbal SCC), a recurrence was reported in four of 24 horses (16.7%) (three of which had a lesion measuring ≥10 mm in diameter). Two of the recurrences underwent repeat treatment and were reportedly free of recurrence at 44 and 60 months, and the third underwent surgical removal along with cryotherapy with no recurrence reported at 12 months. Follow-up ranged from 14 months to 99 months with an average of 40.3 months (±24.6 months SD). The authors concluded that adjunctive therapy in the form of CO_2 laser ablation along with keratectomy and bulbar conjunctivectomy was successful in 87.5% of horses after a single treatment. Of those who received a secondary application of the overall treatment success was 91.7% (22/24) at last follow-up.

5.5. Radiofrequency Hyperthermia

Radiofrequency hyperthermia uses temperatures of 50°C directly applied to lesions with the use of commercially available probes. The high temperatures are maintained in place for approximately 30 seconds [32]. A study by Grier et al [30] used radiofrequency hyperthermia to treat eight horses (n = 8 OSCC). The exact anatomic locations of the tumors for each horse were not described, rather the locations are referred to as OSCC. Hyperthermia was used alone to ensure the evaluation of treatment effects was directly correlated to the hyperthermia application. Many of the tumors were >1.5 cm in diameter (again, no specific details for each lesion was noted). Of the eight horses treated and reevaluated at 4–6 weeks, no clinical evidence of tumor was noted in seven cases. Six of the eight horses (75%) remained recurrence free at 2–10 months postoperatively. The authors claim that hyperthermia is technically easier than excision or keratectomy and eliminate the need for equipment and training required for the application of cryotherapy and RT, respectively.

5.6. Cryotherapy

Cryotherapy uses liquid nitrogen, nitrous oxide, or CO_2 to target malignant tumor cells with tissue temperatures between −20°C and −40°C [32]. Cryotherapy may be applied in two different forms, via cryospray or via a contact probe. The use of cryospray has the potential to cause collateral tissue damage at a site that is distant to the lesion, and furthermore, there is a potential for overfreezing, resulting in posttreatment ulcers, depigmentation, and

necrosis of normal tissue [32]. Because of the location of the OSCC and/or POSCC lesions, a contact probe has been advocated [39]. Advantages of cryotherapy include minimal postoperative pain, reduced tissue scarring and hemorrhage, and a relatively low cost to the client. However, the length of treatment procedures using cryotherapy can at times be considerable, and multiple treatments may be required over a period of weeks for large or recurrent lesions [37].

Results of a study by King et al [4] noted a higher local recurrence rate for combined surgery and cryotherapy as compared with surgery alone for equine OSCC and/or POSCC: 50% and 44.4%, respectively. Of the six eyes (n = 6 OSCC and/or POSCC) treated with surgery and/or cryotherapy, recurrence was noted at all treatment sites including the limbus, bulbar conjunctiva, and eyelids. The size and grade of the SCCs were not reported.

A smaller study by Hilbert et al [27] described three horses (n = 4 POSCC; third eyelid SCC); one horse had bilateral POSCC with extension to the lower eyelids and right maxillary sinus. They were all treated with cryotherapy using a thermocouple and cyroprobes to achieve tumor temperatures of −20°C for 35 seconds, with two freeze-thaw cycles. The bilateral case with extensive local invasion had recurrence at 11 weeks after treatment; treatment was repeated, but no further follow-up was reported for this case. The overall follow-up period for all cases ranged from 11 weeks–8 months, and all POSCC received a repeat cryotherapy application for varying reasons: detection of extension on lower eyelid and medial canthus (case 1 and case 2, respectively) and invasion (recurrence) in bony orbit (case 3). The overall recurrence rate was 25% (one of four POSCC).

Similarly, a small study by Harling et al [11] of five horses (n = 3 OSCC and/or POSCC) treated with cryotherapy and/or surgery or cryotherapy alone reported a recurrence in one of the three SCCs treated with cryotherapy. There was no recurrence (at 24 months) in the horse that had been treated with a closed cryoprobe and excision as well as second application of liquid nitrogen cryospray (third eyelid). The horse treated with three liquid nitrogen cryosprays alone recorded no recurrence at 30 months (third eyelid). The horse with recurrent disease was treated with three liquid nitrogen cryospray applications and incomplete excision (cornea and conjunctiva). Recurrence was noted at 21 months.

The technique described in a retrospective study by Bosch and Klein [18] consisted of keratectomy followed by cryosurgery in 10 horses (n = 11 OSCC; limbal SCC). Interestingly, limited keratectomies were intentionally performed to spare the normal cornea, minimize scar formation and intentionally leave tumor cells which when frozen and/or destroyed were expected to invoke a tumor-specific immune response. This purported benefit is not supported by any scientific literature. The overall recurrence rate for OSCC in this study was 5/11 (45%). Recurrence rate of the limbal SCC was possibly correlated with the size of the initial lesion. Of the 11 limbal SCC, those with a surface area of <1 cm^2 (n = 3) were reported to have been treated successfully (no recurrence, 12 months to 8 years after treatment; mean, 4.5 years). Of the cases with a tumor surface area between 1 and 2 cm^2 (n = 4 limbal and n = 1 limbal + third eyelid), four of the lesions were successfully treated, although one of the limbal lesions recurred within 12 months and was retreated on four more instances only to be enucleated. The remaining SCC cases >2 cm^2 (n = 2 limbal and n = 1 limbal + nictitating membrane) resulted in enucleation. The authors concluded that use of keratectomy combined with cryosurgery for the treatment of small limbal lesions (<2 cm^2) as an effective therapy.

A study by Schoster [19] reported on the outcomes of combined excision and cryotherapy to treat three horses (n = 4 OSCC; limbal SCC). All three horses had the masses surgically debulked with subsequent cryosurgery. Nonrecurrence was reported for all cases over a postoperative period of 21–36 months. The debulking included a margin of 2–3 mm in every instance, and the lesions ranged in size from 1.5 × 1.5 cm in diameter to 2 × 3 cm in diameter and 1 cm in thickness. One of the cases had been previously treated with surgical removal of the initial lesion followed by β-irradiation (brachytherapy). The authors suggest that none of the lesions could have been removed effectively with surgery alone and that the use of cryotherapy ensured any remaining mass was treated. The authors discuss the possibility of using open spray cryotherapy (with liquid nitrogen), which allows such rapid freeze times as to make the procedure possible under sedation and therefore limiting the risks involved with prolonged general anesthesia in horses.

5.7. Chemotherapy

Chemotherapy most commonly includes intralesional and/or intratumoral or topical (regional) application of the cytotoxic drugs to the neoplasm. Cisplatin is a useful drug for intratumoral chemotherapy because it does not cause tissue necrosis [6,40,41]. Mitomycin C has been used to treat neoplasia in and around the eye in humans since 1994 [42]. Its primary function is to inhibit DNA synthesis, and it continues to act in a therapeutic form for a minimum of 8 months after treatment is completed [42]. Two treatment protocols are currently used in humans, the first involves MMC as a primary treatment with the MMC solution instilled into the eye for 14 days (0.02%–0.04% solution). The treatment is repeated three times with a 7-day rest between each application. The second protocol uses MMC (0.04% solution) in combination with surgical resection and is applied to the resected area for 3–5 minutes at the time of surgery [43,44].

In 2006, a study by Rayner and Van Zyl [26] on the effectiveness of topical MMC used in conjunction with CO_2 laser ablation in eight horses (n = 18 OSCC and/or POSCC) reported a success rate (defined as no signs of recurrence within 11–24 months) of 70%. Diagnosis was made by gross examination. The location of the ocular lesions varied and included the sclera (n = 7) cornea (n = 5), third eyelid (n = 1), and the corneoscleral margin (n = 5). The description of primary scleral SCC as a form of OSCC is misleading; this tissue contains no epithelial component. Given this the authors have interpreted ‘scleral’ SCC to represent either SCC involving the overlying bulbar conjunctiva or adjacent limbus. The length of MMC application

varied from 1 to 5 minutes. Recurrence was observed after 2 and 6 months in one of the scleral SCC and three corneal SCC, respectively. The study concluded that MMC used as an adjunct with CO_2 laser ablation in the treatment of OSCC and/or POSCC demonstrates results comparable with RT alone [26].

A study by Malalana et al [14] described the effects of MMC administration with or without surgery for the treatment of OSCC and/or POSCC including the conjunctiva, sclera, cornea, eyelid, and the third eyelid. A total of 14 horses (n = 17 OSCC and/or POSCC) were treated, and the outcome measured as "clinical resolution" was determined by gross inspection of the site. Eight eyes received MMC only, and nine eyes had the lesions surgically removed and MMC administered as an adjunct therapy. The protocol for the administration of MMC included the repeated application 6 hourly, 7 days on, and 7 days off until full tumor regression was observed. Follow-up ranged between 13 and 32 months. Of the eyes treated with MMC alone, clinical resolution was reported in six of eight eyes (75%). For those receiving MMC and surgery, seven of nine eyes (78%) resolved. No complications were observed overall for any of the cases. The six third eyelid lesions all resolved following treatment with MMC and surgery (n = 5) and MMC (n = 1). Two of the three lesions in the sclera and cornea received surgery and MMC (n = 2) and totally resolved, although the lesion administered with MMC alone required further treatment with Strontium-90 brachytherapy and surgery. Lesions on the cornea (n = 2) and sclera (n = 2) were treated with surgery and MMC and all resolved. The single lesion on the third eyelid and cornea resolved after MMC alone, although the lesion on the eyelid and conjunctiva required further treatment after MMC. The remaining lesions: conjunctiva, sclera, and cornea (n = 1) and third eyelid, conjunctiva, and sclera (n = 1) received MMC and surgery but required further treatment thereafter. The authors concluded that the administration of MMC on its own or in combination with surgery is a safe and effective treatment for OSCC and/or POSCC, in particular, in lieu of the availability and accessibility of RT. The study was limited by the lack of reporting concerning lesion grade, size, or staging of lesions.

Theón et al [28] reported on the use of intratumoral chemotherapy with cisplatin in oily emulsion in horses for 30 lesions, three of which were described as POSCC. None of the POSCC had previous treatment; all had been histologically confirmed. The treatment technique included four intratumoral cisplatin chemotherapy sessions at 2-week intervals. The oily emulsion dosage was 1 mg of cisplatin per cm^3 of tumor. The researchers report partial tumor regression (at least 50%) was observed in all tumors during the course of treatment; however, specific outcomes for periocular locations were only reported on for two of the three lesions. Follow-up established local recurrence for the lower eyelid POSCC (5 months) and for the lower eyelid and medial canthus POSCC (10 months). The third POSCC did not have a specific report on outcome.

The application of chemotherapy and the overall benefits of the therapy require lengthy treatment schedules [28]. Each chemotherapy session requires horse sedation in some format for ease of access to lesions. A high level of commitment from the owners in returning the horse to clinics is required for the treatment to be completed.

Safety procedures should be observed by individuals administering chemotherapy agents and by those handling the horse and its excreta after treatment to ensure inadvertent exposure to the toxic product is avoided. It is also prudent to observe that horses undergoing chemotherapy should be excluded from entering the food chain until long-term analyses of the potential for toxic association in the rendered meat are rejected on an evidenced-based basis [45].

5.8. Radiation Therapy

Radiation therapy is the use of ionizing radiation in the localized treatment of tumors. Localized RT may be delivered in two ways: teletherapy or brachytherapy. Teletherapy is also referred to as external beam RT and is administered using a linear accelerator or, in some instances, a Cobalt-60 teletherapy machine. Brachytherapy uses sealed radioactive sources to deliver a radiation dose directly into the target lesion [46]. Radioisotope sources can be implanted directly into the lesion or into the cavities where the lesions lie. Sources vary depending on the area of interest, the facility's preference, and preexisting recorded success rates; however, the most commonly used radioactive sources within veterinary oncology include Gold-198 (^{198}Au), Iridium-192 (^{192}Ir), Strontium-90 (^{90}Sr), and Iodine-125 (^{125}I) [47,48].

Radiation therapy and/or brachytherapy has particular utility for the localized destruction of neoplastic cells while minimizing any effects on surrounding normal tissue [46]. It has been used successfully to treat a variety of animal tumors with results often comparable with those of human treatment outcomes [49].

Brachytherapy treatment in horses with OSCC and/or POSCC is highly effective with regard to recurrence rates and local control rates after brachytherapy as a sole therapy or in combination with surgery [4,9,12,13,20,31,50]. One of the first studies reported in 1964 by Lewis [24] assessed the outcomes of using Radon-222 (^{222}Rn) implant therapy in horses. Seven horses (n = 8 OSCC and/or POSCC) were treated with ^{222}Rn, a portion of these (three of seven horses) had cytoreductive surgery before ^{222}Rn implant therapy. Locations included eyelids (n = 5 with one horse afflicted with lesions on the upper and lower eyelids), third eyelid (including sclera [bulbar conjunctiva and limbus]) (n = 1) and cornea (n = 1). Recurrence was recorded in the latter of the two locations in two of the horses (25%) at 6 weeks and 3 months follow-up. No correlation was made between the site and size of the tumor and the outcomes of treatment. It was reported that the treatment modality was relatively inexpensive, easy to perform, and resulted in better cure rates than surgery alone. The potential danger when handling radioactive implants was highlighted and the need to "work fast and accurately" when using radon and the need to wear a radiation monitor to determine the amount of exposure the operators receive during implantation.

A retrospective study by Mosunic et al [13] investigated the effects of treatment with and without adjuvant RT in 91 horses (n = 157 OSCC and/or POSCC) over a period of

17 years (1985–2002). A total of 231 treatments were performed, 172 without adjuvant RT and 59 with a combination of RT and cytoreductive surgery. When comparing the two treatment groups, the study reports a significant difference ($P < .001$) in the recurrence rates independent of anatomic location; the recurrence rate when SCCs were treated without adjuvant RT 44.1% (n = 76) compared with 11.9% (n = 7) with adjuvant RT. This study reviewed the impact of anatomical sites on recurrence rate. For eyelid SCCs treated without adjuvant RT, the recurrence rate was 54% (27/50), whereas tumors treated with RT (n = 19) did not recur during the study. Corneal SCCs treated without adjuvant RT had a recurrence rate of 35.3% (12/34), whereas tumors treated with RT (n = 9) did not recur during the study. For limbal or bulbar conjunctival SCCs treated without adjuvant RT, the recurrence rate was 51.3% (17/33), whereas tumors treated with RT had a recurrence rate of 33.3% (2/15). There was no statistical difference in recurrence rate for third eyelid SCCs treated with and without RT, and for SCCs of the palpebral conjunctiva, statistical analysis was not possible because of sample size. In summary, surgery combined with ^{90}Sr (n = 33), ^{125}I (n = 19), or ^{60}Co (n = 2), as well as in combination with ^{90}Sr and cryotherapy resulted in overall recurrence rates of 15.1%, 10.5%, 0%, and 0% respectively. Surgery alone resulted in the highest measured recurrence rate (61.7%) [13].

Plummer et al [20] evaluated the effectiveness of superficial keratectomy and permanent bulbar conjunctival graft followed by the application of topical β-irradiation with a ^{90}Sr applicator to the surgical site in 38 horses (n = 38 OSCC; limbal and/or corneal SCC). Follow-up data were available for 25 horses (n = 25 OSCC; limbal and/or corneal SCC) with follow-up >1 year. A total of 23 of 25 horses remained disease-free past 1 year (8% recurrence rate). Of these 23 cases, three eventually recurred at the original tumor site at 537, 690, and 900 days. Of the remaining 20 horses with follow-up information for 24 months or more, four had recurrences before 24 months. A fifth recurrence occurred beyond 24 months.

A study by Wyn-Jones [31] investigated the application of ^{198}Au seeds for the treatment in five histologically different tumor types in 19 horses of which three horses (n = 4 POSCC) had SCC lesions on the upper and/or lower eyelid. For the POSCC cases, no recurrence was recorded at 1 year; however, one horse was euthanized because of metastatic disease.

In a comparable study conducted by Walker et al [21], a total of 17 horses (n = 18 OSCC and/or POSCC) were irradiated with either a ^{90}Sr surface applicator or interstitial implants (^{222}Rn, ^{192}Ir, or ^{125}I); 15 of the 17 horses also had cytoreductive surgery. Third eyelid POSCC (n = 10) was treated with cytoreductive surgery followed by either ^{90}Sr beta-therapy (n = 2) or interstitial (gamma emitting) implants (^{222}Ra, ^{192}Ir, or ^{125}I) (n = 8). Of these third eyelid POSCC, four (four of 10) had prior surgical resections. Recurrence was evident in two horses, which received interstitial implants; ^{222}Ra at 12 months and ^{125}I at 3 months. Both recurrences involved concurrent upper and lower eyelid involvement. Limbal OSCC (n = 5) were treated with cytoreductive surgery (n = 4) (before RT) and ^{90}Sr therapy (n = 5). No recurrences were observed in the 2-year study period. The eyelids were involved in four cases (n = 4) including the lower eyelid (n = 2), lower eyelid and conjunctiva (n = 1) and upper and lower eyelids and third eyelid (n = 1). Treatment involved pre-RT cytoreductive surgery (n = 2) and ^{90}Sr therapy (n = 1) or interstitial ^{192}Ir implants (n = 2) or ^{125}I (n = 1). All cases recurred before the 2 year follow-up period (at 3, 4, 6 and 18 months). This study reported a 60% (70% when corrected for nontumor–related deaths) 2-year nonrecurrence rate as a result of the interstitial implantation with ^{222}Ra, ^{192}Ir, or ^{125}I (n = 10 POSCC) and a 87.5% 2-year nonrecurrence rate with superficial ^{90}Sr beta-therapy (n = 8 OSCC and/or POSCC). If anatomic location is studied, the 2-year nonrecurrence rate was 100% (limbus; n = 5), 80% (third eyelid; n = 10), and 0% (eyelids; n = 4).

In 1964, Lewis [24] investigated the use of Radon-222 for equine SCC and sarcoid. Seven horses (n = 8 OSCC and/or POSCC) were treated with cytoreductive surgery (n = 5) followed by adjunctive interstitial radiotherapy using ^{222}Ra. Nonrecurrence was 75% (six of eight POSCC) at 6–18 months; these POSCCs involved the eyelids with four of six having cytoreductive surgery before ^{222}Ra therapy. Recurrence of the two OSCC (one of which had cytoreductive surgery before ^{222}Ra) occurred at <3 months.

Rebhun [22] reported on the treatment of advanced OSCC (>2 cm diameter) in 25 horses (n = 26 OSCC; cornea and/or limbus and adjacent bulbar conjunctiva). Surgical keratectomy followed by ^{90}Sr was used to treat 24 OSCC. The radiation was applied to the postsurgical site with a prescription dose of 8,000–10,000 rad (80–100 Gy) being delivered to the base of the lesion. Two of the cases required enucleation due to the extensive local tumor spread. Of the 24 eyes treated with keratectomy and ^{90}Sr, 20 of 24 (83%) recorded no recurrence 12 months after treatment. Another horse received a second treatment and remained tumor free and three recurred. Of the recurrences, one was euthanized, one lost to follow-up and another had an enucleation.

A study by Ollivier et al [23] reported permanent amniotic membrane (AM) transplantation as an adjunctive therapy to keratectomy combined with ^{90}Sr or keratectomy alone for the treatment of OSCC (corneolimbal SCC). The overall purpose of the study was to assess the effectiveness of permanent AM transplantation as adjunctive therapy for corneolimbal SCC with respect to corneal scarring and recurrence. A single case of cryotherapy was also recorded. Of the 12 eyes, (n = 12 OSCC; corneolimbal SCC) treatments included keratectomy, ^{90}Sr and AM (n = 7); keratectomy, ^{90}Sr and bulbar conjunctiva transplantation (n = 2); and keratectomy and AM (n = 2). A single eye (n = 1) received keratectomy, cryotherapy, and bulbar conjunctival transplantation. For those lesions receiving ^{90}Sr, a dose of 20 Gy was delivered with a range of one to four sites irradiated per eye. Although the size of the lesions is not reported on, the keratectomy size is tabled within the research, with a range from 10 × 15 to 20 × 25 mm. Of the OSCC treated (n = 12), 100% remained tumor free for the follow-up term ranging from 21 to 778 days.

The use of brachytherapy in OSCC and/or POSCC has the highest nonrecurrence rate recorded for the treatment of OSCC and/or POSCC [12]. Disadvantages which have limited the widespread availability of brachytherapy include the

high cost and need for specialist education and training for treatment planning, dosing, and delivery; the radiation safety for personnel involved; and the need for isolation of horses when interstitial implants are inserted [12]. Furthermore, when brachytherapy using a β-emitter is used (e.g.,^{90}Sr applicator), there is a limit to the depth of a tumor which can be treated with most of the beta particles being absorbed within the first 3 mm of tissue [50]. For any lesions deeper than this, surgical debulking may be necessary or other therapeutic measures must be considered [51]. When using interstitial brachytherapy, the incorrect placement of wires or seeds may lead to soft tissue necrosis or in the case of OSCC and/or POSCC damage to local radiosensitive tissues such as the lens and risk of cataract [51].

6. RQ4: What Treatment May Be Defined As "Best Practice"?

The clinical management of equine OSCC and/or POSCC is affected by many factors, including treatment availability, evidence regarding treatment efficacy, expertise for more specialized applications including PDT and brachytherapy, cost, and tumor location. This research has considered "best practice" only in terms of clinical outcome; it is accepted that in practice, the other variables may be of overriding importance.

The review highlights the paucity of high-quality evidence for the treatment of equine OSCC and/or POSCC limiting the ability to make cross-study comparisons. With the lack of established best-practice based on scientific evidence, treatment is usually driven by clinician experience, preference, and treatment availability. In most studies, details regarding tumor grade, size, location, and stage of the OSCC and/or POSCC are not reported. Most of the studies are retrospective and suffer from common weaknesses including small sample sizes, lack of controls and randomization, poor follow-up, and recall bias of the surveyed owners. Many of the cases being investigated in relation to a "new" or "emerging" treatment modality had undergone treatment before being included in the studies, thereby confounding the study results. These limitations must be considered when interpreting the conclusions of the reviewed data presented here.

Despite the weaknesses in the reviewed literature, there were some notable consistencies in the reported success rates in terms of recurrence rates. A large number of studies suggested the use of surgery as a sole treatment to have a relatively low success rate 0%–61.7% and mean, 2–168 months (n = 125 OSCC and/or POSCC) [5,9,20,33,36,37]. Not surprisingly, therefore, surgery is commonly used in combination with one or more modalities. These combination treatments have been noted to have strong links to lower recurrence rates and long-term control in comparison with surgery alone [4,5,9,13,20,33,37].

The specific anatomic location of equine OSCC and/or POSCC significantly impacts on treatment decisions [12]. To assess best practice, the following types of OSCC and/or POSCC have been considered: limbal, third eyelid, and eyelids (upper and lower). There were insufficient data on which to consider the cornea, conjunctivae (palpebral and bulbar), and the medial canthi in isolation.

6.1. Site-Specific Observations

6.1.1. Third Eyelid SCC

Surgical excision is commonly performed for cases of third eyelid SCC in equine practice. Although in general, surgical excision alone for equine OSCC and/or POSCC has a relatively low success rate with recurrence reported in 50%–75% of cases, surgery for third eyelid SCC may be highly efficacious [4,13,25]. Payne et al [25] reported that all 19 horses with third eyelid SCC remained tumor free (median, 41 months) after en bloc excision with grossly clear surgical margins. In contrast, Mosunic et al [13] reported a recurrence rate of 51.4% for surgery alone in the management of third eyelid SCC; this is likely to relate to differences in the studied populations with greater recurrence rates in cases with more locally advanced disease.

Adjunctive treatments for third eyelid SCC used after cytoreductive surgeries include cryotherapy [4,11,27] and RT [9,13,21,51]. There were insufficient data to conclude any benefits of adjunctive cryotherapy, but interestingly one study [4] (n = 6 OSCC and/or POSCC) noted a higher local recurrence rate for combined surgery and cryotherapy as compared with surgery alone: 50% and 44.4%, respectively. This incongruence may reflect a clinician bias toward more aggressive use of available adjunctive treatment for more locally advanced OSCC and/or POSCC rather than a true biological effect.

The benefit of adjuvant RT for third eyelid SCC is difficult to interpret, as the reporting is often global with specific anatomic treatment locations not being defined [9,50,51]. In studies where site-specific data are available, the use of cytoreductive surgery and adjunctive brachytherapy for equine third eyelid SCC has reported nonrecurrence rates of 80% at 24 months (^{90}Sr beta brachytherapy or ^{222}Rn, ^{192}Ir, or ^{125}I interstitial implants) [13] and 80% at 24 months (^{90}Sr beta plesiobrachytherapy) [21]. It is difficult to assess a beneficial effect of RT adjunctive treatment in these reports due to a lack of reference or control populations. For example, Mosunic et al [13] reported similar overall (global) nonrecurrence rates for OSCC and/or POSCC (78% over 25–68 months), but analysis revealed no statistical benefit for adjunctive RT (^{90}Sr, ^{125}I, or ^{60}Co) after cytoreductive surgery for third eyelid SCC.

6.1.2. Limbal SCC

Limbal SCC has been managed with surgical excision [13], surgery and CO_2 laser ablation [15], CO_2 laser ablation alone, CO_2 laser ablation and topical MMC [26] surgery and topical MMC [14,17], topical MMC alone [14] surgery and cryotherapy [13,18,19], and surgery with ^{90}Sr brachytherapy [13,20,22,23,50].

Surgical treatment of limbal SCC is affected by the limited thickness of the ocular coats (cornea, limbus, and sclera) and the close proximity of sensitive local intraocular structures including the lens and neurosensory retina. Cytoreductive surgery is limited to the resection of the grossly affected cornea, limbus, sclera, and conjunctiva, with the acceptance that the clear deep surgical margin will not be possible in most cases. In some cases, histologically clear margins may be achieved if the limbal SCC is a CIS

where the tumor cells have not penetrated the epithelial basement membrane. Given that in most cases, complete surgical excision is not possible, adjuvant treatment is usually given after limbal SCC excision. In one study, surgery alone for limbal SCC was associated with recurrence rate of 83.3% [13].

There are numerous reports on surgery and adjunctive treatments and some nonsurgical regimes reported in the literature. Poor outcomes for cytoreductive surgery and cryotherapy for limbal SCC have been reported with nonrecurrence rates of 65% (global follow-up of 10 days–101 months; n = 8 from 20 SCC) [13] and 55% (12 months–8 years; n = 11 SCC) [18]. In contrast, one small study with n = 2 cases having surgery and cryotherapy had nonrecurrence rates of 100% (21–36 months) [19].

Management of limbal SCC with surgical excision and CO_2 laser ablation has reported nonrecurrence rates of 87.5% (14–99 months; n = 24) [17] and 100% (7–14 months; n = 2) [15]. One study compared cytoreductive surgery with CO_2 laser ablation with cytoreductive surgery and topical MMC and found no difference in recurrence rates 86.7% (7–75 months; n = 10) and 84.4% (1–35 months; n = 17), respectively [16]. Cytoreductive surgery and topical MMC reported nonrecurrence rates of 75% (13–32 months; n = 8) and 78% (13–32 months; n = 9) [14].

Reported treatment using ^{90}Sr brachytherapy for limbal SCC included cytoreductive surgery and ^{90}Sr RT of 83% at 12 months, n = 24 [22]; 100% at mean 2.5 years, n = 7 [4]; and 100% at 2 years, n = 5 [21]; cytoreductive surgery with a bulbar conjunctival graft and ^{90}Sr RT of 87% at mean 24 months, n = 25 [20] and 100% at 21–778 days, n = 2; and cytoreductive surgery with an amniotic graft and ^{90}Sr of 100% at 21–778 days, n = 7 [23].

6.1.3. Eyelid (Upper and Lower) SCC

Surgical resection of eyelid SCC is limited by the restricted amount of periocular skin, which can be mobilized for blepharoplasty procedures [12]. A study investigating the effects of treatment of OSCC and/or POSCC with and without adjuvant RT (n = 157) identified surgery alone to have had the highest recurrence rate at all anatomic locations including the eyelids [13].

There are inadequate data to comment on the efficacy of intratumoral chemotherapy [28], cryotherapy [4,11], and radiofrequency hyperthermia [30] in treating equine eyelid SCC. One study reports good results for eyelid SCC treated with PDT with a nonrecurrence rate of 86% for n = 7 at 25–68 months [5].

In studies where site-specific data are available, the use of cytoreductive surgery and adjunctive brachytherapy for equine eyelid SCC has reported nonrecurrence rates of 100% at 25–68 months (surgery combined with ^{90}Sr, ^{125}I, or ^{60}Co), n = 19 [13]; 100% at 12 months (interstitial ^{198}Au seeds), n = 4 [31]; 100% at 3–18 months (surgery and interstitial ^{222}Rn) [24]; and 0% at 24 months (^{90}Sr beta plesiobrachytherapy) [21].

7. Conclusions

The treatments and success rates reported for equine OSCC and/or POSCC must be interpreted with caution because of study weaknesses in particular relating to retrospective data already discussed. Despite the variation in reports with respect to patient numbers, methodology, and reportable outcomes, combination therapies are generally supported for the treatment of equine OSCC and/or POSCC [4,37,45]. These treatments often include cytoreductive surgery as a precursor to other treatment types including PDT, cryotherapy, CO_2 laser ablation, chemotherapy, or RT.

For site-specific outcomes, the review highlighted effective treatments for limbal SCC, third eyelid SCC, and eyelid SCC. For POSCC involving the third eyelid, total excision with clear surgical margins is potentially curative [25], whereas in cases where complete excision is not possible, adjunctive brachytherapy provides nonrecurrence rates of 80%–100% [13,21]. For equine limbal SCC, management involves cytoreductive surgery and adjunctive CO_2 laser ablation, topical MMC, or ^{90}Sr brachytherapy has nonrecurrence rates of 75%–100% [4,8,14–17,20–23]. Although cytoreductive surgery and adjunctive brachytherapy for equine eyelid SCC has reported nonrecurrence rates of 0%–100%, most reports show positive outcomes with brachytherapy [13,21,24,31]. Preliminary results on the use of adjunctive PDT for equine eyelid SCC appear promising [5] and further research into treatment protocols for equine POSCC are currently underway.

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2.8 IS THERE A ROLE FOR RADIATION THERAPISTS WITHIN VETERINARY ONCOLOGY? (PAPER TWO)

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Review Article

Is there a role for radiation therapists within veterinary oncology?

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ABSTRACT

Role expansion recognises enlargement of existing scope of practice within radiation therapy (RT). Over the past decade, there has been increasing involvement and movement towards advanced practice in the form of role extension in specialised areas of practice including brachytherapy, image fusion and quality assurance. It is also recognised that radiation therapy expert practitioners exist in the areas of imaging immobilisation, treatment, education and research. The acquisition of additional skills has hastened the need for autonomy within the RT profession and with this comes the responsibility to share our knowledge and specialist abilities with the wider community. Radiation therapy is a highly specialised profession working to treat a commonly encountered ailment like cancer and we should ask ourselves what other community members could benefit from our knowledge and skills.

Cancer is not limited to the human population but affects animals as readily and severely. Particular types of cancers have been identified as being comparable with that of humans; one such tumour is squamous cell carcinoma (SCC). Squamous cell carcinoma is the most commonly found tumour of the eye and adnexa in horses. Comparatively, SCC in humans is the most common cancer in Australia. Whilst human treatment is well established with surgery and radiation therapy offering comparable control rates, the treatment within Australia's Veterinary Oncology field is currently at a standstill. It is reported, however, that the use of interstitial brachytherapy has been shown to be highly effective and thoroughly practiced and established within the United States of America (USA). This paper reviews current literature in readiness for the potential for radiation therapy cross-over into the veterinary sphere with regard to the implementation of treatment and radiation safety protocols for the use of interstitial brachytherapy in horses.

Introduction

Whilst cancer is a familiar ailment among our community, radiation therapy and its applications remains a highly specialised and relatively unknown field. Within Australia, veterinary oncologists are faced with animals afflicted by cancer, yet, there appears to be minimal access to radiation therapy (RT) treatments and their benefits, often depending on alternate and less effective treatment therapies. They may opt for the application of second-rate RT treatments that have been passed down to them verbally by other veterinary surgeons. Furthermore, the knowledge and understanding of radiation safety standards, a daily consideration for radiation therapists, appear to be under-developed or non-existent within the Australian veterinary sphere. In contrast, the role of radiation therapy within veterinary oncology has been shown to be highly effective and thoroughly practiced and established within the United States of America.[1]

Equine squamous cell carcinoma is effectively treated with radiation, comparable to that of human SCC.[2,3] It is however, within Australia, limited to less effective treatments as compared to the current radiation therapy treatment options offered in the USA. This is as a result of the inability to have access to traditional radiation therapy treatments within Australia. Alternate treatment regimes for horses include surgery and some applications of adjunct therapies such as photodynamic therapy, cryotherapy, immunotherapy, intratumoural chemotherapy and carbon dioxide laser ablation therapy; these are a less effective means of treatment in comparison to the proven outcomes of brachytherapy and result in multiple complications and potential side-effects.[2] Evidence suggests that the use of interstitial brachytherapy for the treatment of squamous cell carcinoma in horses is a significantly effective treatment regime with minimal side-effects if performed correctly.[1] As an emerging profession, it would seem evident that our involvement in the treatment of cancer within the realm of

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veterinary oncology in the form of treatment expertise and radiation safety protocols would be a logical development.

Advanced practice in the form of role extension within radiation therapy has in the past been at the focus of radiation therapy practice advancement. Whilst the theme of advanced practice within radiation therapy is still in its early stages of development, it is a significant move forward in the application of role extension. The key concepts of advanced practice within Australia are being established following the successful implementation of advanced practice models in the United Kingdom and more recently in New Zealand.[4] Radiation therapists have forged ahead and developed as critically important and essential members in the development and progression of radiation therapy within oncology departments, external professional bodies and academic institutions. In achieving advanced practitioner status recognition, therapists have become aware of the specialist functions they provide in a medical sphere that is very much atypical. It has become evident that the term 'advanced practice' comes with responsibility, accountability and a requirement for leadership in the provision of skills and knowledge to the wider community.[4] It is also acknowledged that advanced practice roles should focus on the needs of patients.[4] With this in mind, and with the awareness that veterinary oncology and in effect patients therein would benefit from our training and expertise, why is it then, that we are not exploring the world of veterinary oncology and assisting this fraternity by providing our expertise, knowledge and skill in the provision of what is proven to be an effective means of therapy for a tumour of universal prevalence such as superficial SCC?

This paper will focus on highlighting the potential for RT involvement in veterinary oncology based on current existing literature and as a pre-cursor to the research conducted into the adaptability and potential cross-over of RT in the form of interstitial brachytherapy for the treatment of SCC in horses, as conducted by the authors.

Treatment options

Periocular squamous cell carcinoma in horses (PSCC)

Superficial squamous cell carcinomas are grouped in the non-melanocytic neoplastic lesion spectrum of conditions.[2] The cause of these tumours may be related to extended exposure to the ultraviolet component of solar radiation, the degree of pigmentation or a genetic predisposition to carcinogenesis. Squamous cell carcinoma, more specifically periocular SCC (PSCC) is the most commonly found tumour of the eye and adnexa in horses.[5] Skin SCC's in horses are generally locally invasive and detected within their early stages due to their visible locations in and around the head and neck. The prevalence of equine ocular/adnexal squamous cell carcinoma increases with the age of the horse and whilst most tumours are slow growing and invade locally, metastases may occur in 10–15% of horses.[2,5] The neoplastic mass may originate from a spectrum of tissues including the cornea, limbus, nictitating membrane, conjuctiva, orbit and eyelid.[5] The lesions develop through progressive pathologic conditions before the carcinoma is identified. The progress begins with a plaque followed by papillomas. A persistent papilloma may progress into carcinoma in situ, the stage before neoplastic cells have penetrated the lamina propria underlying the epithelium.[2]

Current treatment options for PSCC in horses

There are a wide range of treatment options for PSCC in horses currently available, however the reported benefits of each treatment with regard to recurrence, length of recovery, potential side-effects, number of applicable treatments and total cost is minimal. Each therapy reports varied results in treatment outcomes. This may be attributable to the current deficiency in a uniformly satisfactory application of a treatment protocol based on evidence based practice and oncological principles.[5] In effect, reported therapies for ocular PSCC include;

- Surgical Excision;
- Photodynamic Therapy;
- Cryotherapy;
- Immunotherapy;
- Intratumoural Chemotherapy;
- Carbon Dioxide Laser Ablation
- Brachytherapy;

Surgery

Literature illustrates sole surgical resection of equine squamous cell carcinoma *may* be adequate as long as the margins are consistently clear and the tumours are small or identified as carcinomas in situ, however reports of tumour recurrence as a result of inadequate surgical excision are common.[2] In cases where the tumour margins are extensive, enucleation (total removal of organ), in this case the globe, is often necessary.[6] Beyond occasions such as this where extensive spread of a tumour requires the removal of the globe to eradicate the malignancy, it is recommended that squamous cell carcinomas in and around the eyelid and adnexa be treated with methods other than surgery.[2] The recurrence rates within 1 year of treatment with surgery are reported between 50% and 67%. When surgery is performed with radiation or cryotherapy, the results range from 25% to 67%.[5]

Photodynamic therapy (PDT)

The use of light and light-sensitive compounds in an oxygen-rich environment causes localised tissue necrosis.[7] Whilst the treatment has shown promise for SCC in smaller animals, its use in horses and the effects of the volume of drugs required for treatment are highly unrecognised hence it can only be hypothesised that PDT may be an effective means of treatment for equine PSCC.[7]

Immunotherapy (biological therapy) & intratumoural chemotherapy

Immunotherapy; using the body's immune system to fight disease, whilst somewhat effective in the treatment of SCC, is a lengthy process and has been associated with side-effects such as necrosis and suppuration at the sites where the drugs have been injected. Lengthy treatment schedules are also associated with intratumoral chemotherapy.[8]

Cryotherapy

Cryotherapy (the use of extreme cold in a localised part of the body to freeze and destroy unwanted tissues) is an affordable and easily attainable treatment alternative. The procedure requires the application of liquid nitrogen or nitrous oxide to the malignant cells at a temperature between −20 °C and −40 °C. However the application of liquid nitrogen or nitrous oxide has the potential of causing collateral tissue damage at a site that is distant to the lesion. Furthermore, there is a potential for over-freezing resulting in post-treatment ulcers.[2]

Carbon dioxide laser ablation

The use of a CO_2 laser ablation may be used to provide non-invasive treatment to a tumour site as opposed to excising the mass. The procedure is fast, precise and results in minimal pain and inflammation however the cost of the instrumentation is remarkably

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high. Furthermore the lack of specificity for neoplastic cells combined with the resultant corneal ulcer side-effects results in uncertainty in its applications.[9]

Brachytherapy

Internationally, brachytherapy treatment in horses is reported to be highly effective with regard to recurrence rates and local control with one-year local-control rates following brachytherapy being 74% and two-year-non-recurrence rates of 70%.[1,10] Whilst the biological outcomes are favourable, the side-effects resulting from incorrect wire or seed implants include soft-tissue necrosis and potential cataracts. The side-effects are a direct result of the random configuration of the seeds during implantation within veterinary oncology resulting in uneven isotope distribution and dosimetry.[11] Accurate dosing of tumours is reliant on properly calibrated radioactive seeds and the accurate measurements of the mass in order to accurately plot the isodose curves.[12] Currently there is no provision for this type of dosimetry within the veterinary sphere and as a result brachytherapy treatments continue to be applied in a haphazard fashion.

By implementing a standardised treatment regime based on evidence based practice, a decrease in the potential side-effects leading to soft-tissue necrosis and an increase in the local control of PSCC would ultimately result in decreased veterinary intervention post-treatment and hence an increase in economic benefits. Overall, and as a definitive or adjunct treatment regime, interstitial brachytherapy has been identified through literature to be the most effective of the treatment options for equine PSCC with regard to recurrence rates, local control, limiting of side-effects and logistical application.[1,10]

It is clear that no treatment modality is without its potential complications but in view of the multiple treatment applications available and of their substantially varied reported outcomes, it appears that a consistently favourable treatment for PSCC in horses does not currently exist within Australia.

Brachytherapy in Australian veterinary oncology

There has been a substantial growth in the use of Radiation Oncology in the United States of America as a speciality within Veterinary Oncology over the past decade.[1] Veterinary oncology facilities have historically used low energy orthovoltage units with a subsequent shift to cobalt 60 and linear accelerators as the treatment technique.[1]

A survey of veterinary radiation facilities in the USA in 2001 was conducted under the sponsorship of the Veterinary Radiation Therapy Oncology Group. A total of 42 facilities were identified to be currently providing external beam radiation therapy, with 40% of these being academic facilities and 60% private institutions.[1,2] Some of these facilities currently use human centres for the treatment of their clients. Additionally, brachytherapy treatments for superficial SCC are commonly practiced in numerous Veterinary Colleges along the East Coast of the USA and beyond.

In comparison, Australia's veterinary oncology field appears to be under-developed. The high cost of external beam radiation therapy poses a hurdle for veterinary surgeons prepared to utilise the technology. Currently, there are no reported cases of human clinical radiation therapy equipment use in the form of Linear Accelerators on animals other than for the use of experimental purposes.

Long term local control and recurrence for ocular PSCC in horses may be favourable as a result of brachytherapy treatments,[1,10] however the process by which these treatments are routinely performed lack guidelines and protocol. Veterinary surgeons, whilst equipped with the manual skills to implant radioactive seeds and the ability to source and purchase the equipment, lack the background required in radiation oncology that confirms the treatment delivery is optimum and that the dosimetry applied is biologically appropriate and delivered homogenously. Current Australian veterinary brachytherapy reported data is non-existent. Reports on its use and unsystematic applications of the regime are anecdotal and have been obtained from recent verbal interviews with practitioners. These discussions have highlighted the need for further investigation and development of not only standardised treatment protocols based on dosimetry and radiation oncology principles but also a review and implementation of standardised radiation practices. As a result, the authors are conducting an Australian National Survey of veterinary practitioners to gather more information in this area. The initial survey distribution includes a total of 1000 potential respondents from the Australian Equine Veterinary Association (EVA) in its initial phase with a potential additional 1500 participants recruited from the Australian Veterinary Association (AVA) in its second phase. The survey aims to collect data inclusive of demographics, current PSCC presentation statistics, treatment methods, protocol use and radiation safety principles. It also investigates the perceived needs of veterinary surgeons in regard to using brachytherapy. Preliminary data from this survey have been used to augment this review of the literature.

Permanent radioactive implants (Au^{198})

Permanent interstitial implants require the insertion of radioactive seeds directly into tumour sites. These seeds remain within the neoplastic tissues and are left to decay to a non-radioactive form. Examples of such radioactive seeds include Iodine-125 (I^{125}); Gold-198 (Au^{198}) and Iridium-125 (Ir^{192}).[12] Radioactive Gold-198 seeds have numerous advantages over other radioactive seeds and have been successfully used to treat ocular neoplasms primarily SCC.[13] The half life of Gold-198 is comparatively short (94.4 h—2.70 days), making it a suitable permanent implantation.[14]

The use of interstitial brachytherapy implants in horses requires a permanent radioactive source such as Gold-198 (Au^{198}) to minimise double-handling of the radioactive seeds/wires and reduce potential exposure to staff and owners post-operatively. The seeds remain within the neoplastic tissues and are left to decay to a non-radioactive form. Gold-198 emits a mono-energetic gamma ray of energy (0.412 MeV). It also emits beta particles of maximum energy 0.96 MeV, however these are absorbed by the outer platinum layer surrounding the gold seed.[13,14] The current use of Gold-198 seeds is popular based on the availability, the relatively low cost and the proven efficacy in the treatment of ocular SCC.[11] Additionally, gold does not cause foreign body reactions.

Radiation safety implications

Safety requirements as related to radioactive sources are considerable,[15] however current veterinary radiation safety practice appears inadequate due to a lack of education in this area. With multiple veterinary personnel attending to these brachytherapy procedures it is highly recommended that radiation safety be observed carefully and advised upon by radiation physicists. Currently, and as a result of recent discussions, site visits and the collection of preliminary responses from the National Australian Survey of veterinary practitioners, it is evident that veterinary clinics are inadequately equipped for the application of brachytherapy treatments. Whilst the National survey is in its pilot phase, the current collection of data has further highlighted radiation safety issues, with 40% of respondents from a cohort of 17 indicating radiation monitoring is not used within clinics despite 94% of participants owning or using radiation safety equipment. This

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further adds to the tentative approach many veterinarians take to the possibility of applying the treatment management regardless of its obvious efficacy.

The management of post-operative horses is poorly regulated within veterinary oncology. Post-operatively horses are placed in stables that are generally situated in close proximity to other horses as well as in thoroughfares accessed by staff. Whilst an attempt is made to 'signage' the radiation exposure danger and the 'walk-through' safe distance, the potential for consistent radiation exposure exists. It would seem obvious that outdoor quarantine for an extended period of time is the most logical means of avoiding potential radiation exposure to staff and other animals however this is not always a practical alternative. Thoroughbreds are often reared in enclosed stables due to the nature of their athletic ability and temperament which pre-disposes them to attempt escape at any given opportunity. These horses are therefore unable to be placed in exterior holding stables post-operatively for reasons of safety to them and the general public.

A further implication is in relation to the owner's perceived safety in handling their animals post-operatively. It is, of course the veterinary surgeons responsibility to disclose any potential for exposure in the management of affected animals to the owners. However, regulating the information that is provided by veterinary surgeons who may not have a full understanding of the potential implications unnecessary exposure to radiation may pose is difficult considering reporting on these types of treatments is minimal or non-existent.

The radiation safety implications within veterinary oncology would, to a radiation therapist, seem undisciplined and potentially catastrophic. It is for this reason that radiation therapists and medical physicists should consider transferring their knowledge and expertise with regard to radiation therapy safety principles in order to ensure the veterinary profession is well versed and working within a safe capacity.

Clinics must therefore take into consideration the logistics of applying permanent implants inclusive of;

- Initial implantation of seeds (surgical radiation safety principles);
- Potential for radiation accidents post and pre-operatively;
- Areas for post-operative quarantine;
- Owner instructions on radiation safety observations;
- Transporting of post-operative animals;
- Optimal treatment planning and delivery inclusive of homogenous dose distribution and organ sparing.

Conclusion

In reviewing the current limited literature and executing a series of informal discussions with veterinary surgeons, it is evident that the benefits of radiation therapy and medical physics involvement and intervention in the establishment of a recognised brachytherapy treatment protocol inclusive of radiation safety practice would be a significant outcome for radiation therapy, in what is already becoming a highly specialised profession. The implantation of the seeds by the veterinarian comes under scrutiny when considering the possible implications using radioisotopes pose. The potential for a loss of a radioactive seed/wire as well as the method by which the seeds are implanted make for the need of a highly structured and regulated set of protocols. The authors envisage that a combination of veterinary skills and knowledge, radiation therapy expertise (in the form of application of planning and treatment) and radiation oncology coupled with physics expertise in radiation safety will form the basis for the development and implementation of a brachytherapy treatment protocol within veterinary oncology. The proposal anticipates the end result to be that of a highly adaptable and feasible treatment protocol to be used within Australia for the treatment of equine ocular SCC.

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2.9 OCULAR AND PERIOCULAR SQUAMOUS CELL CARCINOMA IN HORSES: A SHORT COMMUNICATION OF THE POTENTIAL USE OF BRACHYTHERAPY. (PAPER THREE)

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The co-authors of this paper are supervisors and collaborators of the PhD.

Ocular and periocular squamous cell carcinoma in horses: A short communication of the potential use of brachytherapy.

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Introduction

Squamous cell carcinoma (SCC) is the most common tumour involving the equine eye and adnexa.[1] Lesions may originate from various tissues including the cornea, limbus, nictitating membrane, conjunctiva, orbit and eyelid.[2] The management of equine ocular squamous cell carcinoma (OSCC: cornea, limbus and bulbar conjunctiva) and/or periocular squamous cell carcinoma (POSCC: eyelids and third eyelid) remains a challenge despite its high prevalence among horses. Whilst the published evidence base is significant, the quality of reporting is generally poor and lacks conformity, making the ability to make cross-study comparisons problematic. Adding to the complexity of identifying a best practice treatment is the overall tendency toward poor global reporting without details of relevance such as exact tumour location, size or previous treatment.

A literature review by Surjan[3] on current and previously used treatments for OSCC/POSCC in horses with the aim at determining the most beneficial technique identified the seven most commonly reported treatment modalities as; surgery, photodynamic therapy, cryotherapy, carbon dioxide laser ablation, radiofrequency hyperthermia, topical or intratumoural chemotherapy, and radiation therapy (RT), predominantly in the form of brachytherapy (implantation of sealed radioactive sources).[3] Although the majority of the 37 studies reviewed by this group reported treatment benefits and success, it was not possible to identify the best technique for the treatment of OSCC/POSCC due to the inconsistency in the presentation of data.[3] It was however apparent that lesion location significantly influenced the choice of treatment approach and that successful treatment of OSCC/POSCC commonly involved one of the above therapies combined with cytoreductive surgery (partial removal of the tumour to enhance RT effectiveness).[3] The value of combining radiation therapy with surgery or using radiation therapy alone was beneficial in decreasing cosmetic and functional defects.[3] In comparison, there is significant evidence based literature supporting the use of radiation therapy, in treating SCC in humans.[3] The choice to use RT for SCC is less dependent on the probability of tumour control, which is typically high, than on the predicted cosmetic and functional results, which can be better with RT than some forms of surgery. For this reason, RT is often favoured for lesions located on or near the nose, ears, lips and eyelids.

Following on from the review, and supported by the known benefits of brachytherapy in humans, research has commenced to identify the utility of brachytherapy in the treatment of OSCC and/or POSCC in horses. In view of the paucity of current and complete literature in the area and to better understand the current needs of the Australian equine veterinarian in relation to treatment of such a globally widespread tumour such as OSCC/POSCC, the research team is conducting a survey to determine current treatment management practices across Australia. The survey also seeks to collect data on specific brachytherapy use, current and past, including adherence to guidelines as outlined by the International Commission on Radiation Units and Measurements (ICRU) and the Codes of Practice as outlined by the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) and to gauge veterinarian interest in the treatment approach.[4,5] The survey may be accessed via the following link; https://www.surveymonkey.com/s/Equine_OPSCC

Brachytherapy

Brachytherapy is a term used to describe cancer treatment with sealed radioactive sources. Brachytherapy allows the delivery of a high radiation dose to a localised affected area (tumour) while sparing surrounding normal tissue as a result of the rapid fall-off of radiation resulting in improved organ preservation and satisfactory cosmetic appearence.[6,7] The sources are implanted directly into or onto a tumour, or within a body cavity, and referred to as interstitial (within tissues), surface (using external applicators such as moulds or plaques), or intracavitary (within cavities),respectively. The location and size of the tumour predicts the type of technique required. Smaller areas that occur superficially are generally better suited to surface applicators, and as the names suggest, tumours located within a cavity are best suited to intracavitary therapy while those located within tissues, treated with interstitial therapy.[8] Radiation dose is delivered continuously, either by temporary implant with the radioactive sources removed after a set length of time, or permanent where the implants are left in-situ. In the latter case, the implant remains in place delivering radiation slowly for days or months until the radioactive source has decayed to a level of minimal radiation.[6] Radioactive sources for brachytherapy use are pre-fabricated and supplied by manufacturers in various forms; needles, wires or seeds.[6]

Diagnosis, tumour delineation and dosimetric planning

Tumour suitability is determined via a clinical evaluation of the lesion and its location and is confirmed histologically. If the u is a candidate for the procedure, the initial

Tumour Volume is identified with the aid of radiographic imaging; X-rays, computed tomography (CT), ultrasound or magnetic resonance imaging (MRI).[5] Target Volume delineation (Treatment Area) follows this process and often includes a margin beyond the Tumour Volume.[5] These volumes are confirmed and may be sometimes altered following dosimetric computer planning.

The radiation dose (prescription) is determined by the treating Radiation Oncologist or qualified veterinarian. This includes specifying dose limits to nearby normal tissues and in particular those organs that are radiation sensitive (Organs at Risk). The choice of permanent or temporary implants, radioisotope type along with position of radioactive sources is made at the time of the dosimetric computer planning. Dosimetric planning refers the use of radiation therapy-specific computerised software systems used to generate and compute dose distributions for patient treatments. Completed treatment plans must be verified by the treating physician before implantation may commence.

Implantation

In surface applications, the radioactive material is placed directly on the surface of the tumour and not inside the tumour. Plaques or moulds are customised to conform to the treatment surface and the sources (radioactive) are then securely positioned on the outer surface of the applicator[8,9] Placing radioactive material into body cavities is referred to as intracavitary brachytherapy. An extension of intracavitary brachytherapy is the intraluminal technique where the radioactive material is placed in the lumen of organs such as the esophagus, bronchus or the bile duct; a less common treatment approach as compared to intracavitary brachytherapy.[9] Interstitial implantation is defined by the permanent or temporary insertion of sealed radioactive sources within the body's tissues.[10] These radioactive sources are implanted directly into the affected tissues.[8]

Radioactive implants require loading after the source containers (applicators or catheters) are placed within the tumour. Traditionally, the afterloading techniques required manual handling of radioactive material. When conducted appropriately manual handling can be performed to maintain radiation exposure to acceptable levels.[5] However, technology has evolved such that the need for manually handling sources is no longer required with the introduction of remote afterloaders. The following details the available loading systems.[8,9]

Loading systems

Manual or 'hot' loading requires the operator to directly introduce the radioactive material into the tumour. The radiation hazards associated with this type of loading are significant hence the technique is very rarely used in current practice.[8-10] Manual afterloading technique involves the manual insertion of radioactive material into catheters, needles or applicators already inserted into the tumour. The radiation exposure is reduced in comparison to manual loading however there is still a risk of exposure to the operator and patient visitors.[8-10] Remote controlled afterloading eliminates the danger of exposure almost completely as compared to manual loading and manual afterloading. The radioactive material is loaded into the inserted applicator by the use of a remote control. The operators are positioned in an area outside the patient's room and observe the patient via cameras. Remote afterloading is a preferred brachytherapy approach considering its favourable radiation safety characteristics.[8-10]

Brachytherapy in Veterinary Science

There has been a substantial growth internationally in the use of Radiation Oncology as a specialty within veterinary oncology over the past decade.[11] Veterinary Oncology has paralleled the human entity in the United States of America (USA) with the establishment of veterinary radiation facilities. These facilities have historically used low energy orthovoltage units with a subsequent shift to cobalt-60 and linear accelerators as the staple treatment technique.[11]

A survey of veterinary radiation facilities in the USA in 2001 was conducted under the sponsorship of the Veterinary Radiation Therapy Oncology Group. A total of 42 facilities were identified to be providing external beam radiation therapy, with 40% of these being academic facilities and 60% private institutions.[11] Furthermore, some of these facilities used human centres for the treatment of their animal patients.

Brachytherapy treatment of equine SCC in Australia is not routinely performed with the authors' being aware of only a small number of facilities that provide radiation therapy (linear accelerators, brachytherapy equipment) for veterinary patients. The high cost of the use of radiation therapy for small or large animals poses a hurdle for veterinary surgeons interested in utilising this technology.

Whilst historically, veterinary medicine has based their radiation treatment applications on human experience, a concerted effort to standardise protocols or procedures explicitly for the purposes of veterinary practice have not been established. This has resulted in a lack of consistency with respect to RT administration and hindered collection and analyses of reportable outcomes.[12]

It is recognised that not all veterinary practices are equipped with advanced imaging technology like CT/MRI, and whilst these are a preferred method in identifying and delineating Tumour Volumes, orthogonal radiographs may also be used. Current available brachytherapy specific planning software adaptive to 2-Dimensional imaging is able to create dose distributions and create treatment plans without the need for CT or MRI imaging.

Advantages & disadvantages of brachytherapy

Brachytherapy used in the treatment of neoplasms located in the vicinity of sensitive organs such as the eye offers various advantages over external beam radiation therapy (EBRT) by delivering a high dose to the tissues of interest whilst sparing surrounding tissues.[13] The delivery of high doses to the neoplastic tissues contributes to improved

local control, limited scarring and distortion of surrounding skin and inconsequential skin loss.[13,14] This benefit is of great importance to the sporting horse where the loss of an eye could result in disqualification from competition.

Brachytherapy allows for the delivery of a highly localised radiation dose to a small tumour volume. The sharp fall-off of radiation dose spares normal tissues surrounding the lesion of treatment. This reduces the side-effects which may normally occur in treatments where the radiation is not limited to the target lesion.[7,8,15] Brachytherapy reduces the amount of time a patient is required to spend receiving treatment (minutes to 7 days) as compared to EBRT (5-7 weeks). Irregular tumour shapes are easily matched by dose distribution manipulation. The possibility of a geographical miss due to patient motion in brachytherapy is lessened as compared to EBRT since the sources are contained within the patient. It must be observed however that geographical misses may still occur as a result of the nature of the sharp fall-off of dose around the periphery.[7,8,15] With reference to patient motion, it is important that movement is reduced to a minimum during the process of implantation, however, general anaesthetics (GA) in horses are not a necessity in most instances with sedation (constant rate infusion) allowing for accurate catheter/needle placement and implantation. This approach is currently successfully used internationally in the UK (Animal Health Trust, Newmarket) among other European clinics. In view of the potential dangers of GAs in horses, it is imperative that alternative sedation methods be considered in order for the benefits of brachytherapy to remain significant.

In contrast, the radiation exposure hazard that exists with the delivery of brachytherapy, however minimised through the evolution of technology, remains a challenge. Interstitial brachytherapy is relatively invasive. The need for radioactive sources for implantation requires a well-organised approach to treatment venues, times and quarantine matters.[7,8,13]

Brachytherapy is a unique treatment form. It requires highly skilled individuals to plan and deliver the treatments.

Radiation Protection and Safety Considerations in Brachytherapy

Brachytherapy is a potentially hazardous procedure, requiring strict adherence to radiation protection measures and control of the radioactive sources, to ensure the safety of both staff and patient.10,16 Use of radiation in Australia is regulated by the Codes of Practice implemented by the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA). Previous studies16 suggest that compliance with Radiation Protection measures may be a stumbling block for practices unfamiliar with radiation.[4,16,17]

Conclusion and rationale

SCC is the most common tumour of the eye and adnexa in horses, however current treatment options vary in their application and reported outcomes. The current literature demonstrates very little benefits of any specific treatment in veterinary medicine. In contrast, radiation therapy for the treatment of skin SCC in humans is highly effective and long-term studies and data are available to support its use.[3] In the absence of a standardised treatment option, veterinarians develop treatment practices based on the experiences of other practitioners, personal preferences and anecdotal information. Informal discussion with veterinary practitioners prior to the commencement of this research provided anecdotal evidence to suggest a range of approaches were being used to treat OSCC/POSCC, including brachytherapy. Current research has identified that the treatment of OSCC/POSCC in horses in Australia is varied and non-standardised. In relation to brachytherapy for OSCC/POSCC, the research also revealed variations in its application, outcomes and a lack of association with recommended guidelines for the application of brachytherapy (ICRU, ARPANSA). The ultimate aim of our ongoing research is to establish brachytherapy protocols for treatment of OSCC/POSCC in horses and appropriate radiation safety guidelines. This will assist veterinarians in meeting ICRU and ARPANSA guidelines, and will ensure treatments are comparative, standardised and delivered with a view to ensuring undue occupational irradiation is avoided.

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2.10 HISTORICAL PERSPECTIVE OF BRACHYTHERAPY

Brachytherapy was first used soon after the discovery of radium by Marie and Pierre Curie in 1898. [28] The term 'brachytherapy' was coined by Forsell in 1931 and is derived from the Greek word 'brachio' which translates to 'short'. [28, 29] The principles of brachytherapy include the delivery of a high radiation dose to a localised affected area (cancer) and the sparing of surrounding normal tissue due to the effects of the fast fall-off of radiation. [30] It is a form of radiation therapy that uses sealed radioactive sources to deliver radiation by interstitial, intracavitary or surface application. [30] Radium was the first radioactive source used for therapeutic purposes in 1903. [28] The treatment application was through the use of a radioactive plaque and for the treatment of basal cell carcinoma (BCC) on two separate patients. [31] Following the initial application in 1903, brachytherapy was further developed and applied in the form of intracavitary techniques for cancers of the cervix, the uterus and the endometrium. [31] Briefly after the success of the intracavitary implants were noted, brachytherapy was applied interstitially and by the end of the first decade of the 20th century, radium brachytherapy was used on most body sites that are commonly treated today. [31] Whilst radium is no longer used, the outcomes of these treatments varied in success and it was noted that more investigation into the intricacies of the delivery of these treatments was necessary before a viable treatment protocol may be established.

2.11 BRACHYTHERAPY TREATMENT

Brachytherapy is a standard technique in the treatment of a considerable number of human malignancies which include, but are not limited to; prostate, lung, uterine cervix, uterus, breast, head and neck and skin cancer. [21, 32] Brachytherapy is increasingly aligned with organ preservation and the satisfactory cosmetic results the technique offers. [21] In the case of early stage prostate and breast cancers, brachytherapy may be used as a sole treatment or for later-stage cancers of the prostate, gynaecological tumours or head and neck cancers, in combination with EBRT. Clinical indications for brachytherapy treatment are site-specific [33] however a standard process-flow with generic key components is depicted in Figure 2.3 below.

2.11.1 INDICATIONS FOR BRACHYTHERAPY

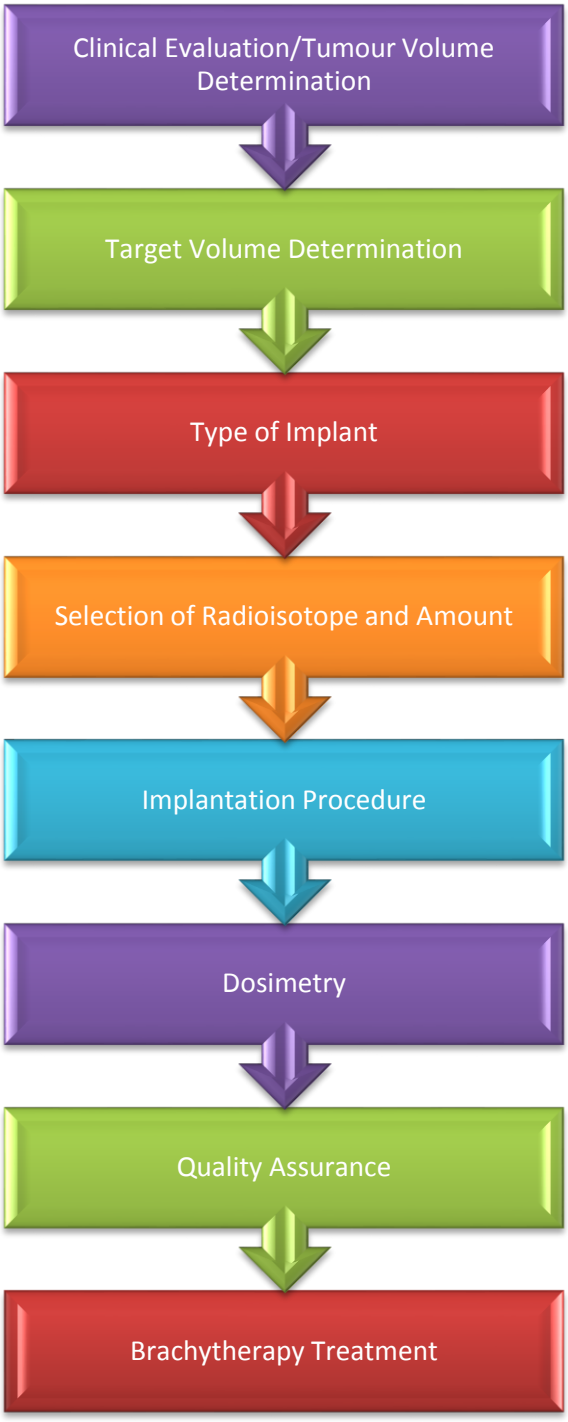

Figure 2.3: Approach to Brachytherapy Treatment

2.11.2 Clinical Evaluation

The Tumour Volume (TV) is identified with the aid of radiographic imaging; X-rays, computed tomography (CT), ultrasound or magnetic resonance imaging (MRI). [34]

2.11.3 Target Volume Determination

The Target Volume includes the Tumour Volume with a margin. [34]

2.11.4 Type of Implant

The type of implant to be used is determined based on the clinic's protocols. The decision to use a permanent or temporary implant is made at this point. [28, 35]

2.11.5 Selection of Radioisotope and Amount

The choice of permanent or temporary implants will guide the choice of radioisotope. Again, the clinic's protocols would provide guidelines for the choice of radioisotope and the amount required. [28, 35]

2.11.6 Implantation Procedure

The implantation procedure is dependent on the equipment contained within the clinic and the form of treatment; interstitial, intracavitary or surface. [28]

2.11.7 Dosimetry

Dosimetry can be calculated manually or with a computerised system. Advances in technology suggest the application of manual planning (dosimetry) has been surpassed by computerised methods in most clinics. [28]

2.11.8 Quality Assurance

Quality assurance includes the assessment of the treatment parameters to ensure optimal treatments ensue and also the consistent monitoring of radioactive sources to ensure the safety of personnel and the patient. [28, 36]

2.12 BRACHYTHERAPY TREATMENT PLANNING

The treatment planning process for brachytherapy aligns almost exactly with that of EBRT. The process involves treatment parameter determination including tumour volume, organs at risk (dose-limiting structures), treatment volume, dose prescription, and positioning of the patient. The difference beyond this includes the use of radioactive sources, temporary or permanent. Like in EBRT, tumour localisation is pivotal in dose delivery. This is achieved following clinical examination, radiographic imaging and/or CT scanning. Planning in brachytherapy involves computerised dosimetry in most instances. It must be noted that this is all done in the context of available equipment within a clinic. The quality of treatment planning and ensuing brachytherapy treatment is dependent on the facility's equipment and expertise. [37]

2.13 TYPES OF BRACHYTHERAPY

Brachytherapy may be categorised in various ways; by the location of the implant, the type of loading used, the dose rate, the type of radiation emission or the length of the treatment. [28] Brachytherapy sources are applied in one of three ways; interstitial implantation, intracavitary implantation or by using external applicators such as molds or plaques. The size and location of the tumour predicts the type of technique required. Smaller areas that occur superficially are generally better suited to surface applicators, and as the names suggest, tumours located within a cavity such as the uterus are best suited to intracavitary therapy and those located within tissues, treated with interstitial therapy. [30]

2.13.1 SURFACE APPLICATION TECHNIQUE (MOLDS OR PLAQUES)

In surface applications, the radioactive material is placed directly on the surface of the tumour and not inside the tumour. The plaques or molds are customised to conform to the treatment surface and the sources (radioactive) are then securely positioned on the outer surface of the applicators (Figures 2.4 & 2.5). [28, 30]

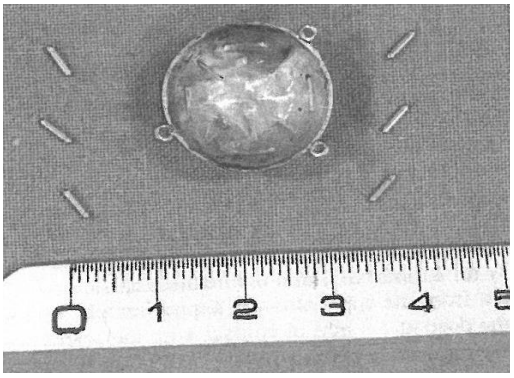

Figure 2.4: Iodine-125 Seeds and Gold-198 Plaque [38]

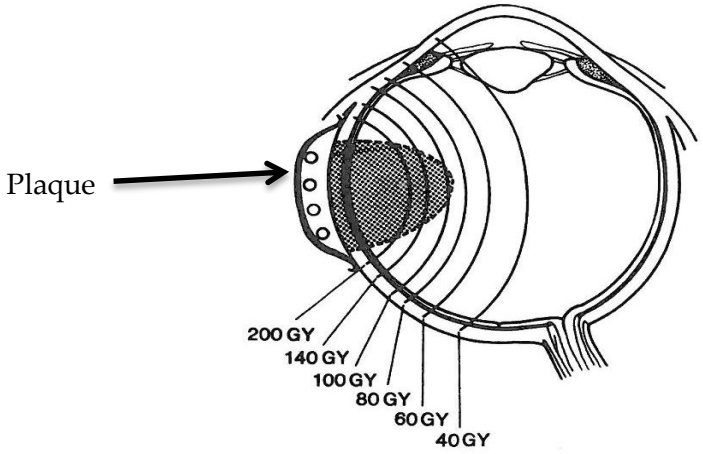

Figure 2.5: Cross-Section of Globe with Plaque Attached and Isodose Lines [28]

2.13.2 INTRACAVITARY TECHNIQUE

Placing radioactive material into body cavities is referred to as intracavitary brachytherapy. The technique is most useful for gynaecological tumours and where there is a requirement to place radioactive material in cavities such as the vagina and uterus. An extension of intracavitary brachytherapy is the intraluminal technique where the radioactive material is placed in the lumen of organs such as the esophagus, bronchus or the bile duct; though this is a less common treatment approach as compared to intracavitary brachytherapy (Figure 2.6). [28]

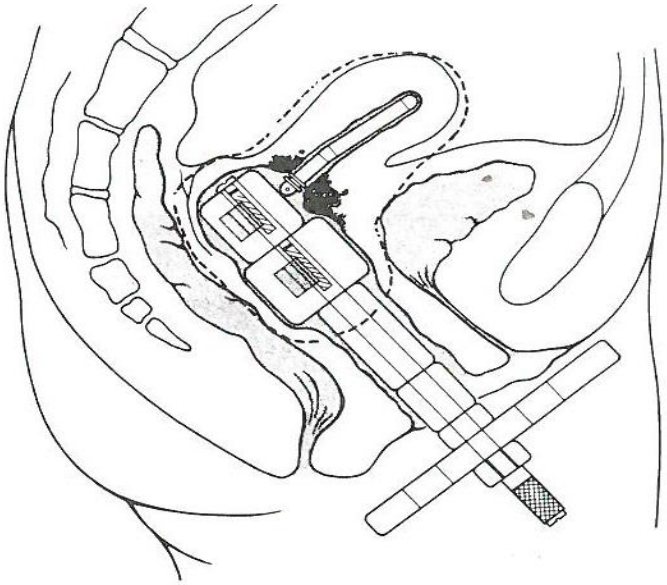

Figure 2.6: Diagram Illustrating an Intracavitary Uterovaginal Applicator [39]

2.13.3 INTERSTITIAL TECHNIQUE

Interstitial implantation is defined by the permanent or temporary insertion of sealed radioactive sources within the body's tissues. [39] Interstitial radioactive sources are pre-fabricated and supplied by the manufacturers in the form of radioactive needles, wires or seeds. These radioactive sources are produced so that they may be implanted directly into the affected tissues (Figure 2.7). [30] The type of implantation varies dependent on the treatment area however there are two types of interstitial implants; temporary and permanent.

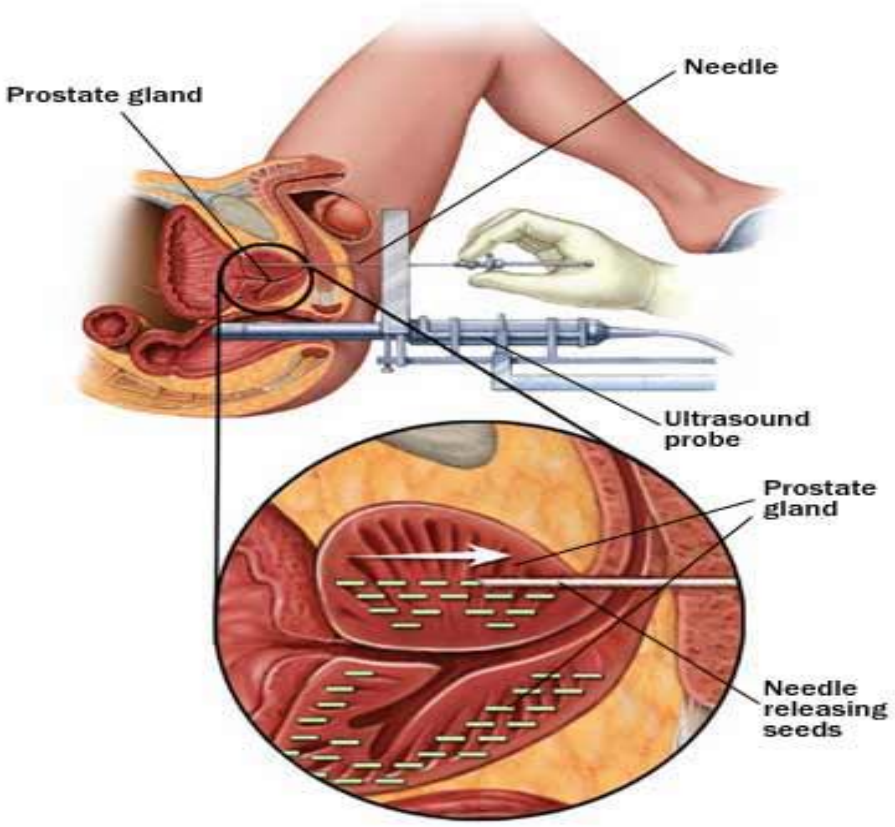

Figure 2.7: Diagram Illustrating Catheters Used for Prostate Treatment [40]

2.13.4 TEMPORARY AND PERMANENT IMPLANTS

2.13.4.1 TEMPORARY IMPLANTS

In temporary implants, the radioactive material, usually of long half-life is implanted temporarily and removed once the required radiation dose is achieved. Temporary implants require a longer time-investment considering the radioactive material is removed following the dose delivery, however the total dose and dose distribution is far better controlled in such treatments as compared to permanent implants. [30] Examples of such radioactive implants include iridium-192 (^{192}Ir), cesium-137 (^{137}Cs) and cobalt-60 (^{60}Co).

2.13.4.2 PERMANENT IMPLANTS

Permanent implants, using short half-life isotopes, are left within the implanted tissues permanently. This requires a one-time implantation procedure. [30] Permanent interstitial implants require the insertion of radioactive seeds or wires directly into tumour sites. These seeds/wires remain within the neoplastic tissues and are left to decay to a nonradioactive form. As a result, the dose or the dose distribution cannot be altered after the initial insertion. It is a simple and fast procedure in comparison to temporary implants. Examples of such radioactive implants include iodine-125 (^{125}I); gold-198 (^{198}Au); iridium-192 (^{192}Ir); and cobalt-60 (^{60}Co). [41]

2.14 TYPES OF LOADING

Radioactive implants require 'loading' after the source containers (applicators or catheters) are placed within the patient. Traditionally, the afterloading techniques used required manual handling of radioactive material. The danger posed by such manual handling led to the development of alternative techniques to allow procedures to be completed whilst maintaining the radiation exposure to acceptable levels as per the nationally or internationally accepted levels. [34] The technology to ensure the safety of the operator and patient has evolved such that the need for manually handling sources is only required in some instances for wire insertion, with the introduction of remote afterloaders. [28, 30]

2.14.1 MANUAL LOADING

Manual or 'hot' loading requires the operator to directly introduce the radioactive material into the tumour. The radiation hazards associated with this type of loading are significant hence the technique is sparingly used in current practice. [28, 30, 39]

2.14.2 MANUAL AFTERLOADING

Manual afterloading techniques involve the manual insertion of radioactive material into catheters, needles or applicators already inserted into the tumour. The radiation exposure is reduced in comparison to manual loading however there is still a risk of exposure to the patient, operator and visitors. [28, 30, 39]

2.14.3 REMOTE AFTERLOADING

Remote controlled afterloading eliminates the danger of exposure almost completely as compared to manual loading and manual afterloading. The radioactive material is loaded into the inserted applicator by the use of a remote control. The operators are positioned outside the patient's room and observe the patient through cameras. Remote afterloading is a preferred brachytherapy approach for temporary implants considering its favourable radiation safety characteristics. [28, 30, 39]

2.15 DOSE RATES

The dose rate at which brachytherapy can be delivered is variable. It is currently described as low, medium and high dose. Presently, High Dose Rate (HDR) brachytherapy has superseded the use of Medium Dose Rate (MDR) and Low Dose Rate (LDR) for the treatment of the majority of cancer cases. The International Commission for Radiation Units (ICRU) Report No. 38 has defined dose rates in brachytherapy as follows (Figure 2.8). [35]

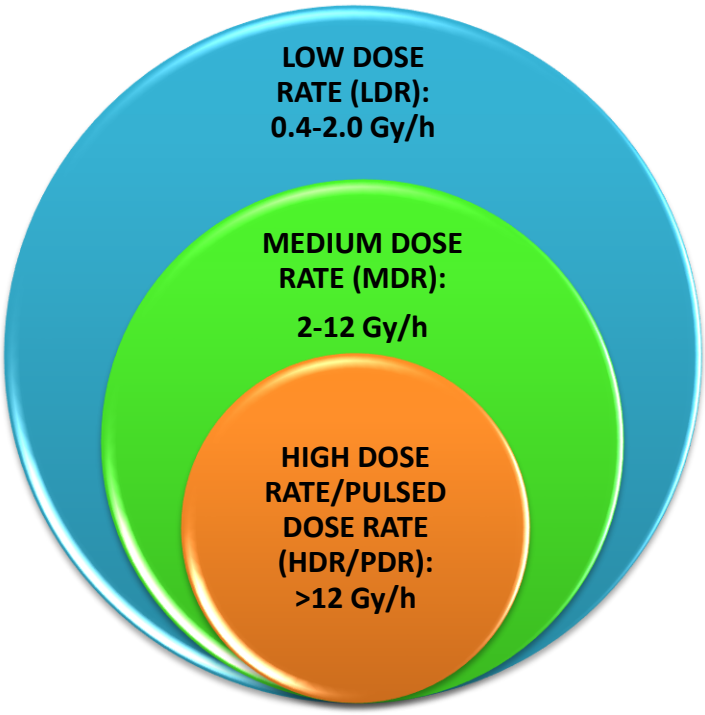

Figure 2.8: Dose Rates for Brachytherapy [28, 34]

2.15.1 Low Dose Rate (LDR)

Low dose rate was traditionally performed with manual loading and can be described to have a dose rate of between 0.4 to 2.0 Gy per hour. LDR remote afterloaders are currently available. [28, 34]

2.15.2 Medium Dose Rate (MDR)

Medium dose rate can also be referred to as intermediate dose rate and ranges from 2-12 Gy per hour. Medium dose rate is rarely used. The excessive nature of exposure (when loaded manually) makes it an unappealing treatment form. [28, 34]

2.15.3 High Dose Rate (HDR)

High dose rates are in the region beyond 12 Gy per hour. High dose rate brachytherapy is only delivered by remote control techniques and never with manual loading. As an example, the dose rate in current HDR units is approximately 100-300 Gy per hour. This allows treatment delivery to be reduced to a few minutes. The remote loading has the added advantage of radiation safety. HDR is the mainstay of brachytherapy treatment for cancer sites including head & neck, gynecologic, breast and prostate. [21, 28, 34]

2.15.4 PULSED DOSE RATE (PDR)

Pulsed dose rate brachytherapy is similar to HDR, but radiation is delivered in short 'pulses' over several hours. The radiation source is typically an iridium-192 source. The source is left in situ (cancer site) for hours or days as with HDR, however positioned at different dwell points along the catheter pathway for short applications giving the technique the name 'pulsed-dose rate'. It is then removed once the required dose is delivered. The remote loading has the added advantage of radiation safety. The patients stay in a dedicated shielded room during the treatment. [28, 34]

2.16 ADVANTAGES & DISADVANTAGES OF BRACHYTHERAPY

Brachytherapy used in the treatment of neoplasms located in the vicinity of sensitive organs such as the eye offers various advantages over EBRT by delivering a high dose to the tissues of interest whilst sparing surrounding tissues. [42] The delivery of high doses to the neoplasmic tissues contributes to improved local control, limited scarring and distortion of surrounding skin and inconsequential skin loss. [33, 42]

Brachytherapy allows for the delivery of a highly localised radiation dose to a small tumour volume. The sharp fall-off of radiation dose spares normal tissues surrounding the lesion of treatment. This reduces the side-effects which may normally occur in treatments where the radiation is not limited to the target lesion. [21, 30, 32] Brachytherapy reduces the amount of time a patient is required to spend receiving treatment (minutes to 7 days) as compared to EBRT (up to 7 weeks). Irregular tumour shapes are easily matched by dose distribution manipulation. The possibility of a geographical miss due to patient motion in brachytherapy is lessened as compared to EBRT since the sources are contained within the patient. It must be observed however that geographical misses may still occur as a result of the nature of the sharp fall-off of dose around the periphery. [21, 30, 32]

In contrast, the radiation exposure hazard that exists with the delivery of brachytherapy, however minimised through the evolution of technology, remains a challenge. Interstitial brachytherapy is relatively invasive. The need for radioactive sources for

implantation requires a well-organised approach to treatment venues, times and isolation matters. [21, 30, 42]

In view of the possibilities for large volume treatment in EBRT, brachytherapy's ability to deliver maximum dose to a small volume/area limits the applicability of the therapy in large tumours. Brachytherapy is a unique treatment form, it requires highly skilled individuals to plan and deliver the treatments. This at times may add to the inability to incorporate the treatment method in some clinics and the development of its treatment form (Figure 2.9).

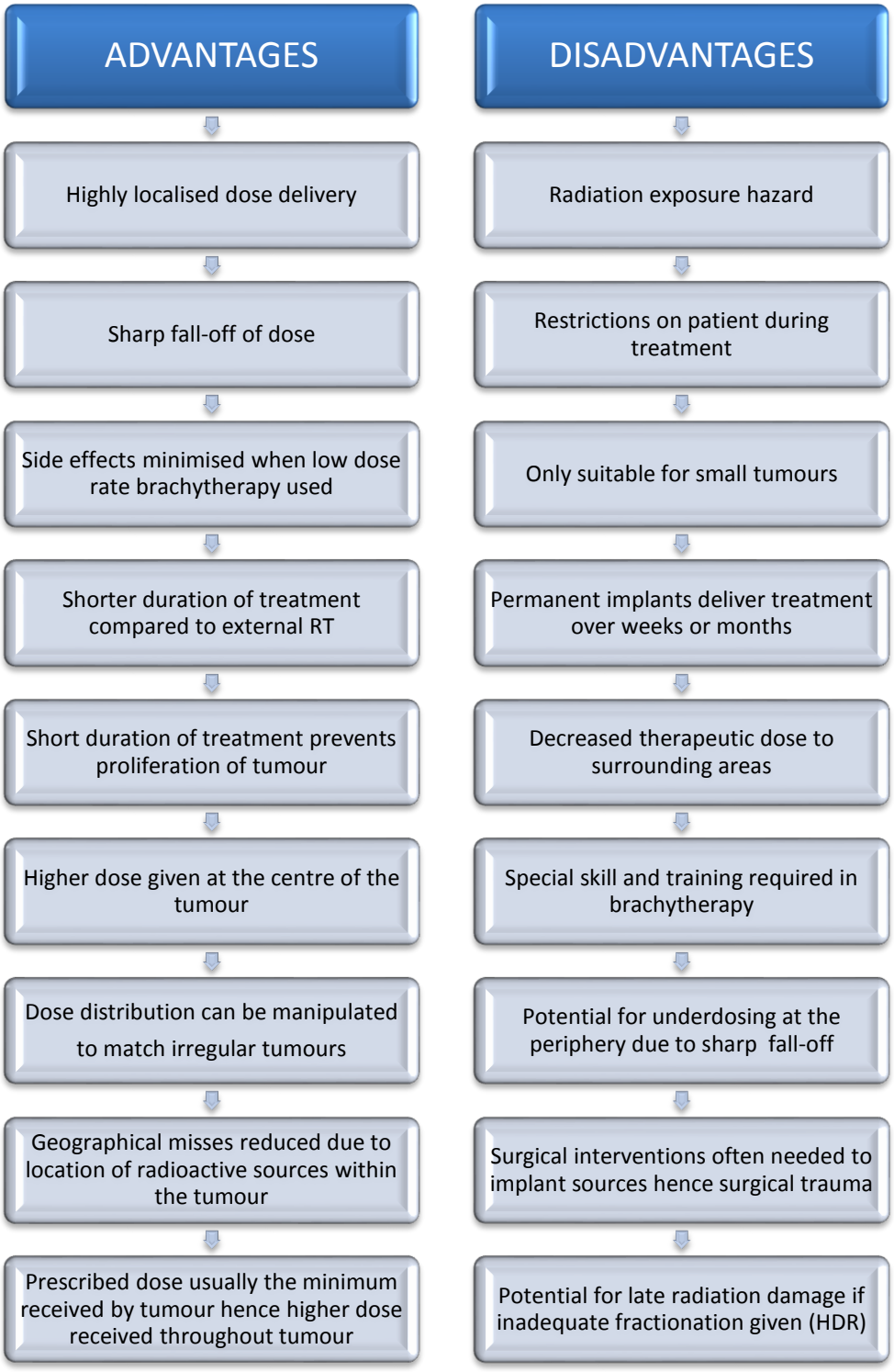

Figure 2.9: Advantages and Disadvantages of Brachytherapy [28, 30]

2.17 RADIOACTIVE SOURCES USED IN BRACHYTHERAPY

Historically, radium has been the radioisotope of choice in brachytherapy since its discovery in 1898 [30], however the advantages (including gamma-ray energy, source flexibility, half-life and source size) posed by artificially produced radioisotopes has seen a trend in the use of the radioisotopes other than radium (Table 2.1). Many radionuclides have over time been commercially marketed and trialled and many of those have been abandoned. [37] The selection of the type of radioisotope used depends on whether the implant is to be permanent or temporary. Permanent implants generally have lower energy emissions and a shorter half-life (gold-198, palladium-103 or iodine-125). Temporary brachytherapy is performed with radioisotopes that commonly have a longer half-life and have high energy emissions (iridium-192, cesium-137 or cobalt-60). [28, 30, 39]

2.18 PHYSICAL CHARACTERISTICS OF RADIONUCLIDES IN BRACHYTHERAPY

Brachytherapy sources are characterised by the rate at which their activity decays (half-life), the amount of radioactivity that can be obtained for a given mass (specific activity), and by the energies and types of radiation particles emitted from the source (energy spectrum). The suitability for a radionuclide for clinical use is dependent on these factors. [32, 43]

Table 2.1: Physical Characteristics of Radionuclides Used in Brachytherapy [28, 30, 37, 39]

Nuclide (symbol)	Half-Life	Type of Emission	Energy (keV)	Half Value Layer
Californium-252	2.65 years	neutron	2350	5cm of water
Cesium-137	30 years	gamma	662	6mm of lead
Cobalt-60	5.26 years	gamma	1173-1332	12mm of lead
Gold-198	2.7 days	gamma & beta	412 (γ) & 960 (β)	3mm of lead
Iodine-125	59.4 days	gamma	27-35.5	0.02mm of lead
Iridium-192	73.8 days	gamma	340	3mm of lead
Palladium-103	17 days	gamma	20-23	0.01 of lead
Phosphorus-32	14 days	beta	1710	Minimal
Radium-226	1, 600 years	gamma	47-2450	12mm of lead
Radon-222	3.83 days	gamma	47-2450	12mm of lead
Ruthenium-106	367 days	beta	2390-3550	Minimal
Strontium-90	28.1 years	beta	2280	Minimal

2.18.1 HALF LIFE

An isotope's disintegration is referred to as ***half-life***; the time it takes for an isotope to decay to one-half the original value. It is the half-life of a radionuclide that largely determines if the radionuclide is to be used as a temporary or permanent implant. [31] For a radionuclide to be useful, its half-life must be long enough that it allows for transportation and the preparation of the source once it arrives at its destination. [31] It also requires the half-life to be short enough that when required for a permanent implantation, it will decay at a rate that will be adhesive with the dose delivery specifications and hence pose no potential risk of undue exposure. [31] The half-life of a radionuclide also denotes its usability with reference to the timeline of source renewal.

The cost implications of a short half-life then need to be weighed against its practicability in clinical practice. [31]

Half-life ($t_{1/2}$) is related to the decay constant (λ) as per the formula below;

$$t_{1/2} = \frac{0.639}{\lambda}$$

The relationship between the activity and half-life is as follows:

$$A = \lambda N = \frac{0.639}{t_{1/2}}$$

Hence, the relationship between activity and half-life is inversely proportional, that is, as half-life increases, overall activity decreases. [21, 30]

2.18.2 SPECIFIC ACTIVITY

Practical use of a brachytherapy source is limited by its strength referred to as ***specific activity***. This is defined as the activity per unit mass of the source. Specific activity is particularly important in HDR treatments where there is a requirement for small source dimensions as well as high source strengths. [32]

2.18.3 AVERAGE ENERGY (E_{AVE})

The penetrability of a brachytherapy source is determined by its average energy and type of radiation emitted from the source. The ***average energy*** (E_{AVE}) of emitted photons is derived from the decay schemes of each isotope. [21] Higher radiation doses are delivered to tissues at larger distances from the source by high energy photon sources than by low energy photon sources. [21, 28, 30] As with the half-life of radionuclides and the financial implications this has, the energy also impacts on the ultimate cost of the radionuclide when determining the amount of shielding required for radiation protection. [21, 30, 31]

2.18.4 LINEAR ENERGY TRANSFER (LET)

The term ***linear energy transfer*** (LET) describes the energy that a particle disperses to the absorbing medium per unit length of its path. LET is expressed in kilo electron volts per micron ($keV\mu m^{-1}$). It is important to know the LET of the radiation used since it is

known that different LET radiations produce different degrees of biologic response. This is referred to as the relative biologic effectiveness (RBE). [21, 39]

2.18.5 RELATIVE BIOLOGIC EFFECTIVENESS (RBE)

Relative biologic effectiveness (RBE) of the radiations with different LET values is defined as the ratio of doses of two different types of radiation that are required to produce the same type of biologic effect. The standard comparison for calculations for RBE are X-rays generated at 250 kVp. RBE is defined as:

$$RBE = \frac{Dose\ of\ 250\ kVp\ xrays\ for\ a\ given\ biologic\ effect}{Dose\ of\ test\ radiation\ to\ produce\ the\ same\ isoeffect}$$

2.18.6 TYPES OF RADIATION EMISSIONS FROM RADIONUCLIDES

The energy and type of a radionuclide (emitted radiation) predicts its penetration within the specified tissues and hence the amount of radiation protection required in the form of shielding. Emissions are categorised in one of four ways; alpha, beta, gamma or neutron emission. [28]

2.18.6.1 ALPHA EMITTERS

Some types of radionuclides with a high atomic number greater than 82, emit alpha (α) particles (positively charged particles) and have high LET and RBE. Radioisotopes with ***alpha decay*** are much more easily shielded against than other forms of radioactive decay. Their very small penetrability render alpha emitters impractical for the purposes of brachytherapy applications. [28-30, 39]

2.18.6.2 BETA EMITTERS

Beta emissions are absorbed superficially within a few millimetres. Minimal radiation precautions are required considering the beta absorption principles. [28] Some beta-emitters used in brachytherapy include; phosphorous-32 (1710 keV), ruthenium-106 (2390-3550 keV) and strontium-90 (2280 keV). These radioisotopes are generally unsealed sources. [28-30, 39]

2.18.6.3 GAMMA EMITTERS

Gamma rays are emitted from an excited nucleus. [39] Radioisotopes with high energy gamma emissions and low LETs are the most commonly used sources in brachytherapy (e.g. cesium-137: 662 keV, cobalt-60: 1173-1332 keV, gold-198: 412 keV, iridium-192: 340 keV, radium-226: 47-2450 keV, and radon-222: 47-2450 keV). These penetrate deeply and require significant radiation protection to ensure operators, the patient and the patient's family/visitors are not unduly exposed. Other gamma-emitting radioisotopes with low gamma energy emissions include iodine-125 (27-32 keV) and palladium-103 (20-23 keV). These low energy gamma emitters require less radiation protection than high energy gamma emitters. [28-30, 39]

2.18.6.4 NEUTRON EMITTERS

The radiation exposure dangers associated with ***neutron emitters*** are great and hence they are rarely used in medical treatments. The only neutron-emitter of relevance to brachytherapy is californium-252 (2350 keV). Neutron-emitters are highly effective against hypoxic tumours as a result of their higher **LET** as compared to gamma emitters. [28-30, 39]

2.19 RADIATION BIOLOGY

2.19.1 INTERACTION OF RADIATION WITH MATTER

Ionisation is the process by which a neutral atom or molecule gains or loses electric charge. Ionising radiation produces ionisation in matter by depositing energy to the molecules of the absorbing material. Some examples of ionising radiation are alpha particles, gamma-rays, X-rays and neutrons. The most commonly used particles in radiation therapy are electrons (beta particles) and photons (X and gamma-rays). The energy transferred from these particles to tissues in the body have sufficient energy to damage DNA (deoxyribonucleic acid). [29, 30, 39]

There are a number of interaction processes that radiation can undergo, the main three of importance to radiation therapy are: [29]

1. Photoelectric effect
2. Compton effect, and
3. Pair production.

2.19.1.1 PHOTOELECTRIC EFFECT

In the ***photoelectric effect***, an interaction between an incident photon and an inner orbital shell electron takes place. The energy of the photon is totally absorbed by the atom and transferred to the orbital electron. The electron is then ejected from the atom with an energy equal to the original energy minus the binding energy of the electron. [29, 30] This interaction is predominantly at energies below 30 keV in soft tissue, therefore the photoelectric effect is relatively unimportant in radiation therapy other than for the purposes of Superficial Radiation Therapy (SXT) where energies of between 50-200 keV are utilised (Figure 2.10). [29, 30]

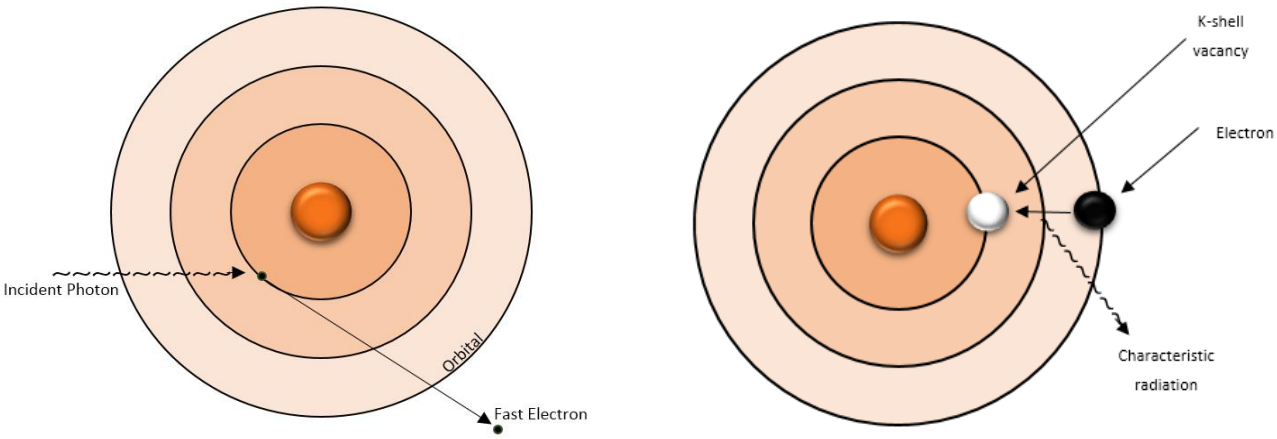

Figure 2.10: The Photoelectric Effect [30, 39]

The ejection of an electron from the atom leaves an inner shell vacancy which may be filled by a higher energy electron, resulting in the emission of characteristic radiation. The probability for photoelectric effect interactions decrease as the incident photon's energy increases. It is the electrons produced by the photoelectric interactions that have

the potential to create successive interactions and deposit their energy into human tissue, potentially causing damage. [30]

$$\boldsymbol{Photoelectric\ Effect} \propto \frac{\boldsymbol{Z^3}}{\boldsymbol{E^3}}$$

Where $\boldsymbol{Z}$ = Atomic number and $\boldsymbol{E}$ = energy of radiation.

2.19.1.2 COMPTON EFFECT

Compton scattering is a process where the radiation interacts with an atomic electron as though it were a 'free' electron. 'Free' refers to the binding energy of the electron being much less than the energy of the bombarding photon and therefore tends to be limited to outer orbit electrons. The result is a particle to particle interaction (scattering) where the radiation transfers some of its energy to the electron in turn scattering it at an angle that is relative to the incident direction (Figure 2.11). Scattered radiation can go on to have other Compton or photoelectric interactions or can leave the body. [29, 30]

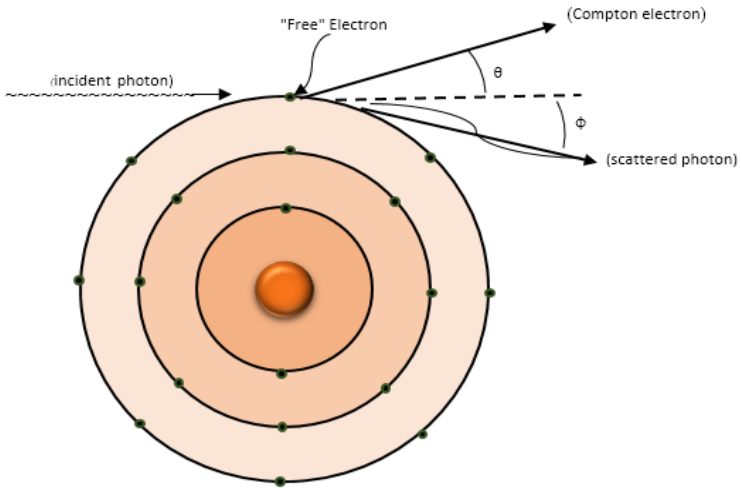

Figure 2.11: The Compton Effect [30]

2.19.1.3 PAIR PRODUCTION

Pair production is the interaction of radiation with the electromagnetic field of a nucleus in which the energy of the radiation is converted into an electron (e^-) and a positron (e^+). The mechanism of pair production occurs at energies greater than 1.02 MeV. As predicted by Einstein's equation; $E = mc^2$, the pair production process is best described by an event in which energy is converted into mass (Figure 2.12). [29, 30]

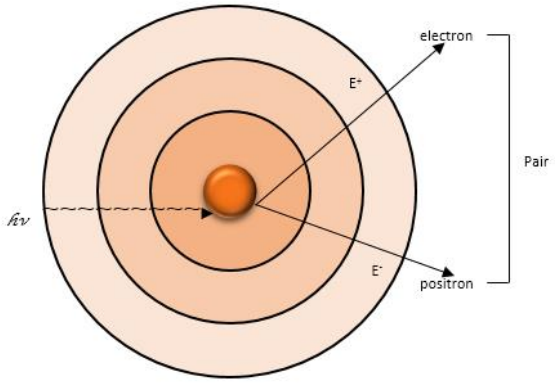

Figure 2.12: Pair Production [30]

2.19.2 RELATIVE IMPORTANCE OF THE THREE PRINCIPAL INTERACTIONS OF RADIATION IN MATTER (PHOTOELECTRIC, COMPTON AND PAIR PRODUCTION)

The ***photoelectric effect*** occurs exclusively at low photon energies, and whilst it is more relevant to diagnostic radiology than radiation therapy, it must be considered that some nuclides which have low energy can interact photoelectrically. The ***Compton effect*** however is the most important photon-tissue interaction for the treatment of cancer and includes nuclides and radiation produced by a linear accelerator (1 -20 MeV). The energy range in which ***pair production*** dominates is ≥25 MeV, whilst this range is possible in some radiation therapy treatments, it is not commonly used. The three interactions discussed above are the basis for energy selection of radionuclides in the application of brachytherapy. Figure 2.13 illustrates where the three different effects occur with respect to energy. It further illustrates that the ***Compton effect*** is predominant in the range~25keV – 25 MeV. [44]

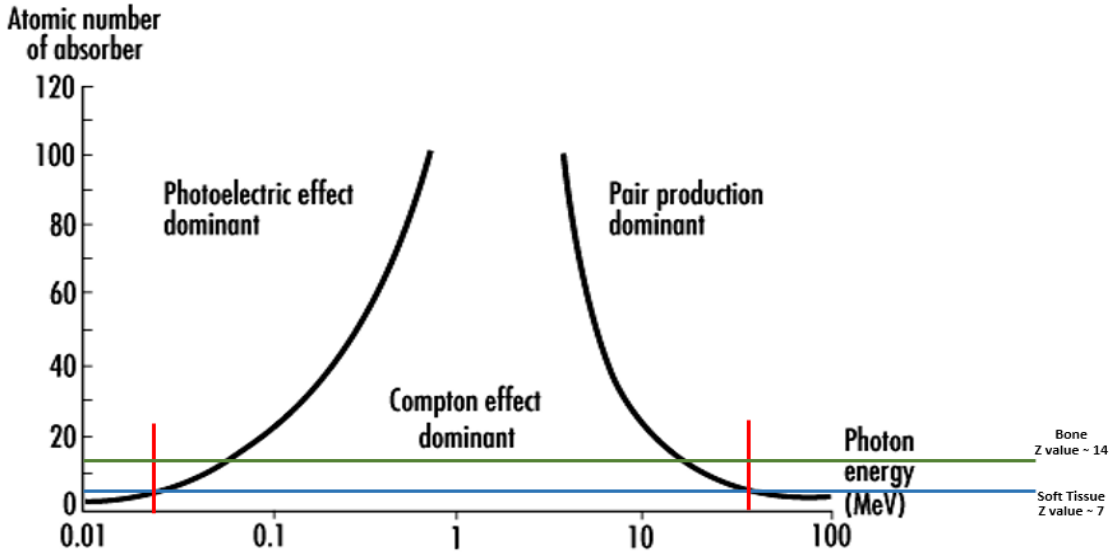

Figure 2.13: Predominating (Most Probable) Interaction vs Photon Energy for Absorbers of Different Atomic Numbers [44]

2.19.3 RADIATION DOSE QUANTITIES

2.19.3.1 ABSORBED DOSE (D)

The biologically significant effects produced by ionising radiation are described by the term ***absorbed dose*** or as is sometimes denoted, ***dose***, the quantity of radiation for all types of ionising radiation. The SI (International System of Units) unit of measurement for absorbed dose is the *Gray* (Gy) and is defined as: [30, 39, 45]

Absorbed dose is defined as (per ICRU):

$$\boldsymbol{D} = \frac{\Delta E_d}{\Delta \boldsymbol{m}}$$

Where ΔE_d is the energy imparted by ionising radiation per unit mass Δm.

2.19.3.2 EQUIVALENT DOSE (H_T)

Absorbed dose delivered by different types for radiation can have different degrees of biological impact (damage) to body tissues. The extent of the damage is not determined by the total energy deposited alone. The concept of ***equivalent dose*** *(H_T)* was introduced to take into consideration the potential for harmful radiation effects based on radiation type, or more specifically, the LET of radiation. It is therefore a measure of the risk

associated with an exposure to different ionising radiation. It is measured in Sieverts (Sv) and defined as:

$$\mathbf{H}_{T=} \sum \boldsymbol{D_{TR}\, W_R}$$

Where H_T refers to the equivalent dose, D_{TR} is the absorbed dose averaged over the tissue or organ and W_R is the radiation weighting factor (Table 2.2). Particles with high LET (such as α) which give up their radiation over a small distance produce greater damage to tissue than those with a lower LET (such as γ particles), hence W_R is greater for γ than for α.

Table 2.2: Radiation Weighting Factors [45]

Radiation Type	Radiation Weighting Factor (W_R)
X-rays, gamma rays, beta particles and electrons	1.0
Protons	2.0
Neutrons (energy dependent)	2.5-20
Alpha particles and other multi-charged particles	20

2.19.3.3 Effective Dose (H_E)

Dose equivalents for various tissues differ markedly for a given exposure received. Tissues differ in sensitivity to radiation and result in varied radiation-induced effects. To allow for these non-uniform irradiation conditions, the ICRP has adopted the concept of ***effective dose*** (measured in Sieverts). The effective dose (H_E) is defined mathematically as:

$$\mathbf{H}_{\mathbf{E}=} \sum \boldsymbol{W_T\, H_T}$$

Where W_T is the weighting factor for tissue T and H_T is the mean equivalent dose as received by tissue T. The weighting factors (Table 2.3), represent the risk (proportionate) of tissue when the body is irradiated equivalently. The weighting factors are derived from risk coefficients (risk per unit dose equivalent).

Table 2.3: Tissue Weighting Factors [45]

Organ or Tissue	Tissue Weighting Factor (W_T)
Breast, bone marrow, colon, lung, stomach, remainder tissues*	0.12
Gonads	0.08
Bladder, oesophagus, liver, thyroid	0.04
Bone surface, brain, salivary gland, skin	0.01

* Remainder tissues: adrenals, extrathoracic region (ET), gall bladder, heart, kidneys, lymphatic nodes, muscle, oral mucosa, pancreas, prostate, small intestine, spleen, thymus, uterus/cervix.

2.19.4 BIOLOGICAL EFFECTS OF IONISING RADIATION

Estimating the risks involved due to radiation exposure is challenging [46] however occupational exposure to ionising radiation endures as a significant and widespread potential risk for practitioners, patients and the public alike. [47, 48] The relative risk associated with ionising radiation exposure is small in comparison to other causes of death however, it cannot be underestimated.

There are two broad categories of biological effects of ionising radiation (Figure 2.14), these are: [49]

- Deterministic effects,
- Stochastic effects.

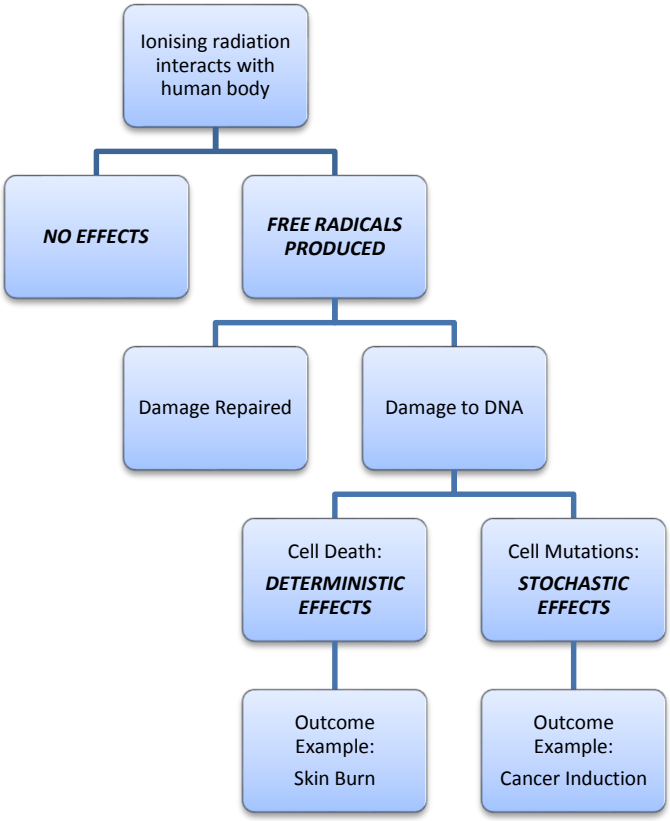

Figure 2.14: Biological Effects of Ionising Radiation [30]

2.19.4.1 *Deterministic Effects*

Deterministic effects are those caused by cell damage in which there is a threshold below which the effect does not occur. Examples include radiation skin burn (erythema), alopecia and cataract. [50]

2.19.4.2 *Stochastic Effects*

Stochastic effects are those that result from radiation changes in cells sometimes resulting in a malignant transformation of a cell. The probability (but not the severity) of occurrence is related to the magnitude of the dose, without a threshold. An example is cancer induction. [50]

2.20 OBJECTIVE OF RADIATION PROTECTION

The objective of radiation protection is to ***minimise*** stochastic effects to within acceptable levels and to ***eliminate*** deterministic effects. Use of radiation in Australia is regulated by the Codes of Practice implemented by the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA), based on ICRP. These Codes provide regulations to which practices must adhere when using radiation, whether it be for human or animal imaging or treatment. [51, 52] An in-depth examination into the Codes of Practice as applicable to veterinary medicine is included within Paper 4 in Chapter 4. The ICRP system of radiation protection mandates exposure to radiation to be controlled through ***justification***, ***optimisation*** and dose or risk ***limitation*****:** [51]

- ***Justification*** is based on the requirement that a net benefit is demonstrated from a practice which requires exposure to radiation. Only practices which are expected to do more good than harm should be selected to comply with 'justification'.

- ***Optimisation*** ensures that the extent of individual doses, the number of people exposed and the potential for exposures actually occurring should all be kept as low as reasonably achievable (ALARA). In general, optimisation refers to the implementation of strategies to reduce the possibility of detriment. The lowest radiation dose which provides the diagnostic information or medical therapy should always be targeted and dose limits as specified by ICRP should be followed.

- ***Limitation*** of risk or dose is in place to ensure risks do not exceed a value that would be considered unacceptable for long-term exposure to radiation. This is supported by the Recommendations on Dose Limits (Table 2.4) and consistent with the dose limits proposed by ICRP and detailed in ICRP Publication 103.

2.20.1 DOSE LIMITS

International large scale studies of cancer risk in people exposed to radiation exposure conclude that the risk from exposure to high radiation doses is relatively well quantified, however the evidence base relating to the effects of low radiation doses is less apparent (Figure 2.15 & Table 2.5). [53] The risk of cancer and hereditary effects at low radiation doses and/or for radiation dose delivered over a long time is possible but difficult to detect in scientific studies. It is known however that their likelihood increases as the dose increases.

Table 2.4: Dose Limits for Ionising Radiation [45, 51]

Application	**Occupational Dose Limit**	**Public Dose Limit**
Effective Dose	20 mSv per year, averaged over a period of 5 consecutive calendar years	1 mSv in a year
Annual Equivalent Dose in:		
The lens of the eye	20 mSv	15 mSv
The skin	500 mSv	50 mSv
The hands and feet	500 mSv	-

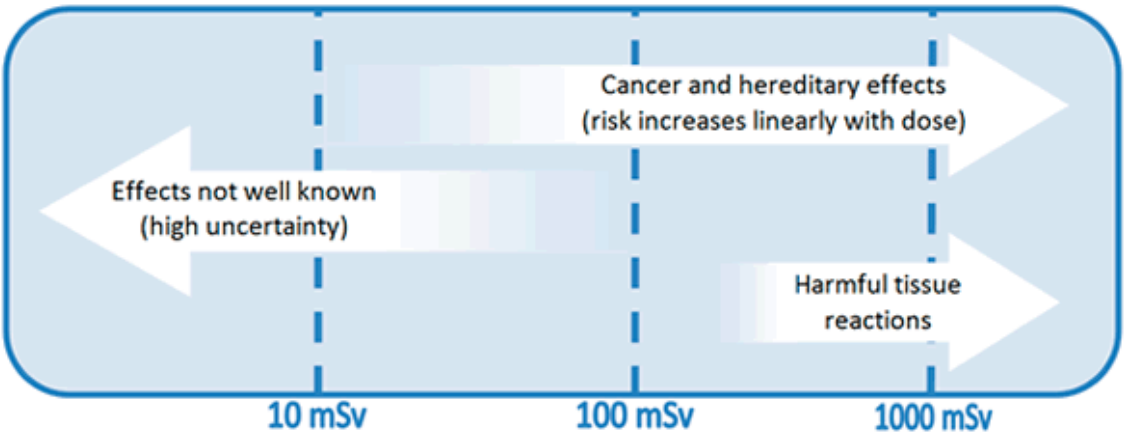

Figure 2.15: Radiation Health Effects at Different Exposure Levels [53]

Table 2.5: Health Effects of Ionising Radiation [53]

Dose Range	Effects on Human Health (including unborn child)
Up to 10 mSv	No direct evidence of human health effects
10-1000 mSv	No early effects; increased incidence of certain cancers in exposed populations at higher doses
1000-10000 mSv	Radiation sickness (risk of death); increased incidence of certain cancers in exposed populations
Above 10000 mSv	Fatal

To limit the potential risk to health from exposure to ionising radiation in the Australian workplace and to develop a common setting for radiation protection requirements for the control of exposure to radiation, the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) provides a National Standard for Limiting Occupational Exposure to Ionising Radiation (RPS1), based on the International Commission on Radiological Protection Recommendations (ICRP) (Table 2.4). [45, 51]

2.21 RADIATION PROTECTION PRINCIPLES IN VETERINARY MEDICINE

Radiation protection principles in veterinary medicine in Australia are governed by ARPANSA and described in detail in RPS-17. Basic radiation protection principles are consistent with RPS-1 however include veterinary-specific guidelines and recommendations for safe operation. The principles of ***justification***, ***optimisation*** and ***limitation*** are repeated as related to the veterinary specialty: [52]

- ***Justification***: No practice involving exposures to radiation should be adopted unless it produces sufficient benefit to the exposed individuals or to society to off-set the radiation detriment it causes.

- ***Optimisation***: Veterinary equipment and methods by which these are used must be nominated to ensure radiation doses as received by members of the public and occupationally exposed persons are maintained as low as reasonably achievable.

Social and economic factors must be taken into account within this decision-making process.

- ***Limitation*:** Dose limits to occupationally exposed persons and members of the public must be managed so that they do not exceed dose limits as specified by RPS1.

2.22 SUMMARY

This review of the literature discusses current and past treatment options for OSCC/POSCC, brachytherapy, ionising radiation, and equine ocular anatomy along with squamous cell carcinoma properties. The review highlights the lack of a standardised treatment for OSCC/POSCC and introduces the possibility of radiation therapy in the form of brachytherapy as a potential 'best practice' option. The review also highlights the importance of using guidelines and recommendations in the delivery of radiation for the purposes of treatment in the form of treatment protocols as well as radiation safety considerations.

A series of research strategies to further develop the project have resulted from the literature review and its findings. The lack of available data within the literature has steered the researchers to question the current and past accepted treatment approaches and hence led to the inclusion of 2 separate surveys in the research methodology to gather this information. The results of these surveys are discussed in Chapter 4 and include an analysis on treatment approaches and radiation protection compliance within clinics as the core themes.

The literature review also led the researchers to consider the implications and potential benefits of developing protocols (currently non-existent within literature) in the area of brachytherapy in horses, including radiation protection considerations for potential inclusion within equine clinics. A developed Treatment Protocol based on evidence based human treatments has been developed and is included in Chapter 5. Additionally and intended to be a compendium to the Treatment Protocol, Chapter 6 includes a developed Radiation Protection Flow-Chart and summary for specific veterinary use.

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CHAPTER 3: RETROSPECTIVE STUDY

3.1 CHAPTER OVERVIEW

Publications in the area of radiation therapy treatment in the veterinary field indicate that the use of the therapy is currently active internationally. Upon review however and in direct relation to brachytherapy, it is evident that the reporting methods lack consistency and a standardised approach on how treatments are delivered, reported on and validated is non-existent. In view of the existing expertise developed over five decades in human radiation oncology and the resulting universally accepted recommendations for brachytherapy treatment delivery (ICRU-58)[1], the researchers began to question veterinary practice in terms of its technical applications of brachytherapy with a particular focus on horses and the potential outcomes of such treatments. Investigations led the research team to a veterinary site (anonymity maintained) located within Australia that had previously used brachytherapy to treat ocular and/or periocular squamous cell carcinoma (1999-2007). Upon approach, the clinic was liberal in providing their medical treatment records and explanations of their techniques to support our intention to replicate their technique using conventional human treatment computerised methods. The aim to validate the outcomes of the treatments in question against known ICRU-58 recommendations for human RT treatments (in lieu of equivalent standards within veterinary radiation oncology) was realised and the Australian clinic must be acknowledged for their role in consenting to our involvement.

The objectives of the analyses of the retrospective study reported here were to assess efficacy and toxicity of brachytherapy treatment of OSCC/POSCC by applying contemporary radiation therapy treatment methods to a clinical series of cases (n=75). This study evaluated the effectiveness (efficacy and toxicity) of brachytherapy on OSCC/POSCC in horses treated between 1999 and 2007. Seventy-five horses with histologically or clinically confirmed OSCC/POSCC were treated at an Australian veterinary clinic with permanent gold-198 radioactive wire implants. Medical records included 2-dimensional schematic diagrams of treated lesions, number of implanted radioactive wires, wire arrangement and radioactivity for each treatment. Each case was

replicated with the use of radiation therapy treatment planning software Varian BrachyVision™ (Varian, Palo Alto, United States of America) and a prescription of 50 Gy applied (Minimum Target Dose). Exploratory statistical analysis was performed on radiation dose distribution parameters, including; treated volume coverage (Target Volume – TV), dose to organs at risk and Maximum, Minimum and Mean doses, with the aim of determining treatment effectiveness in terms of meeting conventional human treatment constraints outlined by the International Commission on Radiation Units and Measurements (ICRU), with particular focus on ICRU-58. [1, 2]

Optimal plan outcomes are dependent on homogenous isodose distributions within the TV. In this case series, isodose distributions were highly variable for each case. Analyses revealed the 50 Gy prescription Mean Dose isodose coverage for the TV ranged between 83.6 Gy and 174.1 Gy. Minimums for the TV ranged from 28.5 Gy and 44 Gy. A homogenous 50 Gy distribution within the TV was not evident in any of the 75 cases. Further analyses of data revealed a potentially significant Overall Maximum Dose (determining factor for later effects) of 100 Gy recorded in 68% (n=51) of cases for a volume of 0-2.3 cm^3 within the TV. Mean and Maximum doses were analysed in relation to three organs at risk; the lens, cornea and retina. In this case series the reportable tolerance doses apply to 'partial' organ volumes only. Recorded Maximum Doses to the organs at risk exceeded accepted tolerance levels for the lens and cornea (5-12 Gy and 50-60 Gy, respectively), however the retina remained well below limits (50-70 Gy) when interpreting Maximum and Mean doses. The lens received excessive Maximum Dose beyond accepted tolerance doses in 88% of cases (n=66) and over-tolerance Mean Doses in 64% of cases (n=48). The cornea received a Maximum Dose exceeding 50-60 Gy in 55% of cases (n=41) however all cases were below tolerance when interpreting Mean Doses to the cornea.

When the intended treatment diameter (schematic) was compared to the computer calculated equivalent square sphere diameter, a low positive correlation was observed indicating a slight trend with a highly significant p-value (0.02). However, estimated volumes showed no correlation with the computer calculated volumes that is, the

isodose coverage for each volume was haphazardly inconsistent. The intended treatment volumes (initial treatment as per medical records) demonstrated no correlation with the actual treatment volume once replicated with the planning software and following the application of a 50 Gy prescription.

It must be noted that whilst statistical analysis demonstrated low or no correlation between intended treatment and computer-generated treatments, visual plan critique of treatment coverage of lesions demonstrated fair to good coverage in most cases. That is, lesions received $V_{(50Gy)}$ between 91.8% and 98.2%. This does not however remove the potential for underdosing/overdosing in areas identified to be low-dose or high-dose regions within the TV, associated with recurrence and side-effects, respectively.

The non-homogenous 50 Gy distributions within the Target Volume further add to the conclusions made within this study that the treatment administered lacked a standardised approach. Some speculative conclusions may be made with regard to tolerance levels within the organs at risk (OARs) however, the volumes receiving over-tolerance doses are significantly small in most cases, making conclusive predictions regarding side-effects difficult. Equally, the recorded Maximums for the TV (100 Gy) are related to relatively small volumes (0-2.4 cm^3). Without a pre-determined biologically significant volume (ICRU does not provide a conclusive biologically significant volume related to Maximums in brachytherapy) to correlate the results with, it is impossible to predict if the Maximums would result in adverse effects.

Regardless of the complexity in interpreting results, it appears that when a formal dose distribution is applied to brachytherapy implants initially performed in a free-hand manner, there is likely to be great variability in dose coverage of the TV, and adjacent normal tissues. Given that dose and dose distribution are important correlates of outcome, the variability of dose illustrated in this study highlights the need for a more standardised implant protocol and evidence based dose prescription protocols, supported by computerised planning.

This Chapter consists of a comprehensive analysis of data emerging from the replication (treatment modelling using conventional human brachytherapy planning software and

principles), of 75 retrospective brachytherapy treatments of horses for OSCC/POSCC. The findings provide a basis for the development of a Treatment Protocol for OSCC/POSCC in veterinary medicine.

3.2 BACKGROUND

3.2.1 OCULAR SQUAMOUS CELL CARCINOMA/PERIOCULAR SQUAMOUS CELL CARCINOMA (OSCC/POSCC)

Ocular and periocular squamous cell carcinomas (OSCC/POSCC) are the most common tumours of the eye and adnexa in horses. [3-6] Causes of OSCC/POSCC may include a genetic predisposition to carcinogenesis, extended exposure to the ultraviolet component of solar radiation, or the degree of pigmentation. [7] Most equine OSCC/POSCC are slow growing and invade locally however metastases may occur in 10% to 15% of cases. [8, 9] Lesions may originate from various tissues including the cornea, limbus, nictitating membrane, conjunctiva, orbit and eyelid. [9] Geographic variation in the incidence of SCC is thought to increase in areas of high sunlight exposure and increased altitude. [10] OSCC includes the cornea, sclera, limbus and bulbar conjunctiva whilst POSCC includes the eyelids and third eyelid.

3.3 OSCC/POSCC TREATMENT

The treatment of OSCC/POSCC in the horse remains a great challenge and a standardised approach remains elusive. [6, 9-11] The various treatments currently used do not have universal acceptance and have a limited supporting evidence base. The methodology of a number of currently used techniques is poorly documented. A literature review conducted on current and previously used treatments of OSCC/POSCC with the aim of determining the optimal technique identified the seven most commonly reported modalities in OSCC/POSCC treatments as; surgery, photodynamic therapy, carbon dioxide (CO_2) laser ablation, radiofrequency hyperthermia, cryotherapy, topical or intratumoral chemotherapy, and radiation therapy. [6] Of the 37 studies emerging from the review, the majority reported treatment success however upon analysis it was clear that no technique could conclusively be identified as the best approach to the treatment of OSCC/POSCC. The presentation of data in the literature and its lack of consistency

rendered it impossible to statistically analyse and make comparative conclusions on treatment outcomes. It was however apparent that lesion location significantly influenced the choice of treatment type. The review also found that successful treatment of OSCC/POSCC commonly involved one of the above therapies combined with cytoreductive surgery. [6] Additionally the value of combining radiation therapy with surgery or using radiation therapy alone was identified in relation to benefits in decreasing cosmetic and functional defects. [6, 12]

3.3.1 International Commission on Radiation Units and Measurements (ICRU)

The quality of reporting in human medicine and veterinary medicine is disparate. Fundamental deficiencies currently exist in completeness of reporting in veterinary radiation oncology. [13] Published veterinary radiation oncology clinical trials, retrospective or prospective are difficult to interpret due to a lack of provision of pertinent information such as radiation dose, dose distribution and uniformity in the treatment protocols applied. Without a sufficiently clear and detailed reporting system, it is impossible for readers to extrapolate the validity and applicability of study conclusions. A universally accepted dose-specification and reporting system exists to avoid such quandaries in human radiation oncology and has been established by the International Commission Radiation Units and Measurements since 1978. [2] The reporting system has been updated over time to maintain currency in a fast-evolving area such as radiation oncology with the latest recommendations updated in 2010. Directly related to brachytherapy is ICRU Report 58 (1997): Dose and Volume Specification for Reporting Interstitial Therapy. [1] Radiation therapy treatments in veterinary radiation oncology are currently not supported by equivalent recommendations and therefore suffer from a lack of consistency and the ability to conclude on best practice for any given veterinary radiation oncological treatment.

3.4 MATERIALS AND METHODS

3.4.1 CRITERIA FOR SELECTION OF CASES

The clinical records of horses with confirmed OSCC/POSCC treated with interstitial gold-198 brachytherapy between 1999 and 2007 were retrospectively analysed. A total of 160 cases were accrued over the nine year period. Of these, 85 were excluded from the study on account of a diagnosis other than SCC, treatment site other than ocular/periocular, and lack of data on radioactivity dose and/or wire arrangement. Thus a total of 75 horses (85 SCCs) were included in this study (Figure 3.1). Any cases with a single wire were also excluded from the research due to the inability to calculate a volume or comparative diameter.

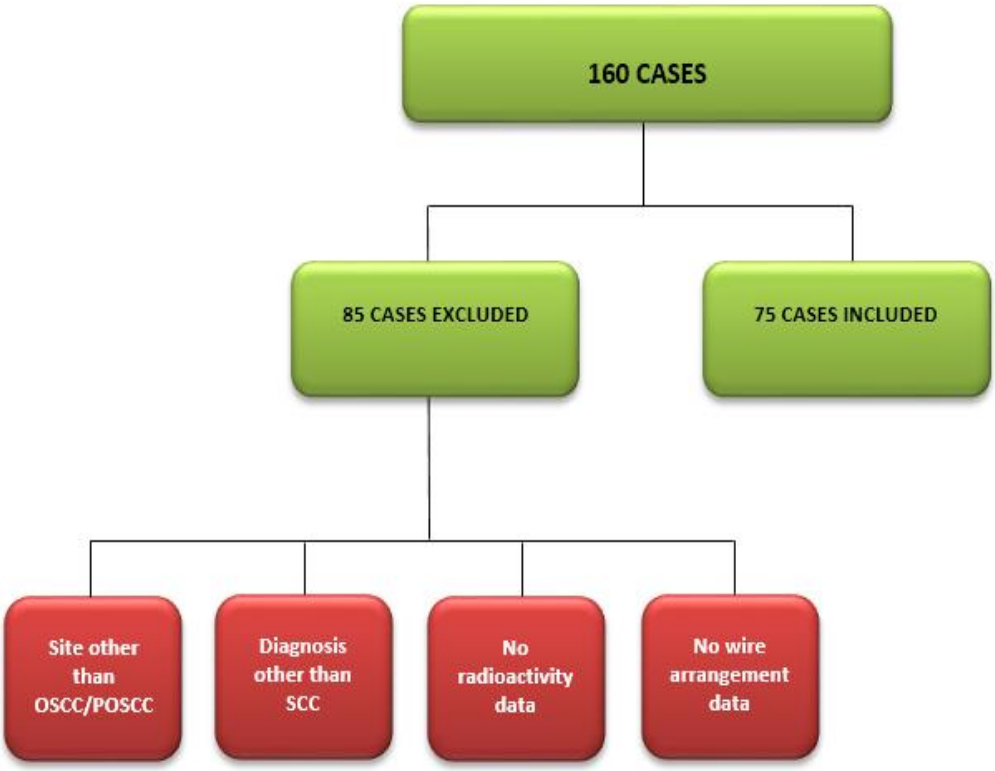


Figure 3.1: Case Exclusion Flowchart

The records of the 75 horses were evaluated and the following information retrieved; anatomical site involved (lesion location), number of lesions and tumour dimension (maximum diameter), wire location (arrangement), number of wires implanted, and recorded radioactivity (Table 3.1). Available records show the clinic used radioactive gold-198 wires. Follow-up data (recurrence rates) or resulting side-effects were not available in the original medical records therefore an attempt to collect this information was made in 2012 via a mail survey of owners. The survey was used to determine the progress of the animals post-treatment with a view to identifying if a recurrence had occurred or if any side-effects had been noted.

Table 3.1: Criteria for Selection of Cases

1.	Site of diagnosis: Ocular or Periocular
2.	SCC diagnosis: available
3.	Lesion location: identifiable as a result of diagram, written report or combination of both
4.	Wire location: discernible in order to be replicated
5.	Number of wires used: available
6.	Wire radioactivity: available

3.4.2 PRESCRIPTION DOSE

There is limited information in the literature for gold-198 or any other radioactive source to guide the determination of the correct dose prescription for the purposes of treatment of SCC in horses. In lieu of this information, previous equine studies have used tumour doses that were comparable to those from human experience. [5, 14-19] A study by Wyn-Jones (1979) used 7000 rads (70 Gy) although this was based on results of a previous study on RT in fibrous connective tissue sarcomas in animals (1976). [19, 20] Beyond the Wyn-Jones study, various other treatment prescriptions have been used in equine SCC therapy with other radioactive sources. The doses delivered have ranged from 32 Gy to

250 Gy. The radioactive sources have included; strontium-90, iridium-192, cobalt-60, cesium-137 and radon-222, iodine-125 and gold-198 (Table 3.2). [5, 14-19]

Table 3.2: Range of Prescription Doses used in Treatment of OSCC/POSCC in Horses Documented in the Literature [6]

Author	Type of Therapy	Year	Dose	Number of Cases
Mosunic[14]	Strontium-90 [14]	1985-2002	80-100 Gy (cornea) 100-120 Gy (eyelid)	33
Plummer[5]	Strontium-90[5]	1990-2002	200 Gy dose per site	25
Walker[15]	Strontium-90 [15]	1980-1984	100 Gy surface dose	8
Mosunic[14]	Strontium-90 [14]	1985-2002	80-100 Gy (cornea) 100-120 Gy (eyelid)	5
Rebhun[16]	Strontium-90 [16]	Prior to 1990	80-100 Gy	24
Ollivier[17]	Strontium-90 [17]	2002-2006	20 Gy	12
Mosunic[14]	Iridium-192 [14]	1985-2002	58-65 Gy	19
Walker[15]	Iridium-192, Radon-222, Iodine-125 [15]	1980-1984	36-100 Gy	10
Mosunic[14]	Cobalt-60 [14]	1985-2002	32-36 Gy	2
Lewis[18]	Radon-222 [18]	Prior to 1964	6000 Roentgens (approximately 52.17 Gy)	8
Wyn-Jones[19]	Gold-198 [19]	Prior 1979	70 Gy	4

SCC can be treated effectively with various radiotherapy methods in humans. [21] These include external beam RT and occasionally brachytherapy. The choice to use RT for SCC is less dependent on the probability of tumour control, which is typically high, than on the predicted cosmetic and functional results, which can be better with RT than some forms of surgery. [22] For this reason, RT is often favoured for lesions located on or near the eyelids, nose, ears and lips. [22] In the case of brachytherapy, and dependent on the

dose exposure rate and the radioisotope used, the accepted prescribed (recommended) brachytherapy dose for skin cancer varies widely. Dosing and fractionations vary from trial to trial based on individual physician choice, the activity of the radioisotope, the type of cancer and the size of the lesion as do the RT application methods which have included interstitial brachytherapy, contact therapy and external RT. [22-25]

For this research it was decided to use a 50 Gy prescription (Minimum Target Dose) as the standard for dosing of each plan. The validity of this choice was based on the comparable nature of the more commonly used doses in the equine literature, and was known to be highly effective for the brachytherapy treatment of human cutaneous SCCs. Furthermore, it was necessary to choose a single dose as a means of having a basis for comparison between each treatment case.[23, 24]

3.4.3 INITIAL BRACHYTHERAPY PROCEDURE 1999-2007

The clinic's implantation of the radioactive gold-198 wires was carried out under general anaesthesia in all cases. Horses were routinely pre-medicated with Xylazine (1.5 mg/kg of body weight) and anaesthesia was induced with Ketamine (3.0 mg/kg) and Diazepam (0.04 mg/kg). Anaesthesia was maintained throughout the procedure by Halothane Inhalation Anaesthesia at 2-5% Oxygen. Procedure times typically did not exceed 30 minutes.

All horses were manually implanted directly with permanent gold-198 wire supplied by the Australian Nuclear Science and Technology Organisation (ANSTO): Radiopharmaceuticals and Industries. The Gold wire specifications included 99.99% purity, a diameter of 0.78 mm ± 0.02 mm, a nominal length of 12 mm and a weight of 100 mg ± 3mg. The activity of the gold-198 was measured just prior to despatch in an argon filled (20 atmospheres) ionisation chamber calibrated against a source certified output and apparent activity as supplied by the Isotopes Standards Laboratory (ANSTO). Measurement accuracy was recorded at ±5%. In readiness for implantation, wires measuring 12 mm in length and with a nominal activity of 800 MBq (although this varied significantly from shipment to shipment), were manually cut by the treating veterinarian into approximately 10 pieces equating to approximately 1.2 mm per piece. The date of

implantation was decided upon prior to ordering the radioactive wires and decay of wires was closely monitored according to the standard decay curve (Figure 3.2). [26]

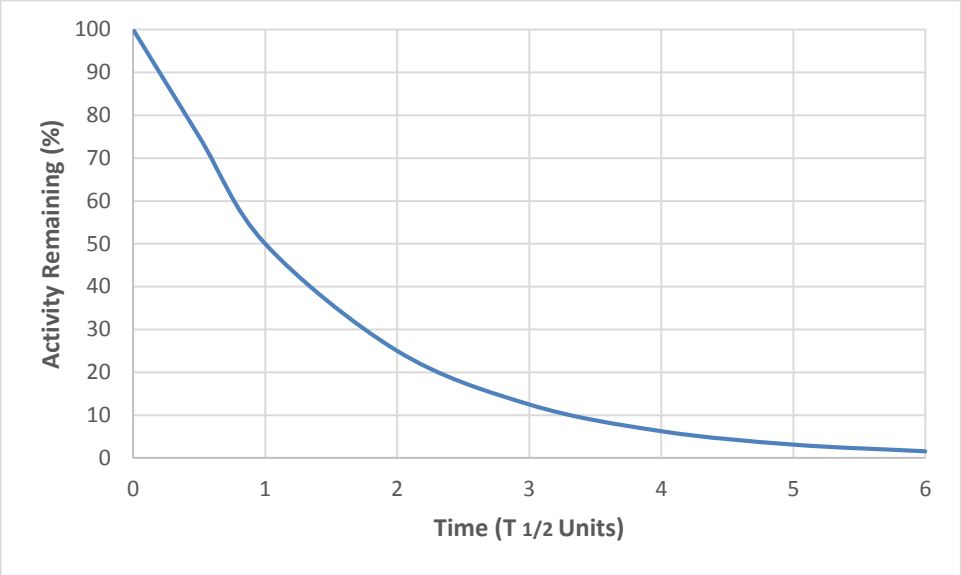


Figure 3.2: General Decay Curve; Activity as a Percentage of Initial Activity Plotted Against Time in Units of Half-Life (plot on linear graph) [26]

Depending on lesion size, the separation between wires varied (≤0.5-1.0 cm), and wires were placed nominally in one to four parallel lines, however wires were frequently implanted in off-set patterns (irregular, non-parallel). Wires were generally embedded subcutaneously/submucosally however in larger lesions the wires were implanted throughout the lesion in layers. Wires were implanted using a 16 mm gauge needle with a stylette. The treating veterinarian implanted the wires manually. Radiation therapy treatment computer planning software was not used in any of the treatment applications hence a record of dose distribution is not available. Following recovery from general anaesthesia, the horse was placed in an isolation stall. The owners were warned of the dangers of radiation exposures and given care instructions once the horse was discharged. Care instructions included the following advice:

- The radioactivity rapidly declines within a week of implantation
- The remaining gold is inert and may remain or be extruded
- The level of radiation is small and poses no risk to humans if proper precautions are taken

- Handlers should avoid remaining within 1 m of the implanted area during the first week except for routine feeding and care and,
- The maximum radiation effect occurs within 3-4 weeks.

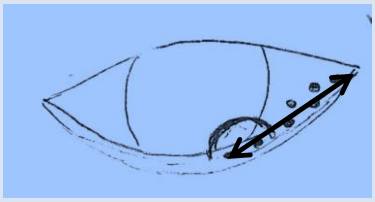
3.4.4 GOLD-198

Gold-198 emits high energy beta particles (0.96 MeV maximum) and gamma rays (0.412 MeV); the gamma rays being the useful component of the emitted radiation. [27] The unwanted β particles are filtered by a platinum sheath (encasing the gold). This process makes gold-198 highly suitable for permanent implantation. [19] The half-life of gold-198 is comparatively short (94.4 hours ~ 2.70 days), again adding to its suitability and allowing patients to be handled in a relatively short time. [28] Beta particles are absorbed superficially (a few millimetres within the tissue) and require minimal radiation precautions. Comparatively, gamma emissions penetrate deeply and require significant radiation protection to operators and the general public. The seeds/wires are considered non-hazardous once completing 10 half-lives (27 days) as the level of radiation emitted is equivalent to background radiation levels. [26]

3.4.5 INTERPRETING THE RETROSPECTIVE DATA

For each treatment case, the criteria for selection of cases as defined in Table 3.1 was evaluated and a series of measurements and assumptions made in order for there to be a standardised approach to the computer replicated modelling of treatments. Table 3.3 defines the measurements taken and their definition for ease of interpretation.

Table 3.3: Measurements and Definitions

Term	Definition	Units
50 Gy Structure	Geometrical representation of the treatment volume (in this case, area covered by 50 Gy created in BrachyVision™	cm^3
Estimated Diameter	Diameter of implant measured (by researchers) from each hand-drawn schematic diagram. Diameter was equated to the largest implant dimension measured. 	cm
Computer Calculated Equivalent Sphere Diameter for 50 Gy volume	Diameter of a sphere with same volume as the structure as calculated by computer software	cm
Estimated Volume	Volume calculated using $\mathbf{V = \frac{\pi d^3}{6}}$ In this case the diameter (d) measurement is the Estimated Diameter	cm^3
Computer Calculated Volume for 50 Gy Structure	50 Gy structure volume for each treatment	cm^3
Computer Calculated Mean Dose for 50 Gy Structure	50 Gy structure mean dose for each treatment	Gy
Computer Calculated Minimum Dose for 50 Gy Structure	50 Gy structure minimum dose for each treatment	Gy
Computer Calculated Maximum Dose for 50 Gy Structure	50 Gy structure maximum dose for each treatment	Gy
Computer Calculated 75 Gy Maximum Dose for 50 Gy Structure	75 Gy maximum for 50 Gy structure for each treatment	Gy
Computer Calculated 100 Gy Maximum Dose for 50 Gy Structure	100 Gy maximum for 50 Gy structure for each treatment	Gy
Number of Wires	Number of ^{198}Au wires implanted per lesion (≈1.2 mm length)	-
Number of Wires (CLUSTERED)	Number of ^{198}Au wires implanted per lesion (≈1.2 mm length) at separations ≤0.5 cm	-
Number of Wires (PLANAR)	Number of ^{198}Au wires implanted per lesion (≈1.2 mm length) at separations of 1.0 cm	-
Number of Wires in 1 Line Arrangements	Number of ^{198}Au wires implanted per lesion (≈1.2 mm length) in a single line	-

Number of Wires in 2 Line Arrangements	Number of ^{198}Au wires implanted per lesion (≈1.2 mm length) in 2 parallel lines	-
Number of Wires in 3 & 4 Line Arrangements	Number of ^{198}Au wires implanted per lesion (≈1.2 mm length) in 3 and 4 parallel lines	-
Number of Wires in Off-Set Arrangements	Number of ^{198}Au wires implanted per lesion (≈1.2 mm length) in an 'off-set' pattern (not in line)	-

3.4.6 TREATMENT MODELLING AND SOURCE MODELLING

Modelling was carried out using a computed tomography (CT) dataset of a horse head (cadaver) as provided by an equine clinic in the UK (Figure 3.3). Medical records indicated lesion location, wire placement and laterality which were all transferred to the dataset. The dataset was pre-processed for planning by adding contouring to identify regions-of-interest including; the retina, lens, cornea, globe and underlying bony anatomy. The dataset represented contiguous 3 mm scans of the horse head.

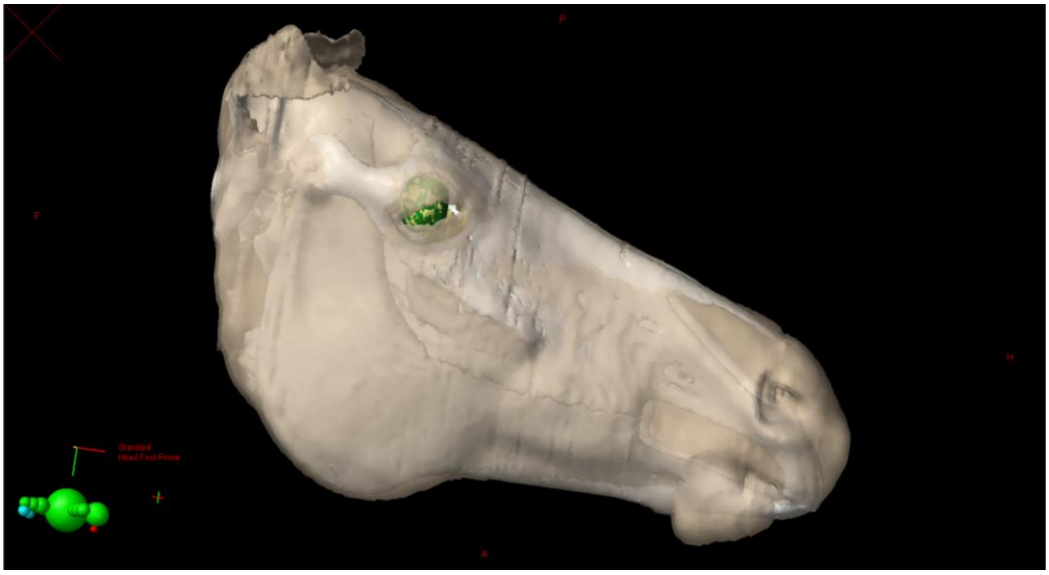


Figure 3.3: Treatment Modelling Cadaver CT Dataset

Radioactive source modelling dosimetry was configured in the BrachyVision™ System and adapted for the gold-198 radioactive source properties. Source modelling properties were based on dosimetry standards for gold-198 as reported by Dauffy *et al* (2005).[29] Data extracted from Dauffy *et al* included; general source model properties, anisotropic values and scatter function values (Figures 3.4, 3.5 & 3.6). Planning of cases occurred

twice for quality assurance purposes. Planning was performed by the student, an experienced Australian Radiation Therapist (registered by the Australian Health Practitioner Regulation Agency - AHPRA). Each treatment was replicated using Brachyvision™. Doses to the volume and critical structures were reviewed on an individual basis and analysed through the use of dose-volume histograms (DVH) for more detailed plan review. Initial planning was ratified by a second plan developed by the same planner to ensure the method and source modelling outcomes were accurate. A Radiation Oncologist (FRANZCR) (researcher on team) also ratified planning methodology including isodose analyses methods, tolerance doses to OARs and overall quality assurance parameters.

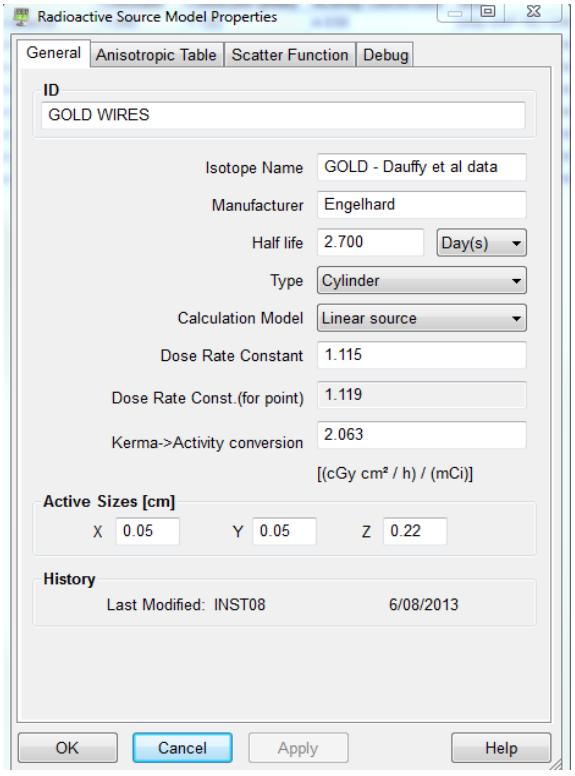


Figure 3.4: General Source Model Properties [29]

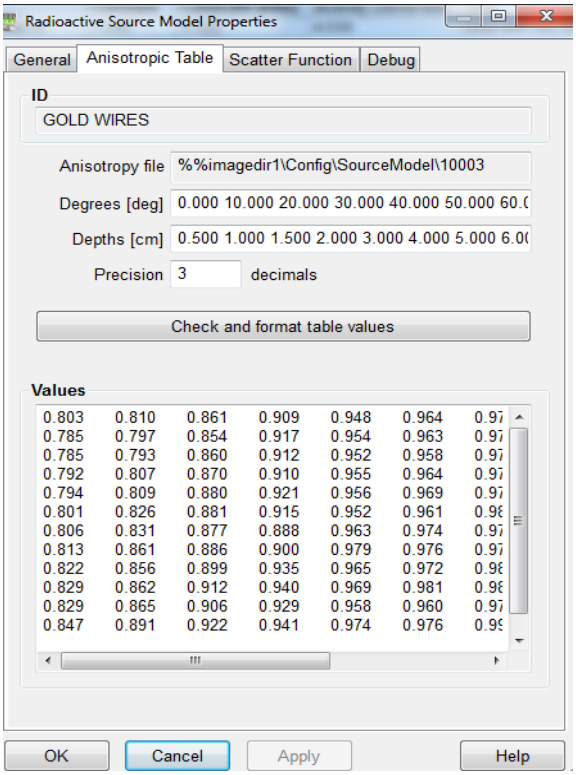


Figure 3.5: Anisotropic Table [29]

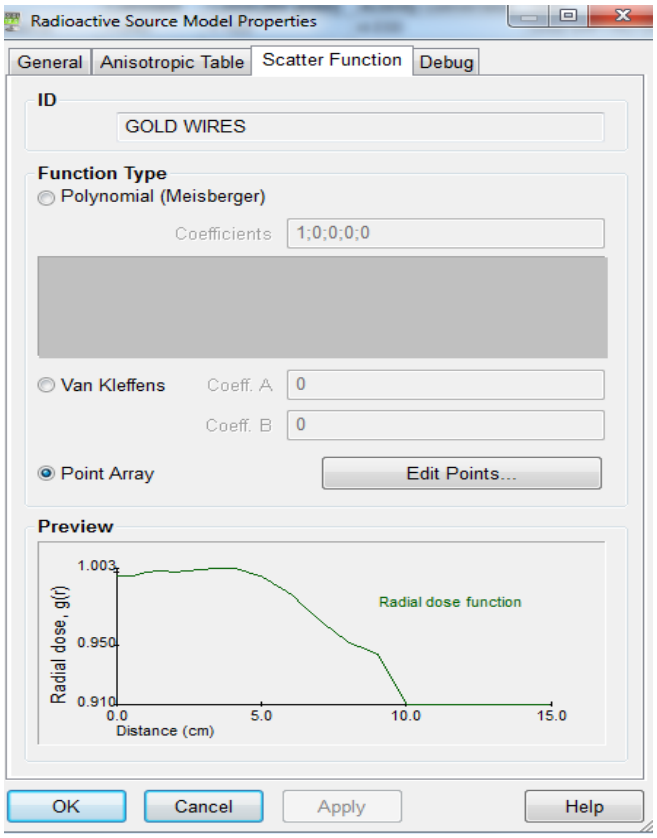


Figure 3.6: Scatter Function [29]

3.4.7 ANATOMICAL LESION LOCATION

The anatomic locations of the lesions were identified in one of two ways;

1. Where the medical records provided specific written information identifying the anatomical location of the lesion, this was recorded as the treatment site;
2. Where the medical records did not provide written confirmation of anatomic lesion location but provided diagrams of treatment sites and where it was considered reasonable to make an informed judgement, lesion location was established by the researchers through the use of the schematic diagrams. The sites were identified by Researcher 1 (Radiation Therapist – Yolanda Surjan) and Researcher 2 (Radiation Oncologist – Associate Professor Chris Milross) separately and ratified upon completion (blind study). No discrepancies in location were identified and all lesion locations were ratified.

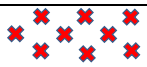
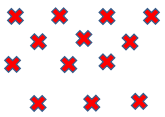
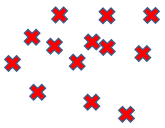
3.4.8 Distance between Implanted Wires

Records of implantation geometry and placement were available via the free-hand schematic representations in the medical records. The distance between each wire implant was classified as ≤0.5 cm or 1.0 cm based on information supplied by the treating veterinarian and analyses of the placement of wires on schematic diagrams in conjunction with known equine eye dimensions.

3.4.9 Wire Number and Implant Arrangement

The number of implanted wires was recorded numerically within the medical notes as well as represented in the schematic diagrams by a '0' or 'X' symbol. The number of implanted wires ranged from between one and 15. Wires were arranged in one of five different configurations; one line, two parallel lines, three parallel lines, four parallel lines and in an off-set configuration (irregular, non-parallel) (Table 3.4).

Table 3.4: Wire Configuration

Configuration	Example
One Line	
Two Parallel Lines	
Three Parallel Lines	
Four Parallel Lines	
Off-set (irregular, non-parallel)	

Wire implant = ✖

To further categorise the treatment plans for ease of analyses, the wire arrangements were classified in terms of the distances they were implanted and their pattern. For those

arrangements where the wires were placed in straight and parallel lines, (n=17) and at distances of 1.0 cm from one another, these were grouped together and referred to as 'planar arrangements'. For those that were implanted at distances of ≤0.5 cms (n=58), these were grouped together and calculated at ≤0.5 cm spacing and referred to as 'clustered'. Those that were implanted in an off-set pattern (irregular, non-parallel) at any distance (≤0.5-1.0 cm) were referred to as off-set (Figures 3.7, 3.8 & 3.9).

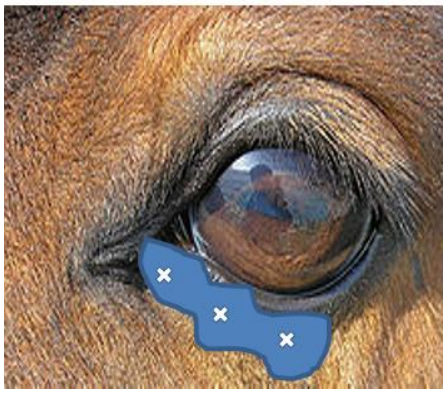


Figure 3.7: Planar Implants (@1.0 cm)

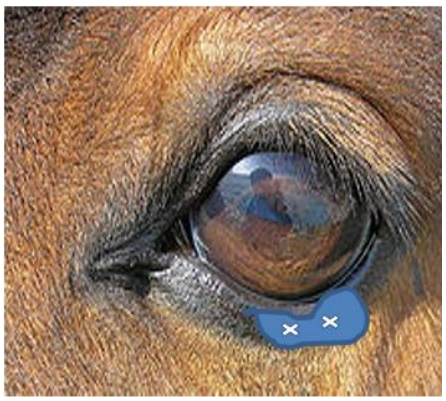


Figure 3.8: Clustered Implants (@≤0.5 cm)

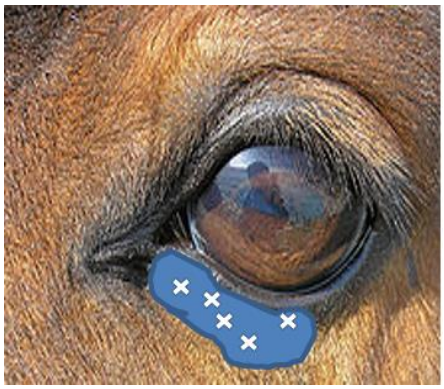


Figure 3.9: Off-Set Implants (Irregular @<0.5-1.0 cm)

3.4.10 LESION SIZE

Information relating to the lesion size was identified through the free-hand schematic representations in the medical records (Figure 3.10). Lesion size or volume was not recorded numerically for any of the lesions within the medical records. Lesion size was calculated objectively by evaluating the number of wires implanted and accounting for the known dimensions of the standard equine eye (36 to 51 mm in the horizontal plane from lateral canthus to medial canthus and 25 mm at its widest vertical dimension) (Figure 3.11). [30] Wire arrangements were examined and the size of the lesion estimated based on whether they were considered clustered or planar arrangements.

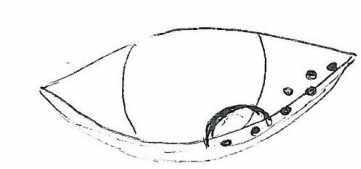


Figure 3.10: Schematic Diagram: Implantation Geometry

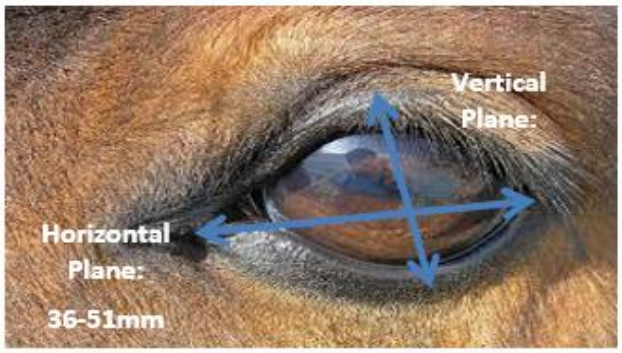


Figure 3.11: Dimensions of the Equine Eye [30]

3.5 BRACHYTHERAPY CONVENTIONS FOR INTERSTITIAL THERAPY

3.5.1 DOSE DISTRIBUTION IN INTERSTITIAL THERAPY: PRESCRIPTION AND THE TREATED VOLUME (TV)

The Treated Volume (TV) is the tissue volume that, based on the radioactive implant, receives at least a dose as specified by the Radiation Oncologist deemed necessary to achieve either tumour eradication or palliation. [1, 31] The isodose surface which encompasses the Treated Volume (in the case of this study, the SCC lesion), equals the value of which is the Minimum Target Dose. The isodose surface which the treatments aimed to cover the Treated Volume equalled 50 Gy (Minimum Target Dose). [1, 31]

3.5.2 HIGH-DOSE REGION (MAXIMUMS)

The dose distribution in interstitial therapy is non-homogenous. It includes very steep dose gradients and in particular, areas of exceedingly high dose surrounding each source. The dose decreases with the distance from the source. [31] In order to correlate radiation dose with late damage, the high dose regions around sources need to be assessed. It must be noted that the exact tolerance dose and volume for interstitial therapy are not known precisely. [31] In lieu of this knowledge and in keeping with the need to report and make comparisons between treatments, the European Society for Radiotherapy and Oncology (ESTRO) [31] guidelines have created an agreement for reporting on high dose volumes based on ICRU-58 recommendations. [1] ESTRO reporting in brachytherapy suggests that a dose of approximately 100 Gy is likely to be

a significant determining factor for later effects. Therefore, in those patients who receive 50-60 Gy Minimum Target Dose or 60-70 Gy Mean Central Dose (MCD – arithmetic mean of the local minimum doses between sources in the central plane/s), 100 Gy corresponds approximately to 150% of the MCD. It is recommended in ICRU-58 that the size of the region that receives more than 150% of the MCD is reported. [1, 25] For the purpose of this study and in lieu of the Mean Central Dose data, the high-dose volumes are reported in relation to the prescribed dose (Minimum Target Dose); that is, a dose equating to 150% (75 Gy) and 200% (100 Gy). It must be noted that whilst this study reports on these values for the purposes of equating dose reporting to human ICRU recommendations, the biologically significant volume for Maximum Doses is not pre-defined. That is, a pre-determined biologically significant volume (cm^3) is not provided by ICRU recommendations for brachytherapy treatments as is provided for external beam radiation therapy.

3.5.3 Low-Dose Region (Minimums)

A low-dose region (where the dose is less than 90% of the prescribed dose) which occurs within the Treated Volume should in all instances be reported in order to better correlate dose distribution with local recurrence. [25, 31] In occasions where the Treated Volume is included within the prescribed dose (or Minimum Target Dose), the occurrence of a low-dose-region is uncommon. The series of cases reported on within this study are planned with the aim of dosing the Treated Volume to 50 Gy, hence any low-dose regions occurring within any of the plans in this study would be an exception but not unfeasible.

3.5.4 Organs at Risk (OARs)

Organs at risk (critical normal structures), are normal structures that as a result of their proximity to the target volume or their radiosensitivity, may influence prescribed doses or the treatment planning approach. [2] The maximum dose of radiation that a tissue will tolerate (tolerance dose) varies with type and amount of tissue. The concept of radiation tolerance of normal tissues poses definite limits to the amount of dose and the method by which the dose is delivered to treat tumours. [21] The OARs identified in this research include; the lens, cornea and retina (Figure 3.12). The tolerance for structures in the eye

varies vastly in human medicine. The most radiosensitive of the structures is the lens. [21] The amount of lens (volume) and the dose delivered dictate the probability of developing cataracts. A clinically significant cataract requires doses of 5 Gy or more to be induced, however, cataracts have been observed at doses as low as 2 Gy in humans. [21] Direct radiation injury to the cornea is difficult to distinguish from indirect injury which may result from dry eye syndrome as a result of radiation exposure, tolerance limits are established at 50-60 Gy. [32] Radiation-induced effects (doses of 30-50 Gy in 4-5 weeks) on the cornea are normally temporary and include local irritation and lacrimation. [21] Dry eye (late effect) may result however if the cornea/lacrimal gland is irradiated to between 50-60 Gy. Vascular late effects are observed in the retina at doses greater than 50 Gy. It expresses RT toxicity as a late reacting tissue. [13] The sclera, being vascular, is a relatively radioresistant structure, that is rarely adversely affected, and doses greater than 100 Gy are required to induce necrosis. [21]

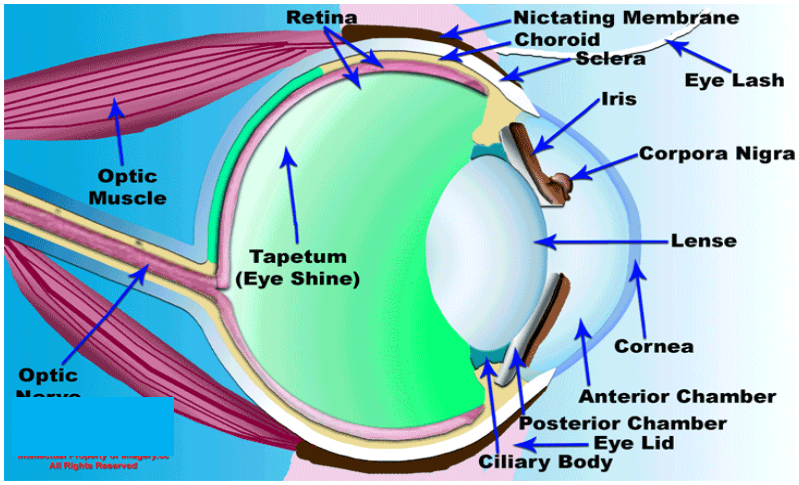


Figure 3.12: Equine Eye Anatomy [33]

Accepted tolerance doses reported in the literature vary for ocular organs. The tolerance doses chosen for this research are adapted from a series of human sources including Bentel (1989)[34] and Washington & Leaver (2010).[35] These sources are supported by a more recent critical review of ocular risks from orbital and periorbital radiation therapy (Jeganathan *et al*, 2011).[36] The lower tolerance limit for each organ (*) represents tissue

dose associated with a 5% injury rate within 5 years. The upper tolerance limit for each organ (**), represents tissue dose associated with a 50% injury rate within 5 years (Table 3.5). It must be noted that recommended limits are not available for horses.

Table 3.5: Tolerance Doses for OSCC/POSCC Structures [34-36]

	Tolerance Limits		
Organ	**(Lower) TD 5/5 (Gy)***	**(Upper) TD 50/5 (Gy)****	**Whole/Partial Organ**
Lens of eye	5	12	Whole
Retina	55	70	Whole
Cornea	50	60	Whole

***TD 5/5 (Gy) = tissue dose associated with a 5% injury rate within 5 years**

****TD 50/5 (Gy) = tissue dose associated with a 50% injury rate within 5 years**

3.5.5 Assessment of Plans

Criteria for assessment included evaluation and recording of; Mean, Minimum and Maximum Doses for the 50 Gy Structure Volume and OAR's including the related computer-calculated volume (cm^3 of tissue receiving recorded dose). Additionally, for the purposes of comparisons, the computer-calculated diameter (referred to as equivalent sphere diameter) for each 50 Gy Structure was also recorded. The criteria by which the plans were assessed allowed the researchers to identify how many plans met the 50 Gy prescription, how many were outside the volume (and hence overdosed) and how many did not encompass the pre-set volume and hence were under-dosed misses. OAR dose analysis was also conducted and comparisons of doses to these normal organs at risk were made against known tolerance levels.

3.5.6 Statistical Analysis

The results were analysed using linear regression and linear correlation to investigate relationships between treatment variables (wire number, arrangement and distance) and treated volumes and tested for significance at the 95% level (0.05). Pearson's Correlation

was used to show the linear relationship between two sets of data. This was used as the expected relationship between the variables of interest is linear. Other analysis performed investigated trends in lesion ***estimated*** diameter and volume in comparison to the ***treated*** diameter and volume. OAR maximums and overall maximums were also analysed statistically. Computer-generated DVHs were analysed and reported upon.

3.6 RESULTS

During the 9 year period, a total of 85 SCCs in 75 horses were diagnosed involving an ocular/periocular location. The eyelid was the most commonly affected site (n=40) with the third eyelid (n=8), palpebral conjunctiva (n=3), ventral conjunctiva (n=2), medial canthus (n=12), lateral canthus (n=9) and limbal conjunctiva (n=3) also involved. The specific anatomical site was undeterminable in eight of the cases. Of the 75 horses with SCC, 8 (11%) had two SCC lesions at initial diagnosis and one horse had 3 lesions, the remaining cases had a singular lesion.

3.6.1 FOLLOW-UP

Recurrence was scored as any lesion that presented in the initially affected eye and/or close to the scar as reported by owners or written in the medical records. Follow-up information was obtained for only 20 (27%) of the 75 horses. Overall, eight had recurrence and one reportedly 'did not respond to treatment'. Three recurred 3 years post-treatment, two recurred 6 years post treatment. Time of recurrence was not provided for the remaining three horses. Recurrence occurred in the eyelid in n=2 cases, the canthus, conjunctiva and eye socket in three separate cases, the remaining four cases did not record location. No reportable recurrence was observed in eleven horses (n=11) between 5-9 years following treatment. Tumour location for horses with no recurrence included eyelid (n=6), canthus (n=1) and third eyelid (n=1). No site was recorded for the remaining n=3 cases without recurrence.

Of the 20 horses with follow-up, only 12 of these cases provided enough information within the medical notes for treatment to be replicated using Brachyvision, of these, four had recurrences, one 'did not respond to treatment' and seven had no reportable recurrences. The collection of follow up data was between June and October 1, 2012.

3.6.2 TREATMENT DIMENSIONS (ESTIMATED DIAMETER/VOLUME & COMPUTER CALCULATED DIAMETER/VOLUME)

Comparisons were made between lesion size as depicted in schematic diagrams (diameter) and the computer generated equivalent sphere diameter. The relationship between the estimated diameters (lesion size as depicted in schematic diagram) and the computer calculated equivalent sphere diameters (as calculated by planning software for each treated volume), demonstrated a weak correlation (r=0.28) with a statistically significant trend (p=0.02) (Figure 3.13).

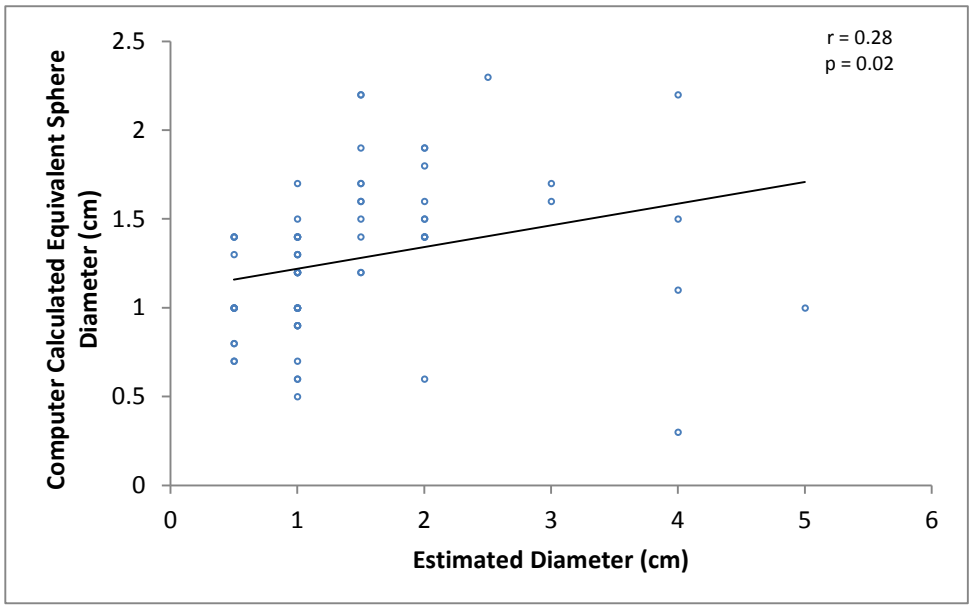


Figure 3.13: Variation between Calculated and Estimated Diameters (cm)

The Treated Volumes (lesions) required to receive 50 Gy were analysed and compared to the estimated volumes (calculated from the estimated diameters using $((4\pi r^3)/3)$ (where r is radius). There was a very low correlation (r=0.10) between volumes with no significant trend line (p=0.39), (Figure 3.14).

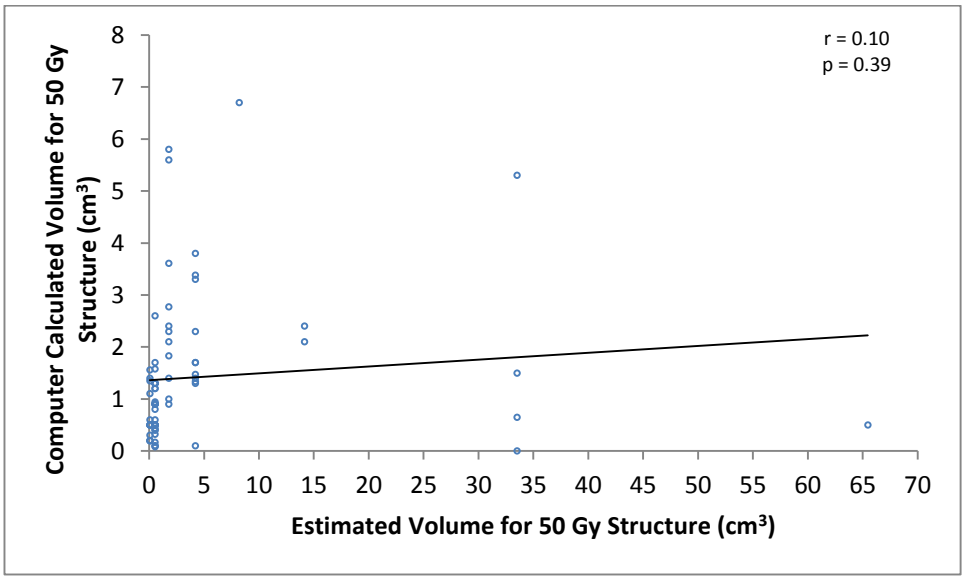


Figure 3.14: Variation between Calculated and Estimated Volume for 50 Gy Structure (cm^3)

3.6.3 Number of Radioactive Wires vs Estimated Diameter/Volume & Computer Calculated Diameter/Volume

As would be expected, there was a strong positive correlation (r=0.88, p=<0.0001) between the number of implanted radioactive wires and the computer calculated equivalent sphere diameter (Figure 3.15). The estimated diameter also increased with increasing number of wire implants (r=0.5, p<0.0001) (Figure 3.16). The computer calculated volume (cm^3) also showed a strong positive correlation (r=0.84, p<0.0001) between the number of wires implanted and volume (Figure 3.17). A weak positive correlation (r=0.28, p=0.01) was noted between the number of wires used and the estimated volume for the 50 Gy structure (Figure 3.18).

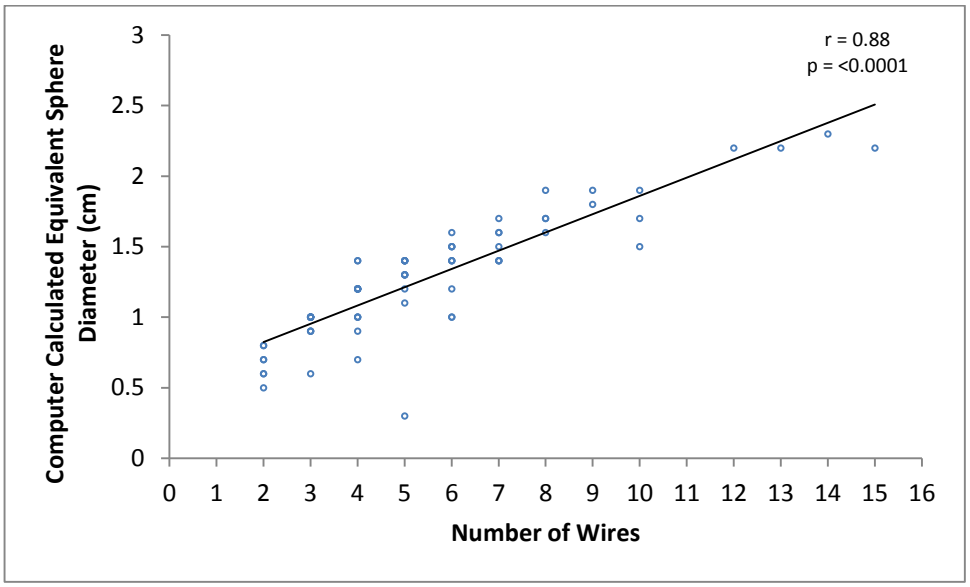


Figure 3.15: Number of Wires vs Calculated Equivalent Sphere Diameter (cm)

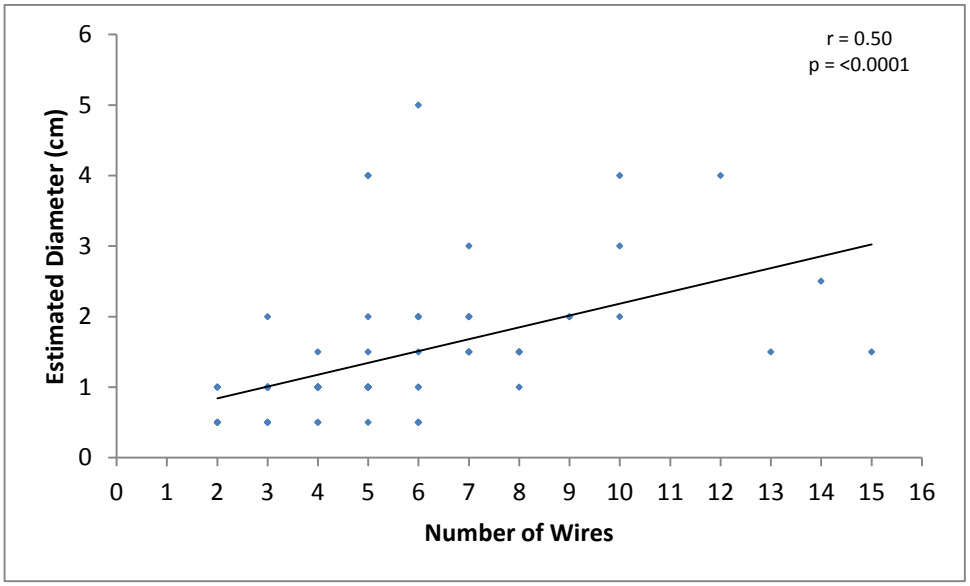


Figure 3.16: Number of Wires vs Estimated Diameter (cm)

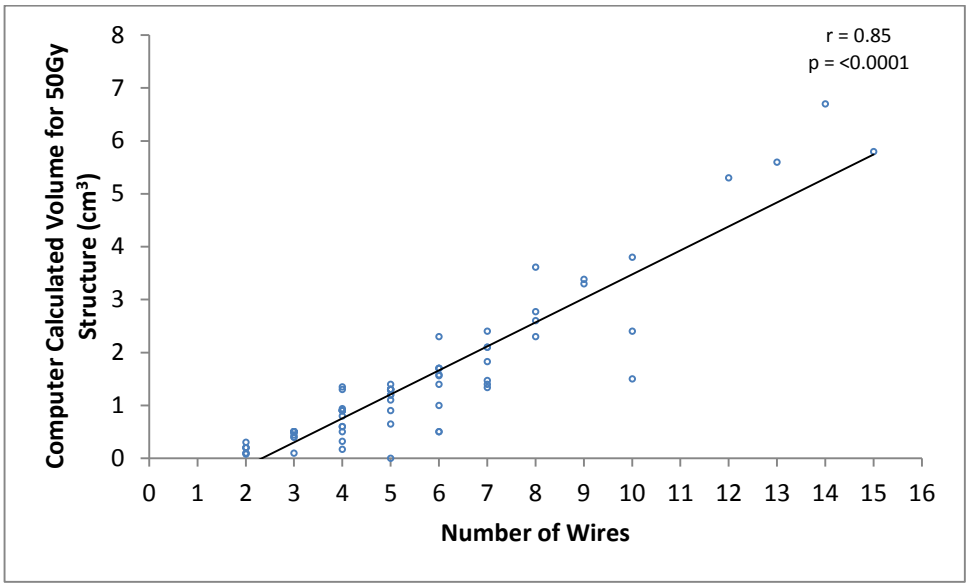


Figure 3.17: Number of Wires vs Computer Calculated Volume (cm^3)

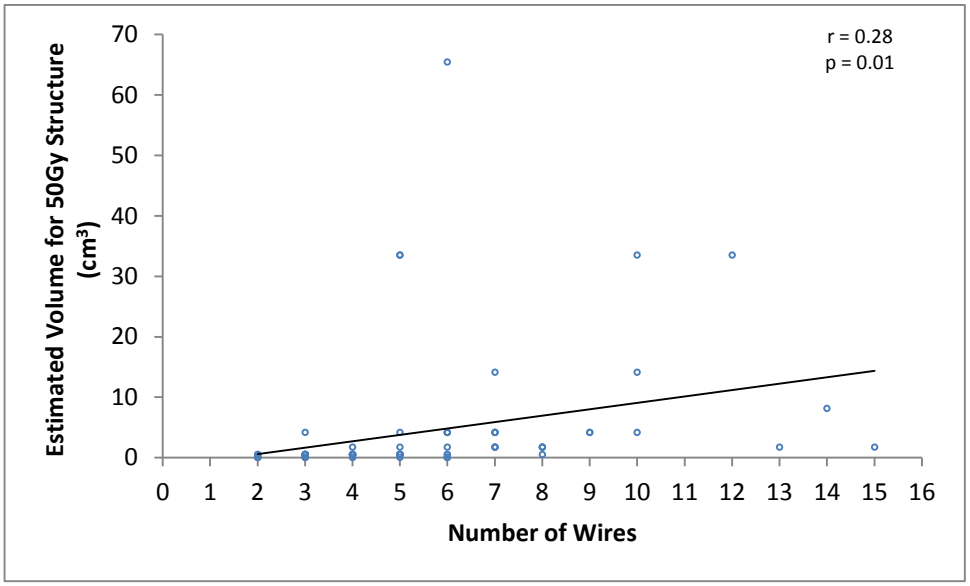


Figure 3.18: Number of Wires vs Estimated Volume (cm^3)

3.6.4 NUMBER OF RADIOACTIVE WIRES VS MEAN DOSE

No correlation was established between the number of wires and Mean Dose (Gy) for the 50 Gy Structure Volume (r = 0.02, p = 0.88) (Figure 3.19).

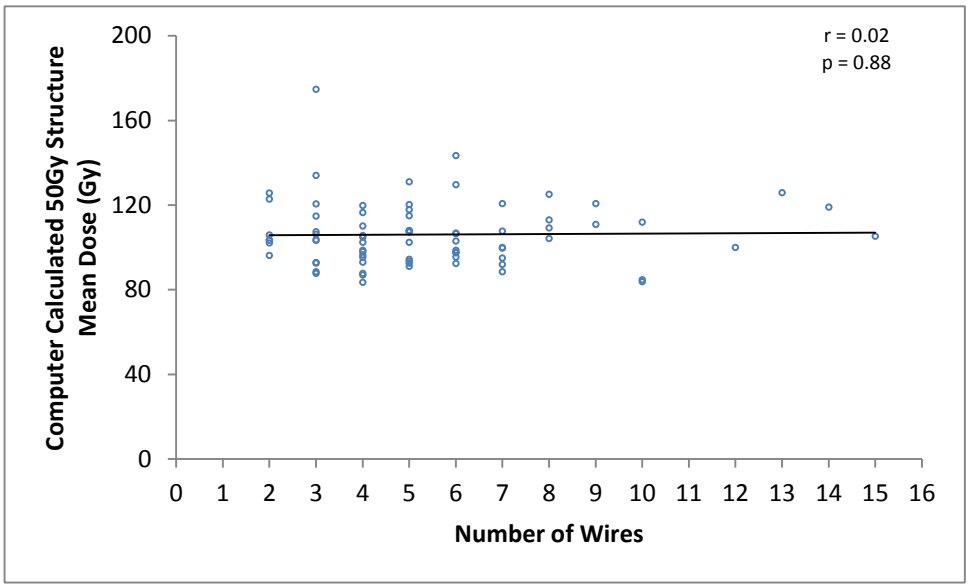


Figure 3.19: Number of Wires vs Calculated 50 Gy Structure Mean Dose (Gy)

3.6.5 NUMBER OF WIRES IN VARIED ARRANGEMENTS VS VOLUMES

For the 58 cases where the wires were implanted in a 'clustered' arrangement (≤0.5 cms apart), a strong positive correlation (r=0.96, p<0.0001) was established against the computer calculated 50 Gy Structure Volume (Figure 3.20). Seventeen cases had the wires implanted in a 'planar' arrangement (1.0 cm apart), these also demonstrated a strong positive correlation (r=0.96, p<0.0001)) (Figure 3.21).

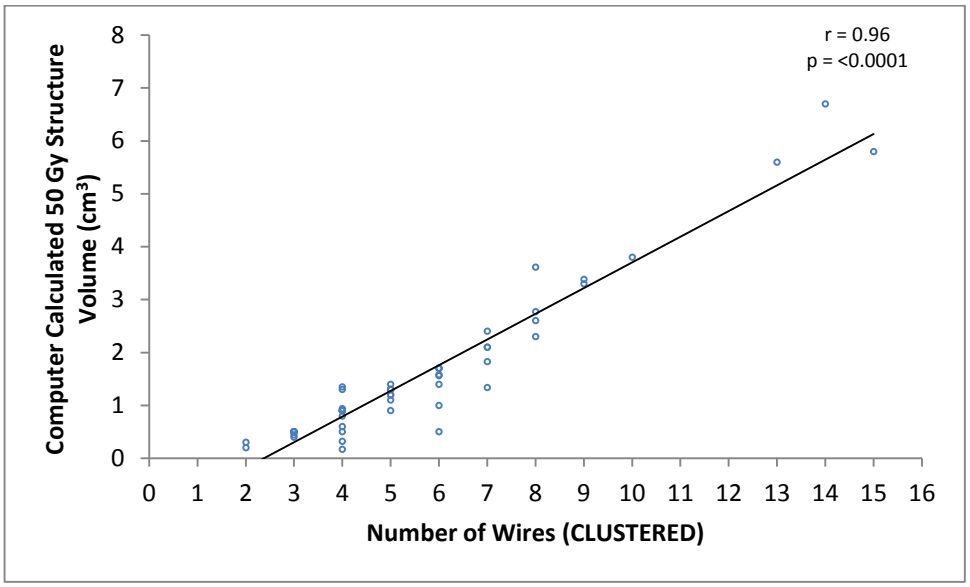


Figure 3.20: Number of Wires in a Clustered Arrangement (≤0.5 cms apart) vs Computer Calculated 50 Gy Structure Volume (cm^3)

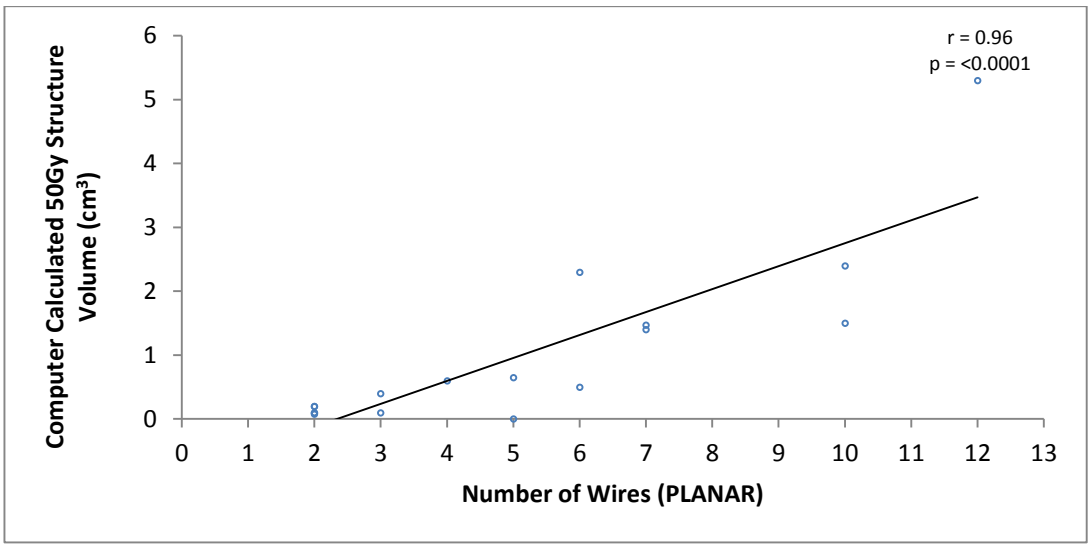


Figure 3.21: Number of wires in a planar arrangement (1cm apart) vs computer calculated 50Gy Structure Volume (cm^3)

Eighteen cases were implanted with the wires in a single line. A moderate positive correlation (r=0.47, p=0.048) was established with the computer calculated 50 Gy Structure Volume coverage (Figure 3.22). Analysis for the two line implants (25 cases) revealed a moderate to strong positive correlation (r=0.72, p<0.0001) (Figure 3.23). A high

positive correlation (r=0.96, p<0.0001) was identified for the implants using three and four line arrangements (11 cases) (Figure 3.24). Figure 3.25 illustrates 21 cases using off-set arrangements (irregular, non-parallel) and shows a highly significant correlation (r=0.96, p<0.0001).

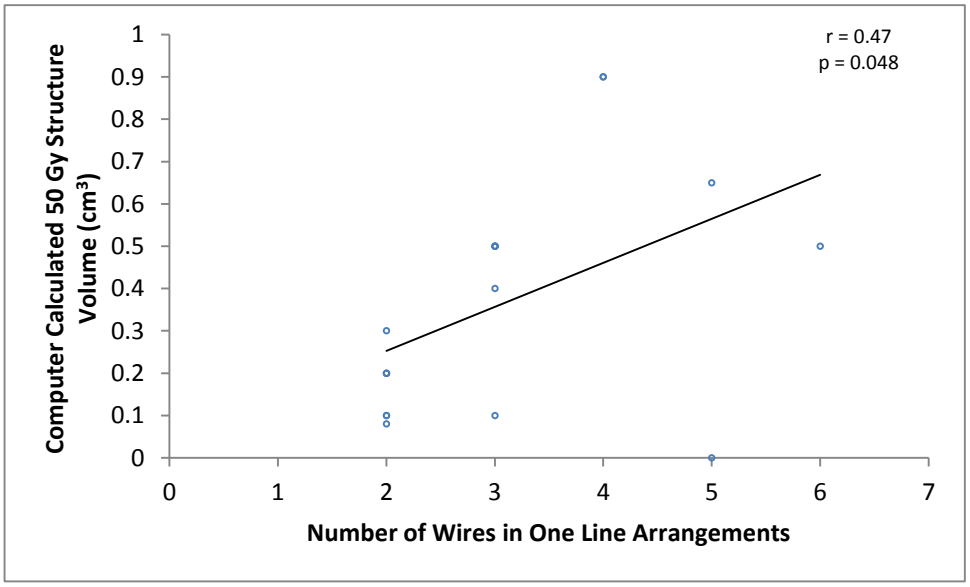


Figure 3.22: Number of Wires in One Line Arrangements vs Computer Calculated 50 Gy Structure Volume (cm³)

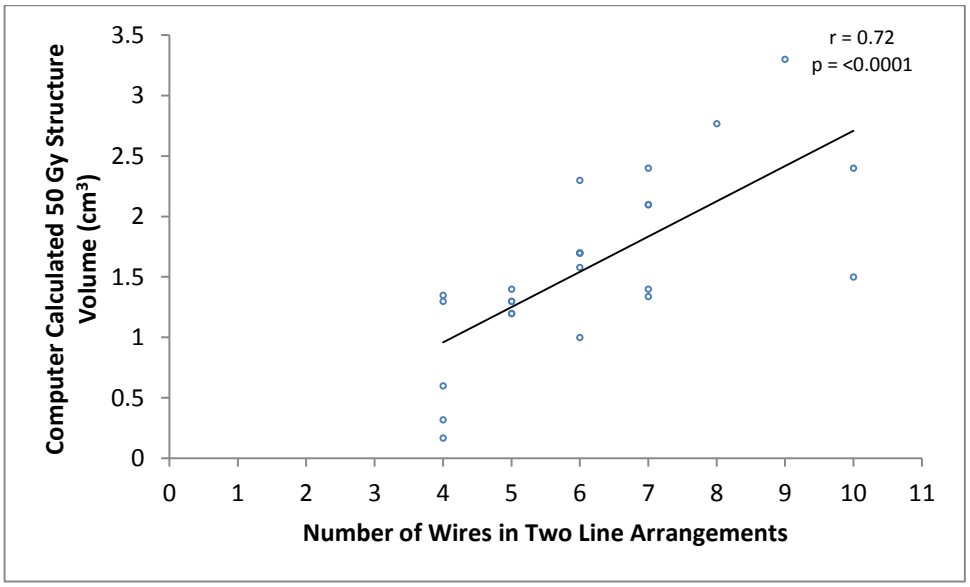


Figure 3.23: Number of wires in two line arrangements vs computer calculated 50 Gy Structure Volume (cm³)

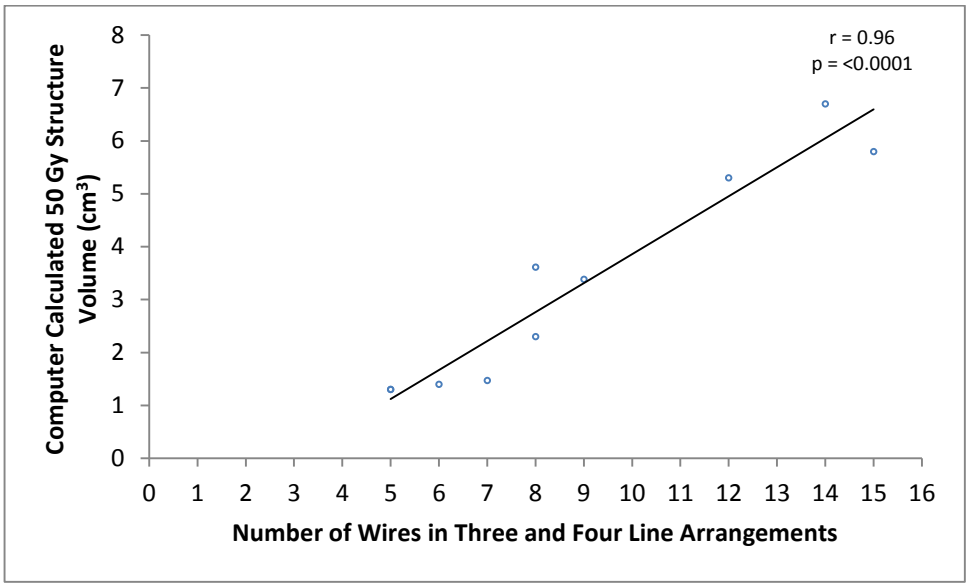


Figure 3.24: Number of Wires in Three and Four Line Arrangements vs Computer Calculated 50 Gy Structure Volume (cm^3)

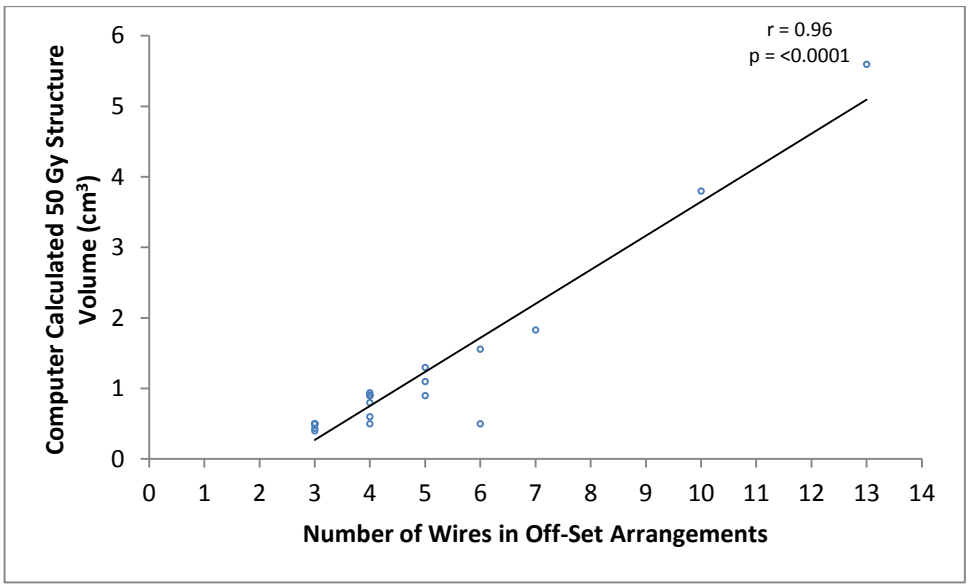


Figure 3.25: Number of Wires in Off-Set Arrangements vs Computer Calculated 50 Gy Structure Volume (cm^3)

3.6.6 Wire Arrangements: Diameter and Volume Comparisons

Statistical analysis was conducted to ascertain the contribution wire arrangements have on achieving the intended diameter as per the schematic diagrams. The analysis was categorised according to the known used arrangements; 1 line, 2 line, 3 or 4 line and off-

set. For each grouping, the diameters (estimated) were compared to the computer calculated equivalent sphere diameters. The volume (computer calculated for the 50 Gy Structure) was also compared to the estimated volume (as derived from the estimated diameter) for each lesion.

Of the 18 cases where the wires were arranged in a single line, no correlation (r=0.003, p=0.99) was established between the estimated diameter (intended treatment diameter) and the computer calculated equivalent sphere diameter (Figures 3.26 & 3.27). Equally, when comparing the computer calculated volume for the 50 Gy Structure Volume to the calculated volume (based on estimated diameter), a trend was not identified and only a weak positive correlation was established (r = 0.07, p=0.79).

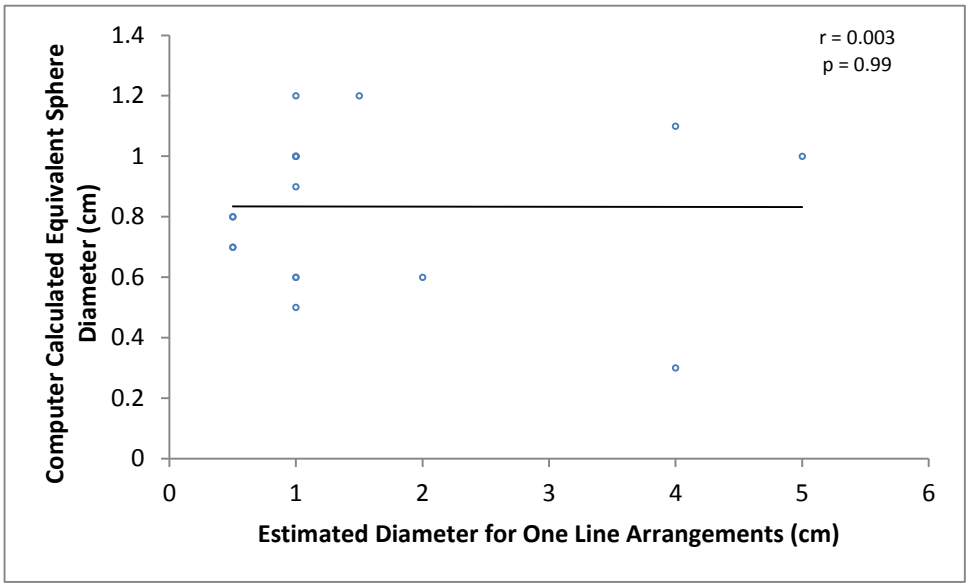


Figure 3.26: Estimated Diameter for One Line Arrangements vs Computer Calculated Equivalent Sphere Diameter for One Line Arrangements (cm)

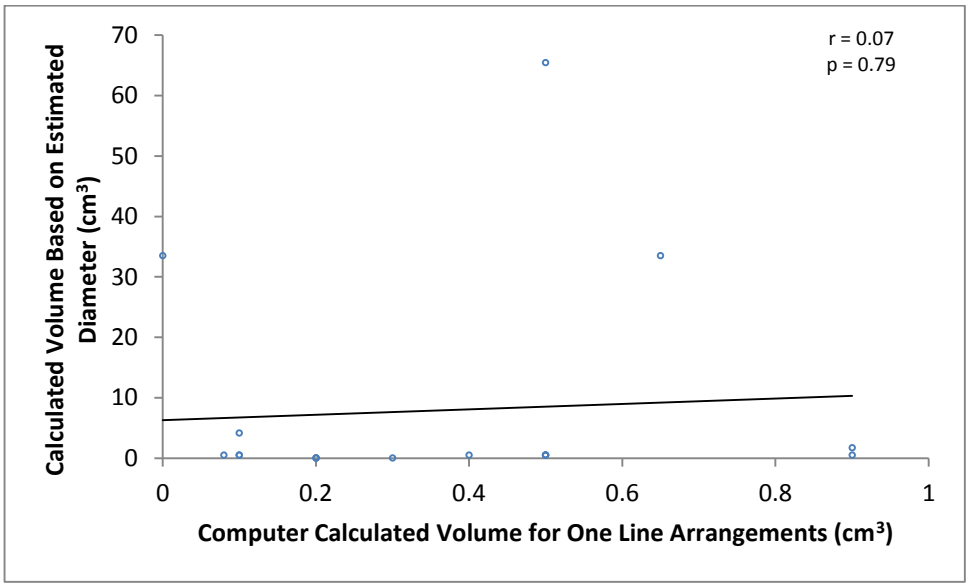


Figure 3.27: Computer Calculated Volume for One Line Arrangements vs Calculated Volume Based on Estimated Diameter (cm^3)

Two-line arrangements were used in 25 cases. When comparing estimated diameter and equivalent sphere diameter, a moderate positive linear relationship was clear (r=0.46, p=0.02) (Figures 3.28 & 3.29). However, in contrast, volume comparisons demonstrated a weak positive correlation (r=0.21, p= 0.31).

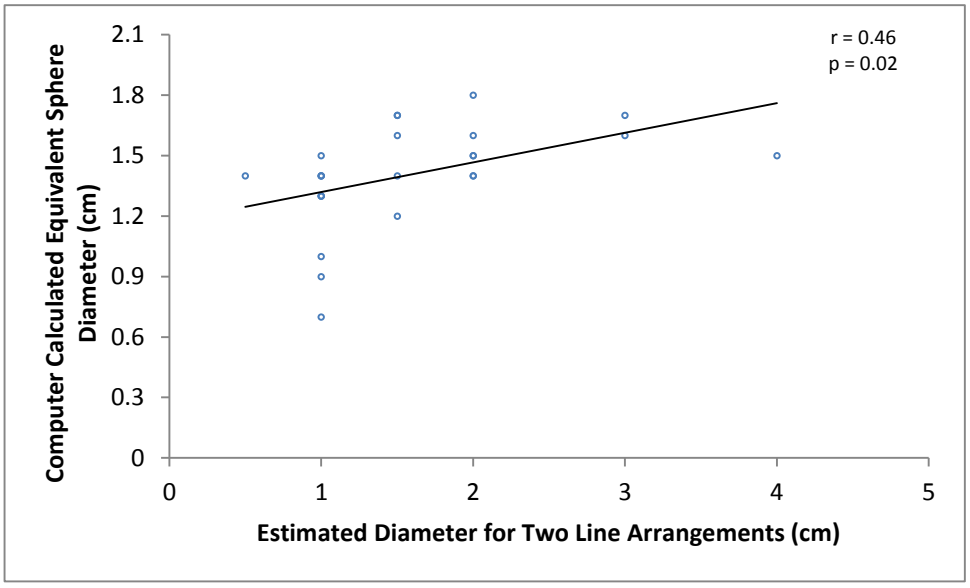


Figure 3.28: Estimated Diameter for Two Line Arrangements vs Computer Calculated Equivalent Sphere Diameter for Two Line Arrangements (cm)

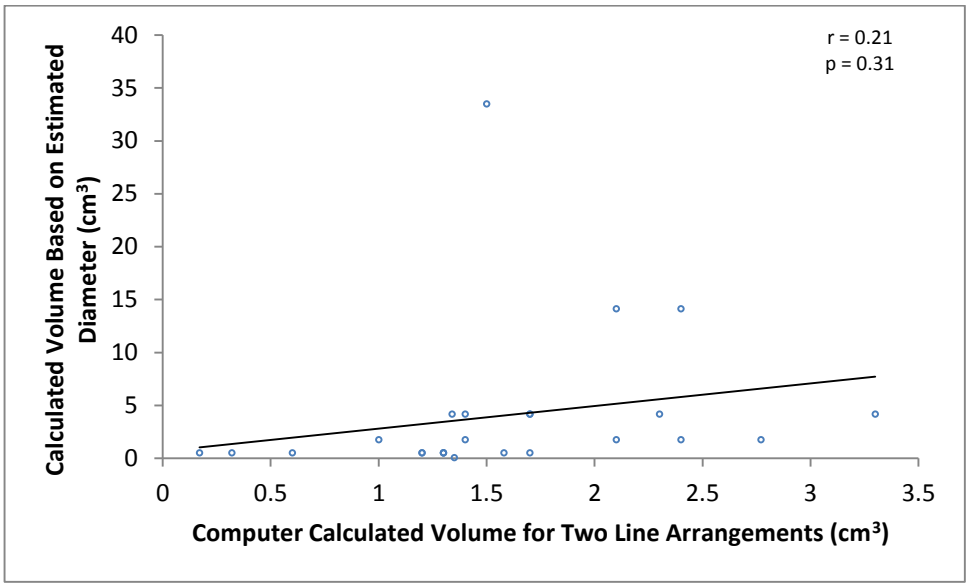


Figure 3.29: Computer Calculated Volume for Two Line Arrangements vs Calculated Volume Based on Estimated Diameter (cm^3)

Eleven cases were analysed to assess three and four line arrangement outcomes. Diameter comparisons demonstrated a moderate positive correlation (r=0.5, p=0.06) (Figures 3.30 & 3.31). A similar result (moderate positive correlation, though not significant) was identified when comparing volumes (r=0.46, p= 0.15).

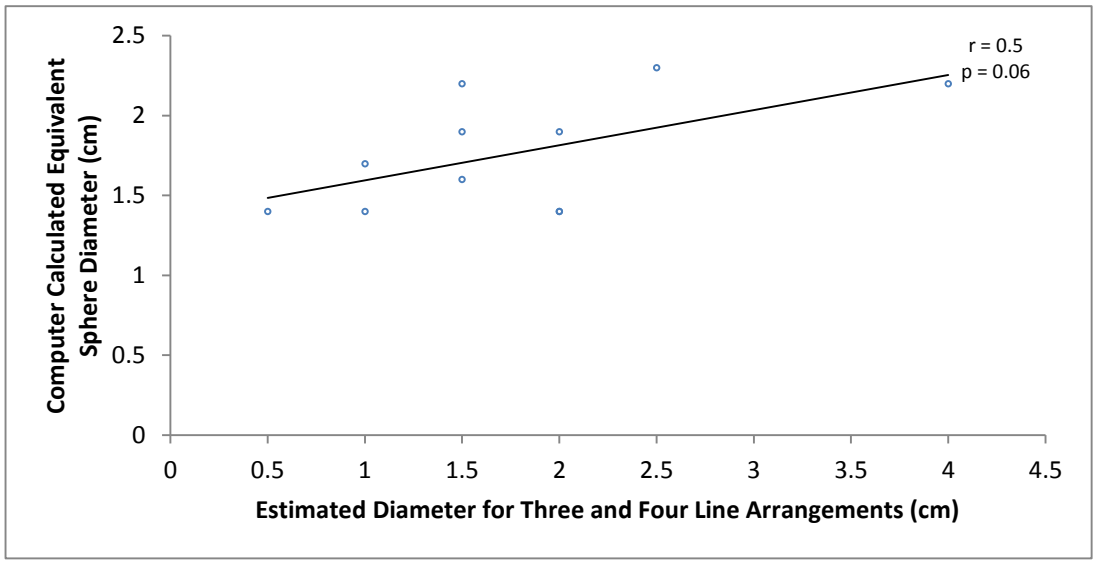


Figure 3.30: Estimated Diameter for Three and Four Line Arrangements vs Computer Calculated Equivalent Sphere Diameter for Three and Four Line Arrangements (cm)

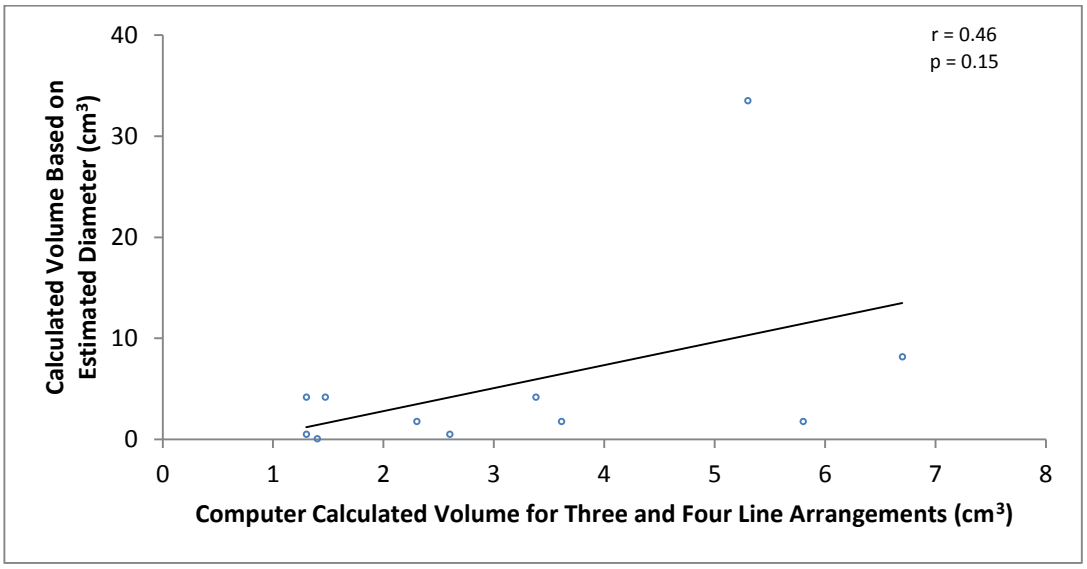


Figure 3.31: Computer Calculated Volume for Three and Four Line Arrangements vs Calculated Volume Based on Estimated Diameter (cm^3)

A total of 21 cases were treated with off-set arrangements. Estimated diameters and calculated equivalent sphere diameters demonstrated a trend (moderate positive relationship) (r=0.67, p=0.0008) (Figures 3.32 & 3.33). Volume comparisons demonstrated a strong positive linear relationship (r=0.73, p=0.0002).

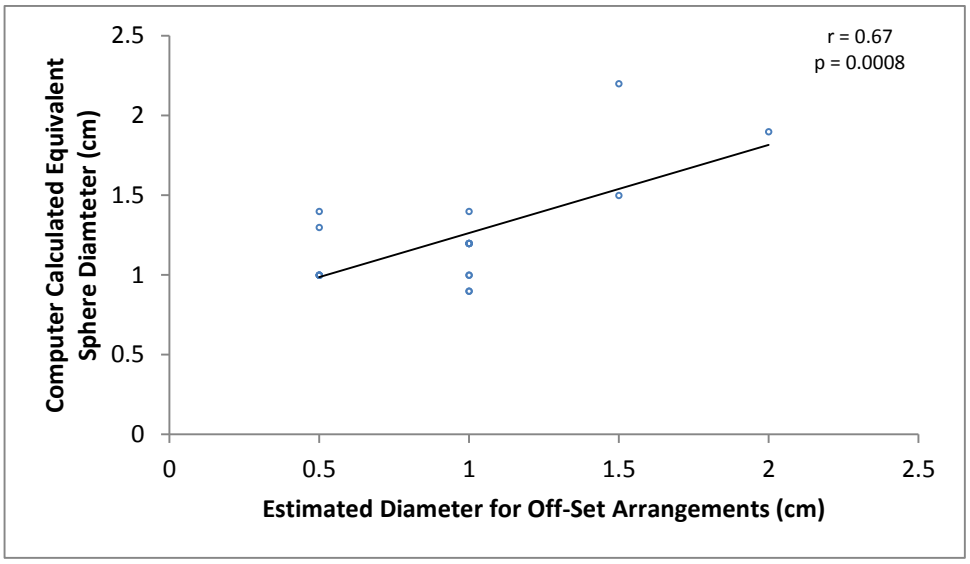


Figure 3.32: Estimated Diameter for Off-Set Arrangements vs Computer Calculated Equivalent Sphere Diameter for Off-Set Arrangements (cm)

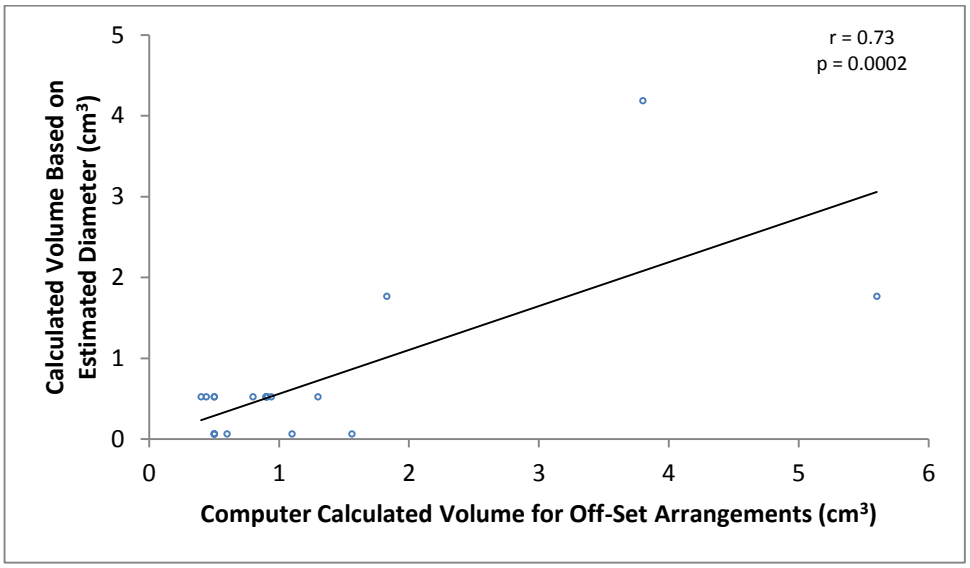


Figure 3.33: Computer Calculated Volume for Off-Set Arrangements vs Calculated Volume Based on Estimated Diameter (cm^3)

3.6.7 MAXIMUM, MEAN & MINIMUM DOSES

Whilst the exact tolerance dose and volume for interstitial brachytherapy are not yet known, guidelines provided by ESTRO in brachytherapy accept that a dose of 150% of the prescription dose (in this case 50 Gy) is significant in predicting late effects. For the purposes of this research and in view of the recommendation that a region that receives more than 150% of the prescribed dose should be reported (equivalent size), high-dose regions of 75 Gy (equivalent to 150%) and 100 Gy (equivalent to 200%) have been recorded for each treatment case. These correspond to the volume of tissue within which the maximums occur. It must be noted that all maximums occur within the prescribed volume.

As expected, the dose decreased with the distance from the source and the following significant maximums were recorded. Of the cases, 92% (n=69) reported a maximum of 75 Gy (150%) for a volume that ranged between 0-1.5 cm^3. The remaining 8% (n=6) received 75 Gy to a volume between 2.0-4.0 cm^3 (Figure 3.34). A maximum of 200% (100 Gy) occurred in a volume of between 0-0.5 cm^3 in 83% of cases (n=62) and between 0.6-2.4 cm^3 in 17% of cases (n=13) (Figure 3.35).

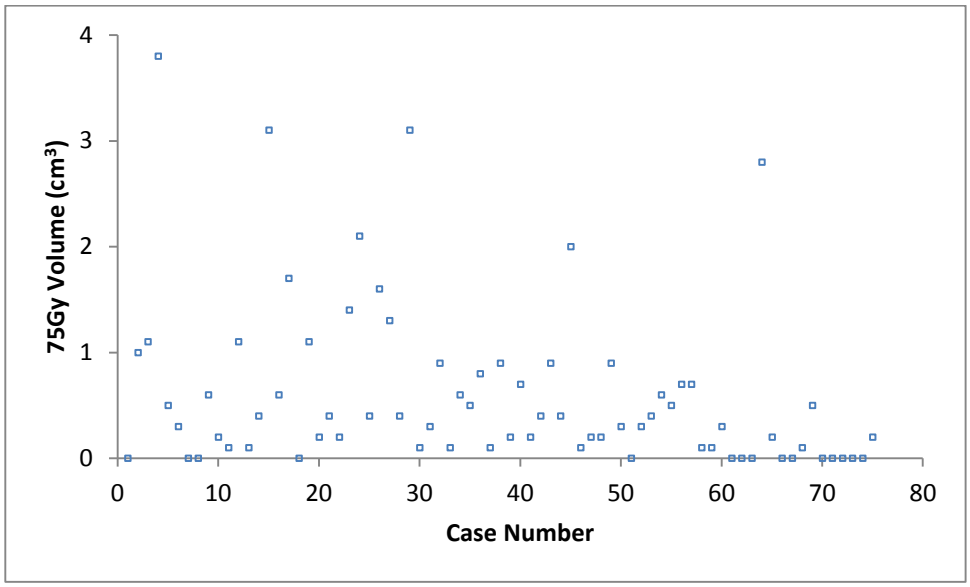


Figure 3.34: 75 Gy (150%) Maximum Volume for Cases (cm³)

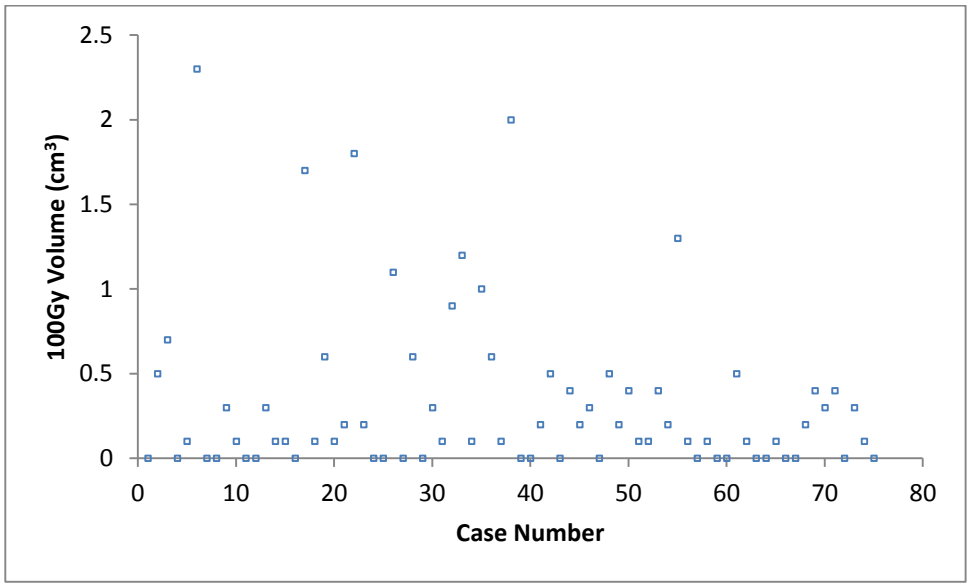


Figure 3.35: 100Gy (200%) Maximum Volume for Cases (cm³)

Analyses demonstrated a strong positive correlation between the 75 Gy ($r=0.85$, $p<0.0001$) and 100 Gy ($r=0.84$, $p<0.0001$) Maximums and the number of wires implanted (Figures 3.36 & 3.37).

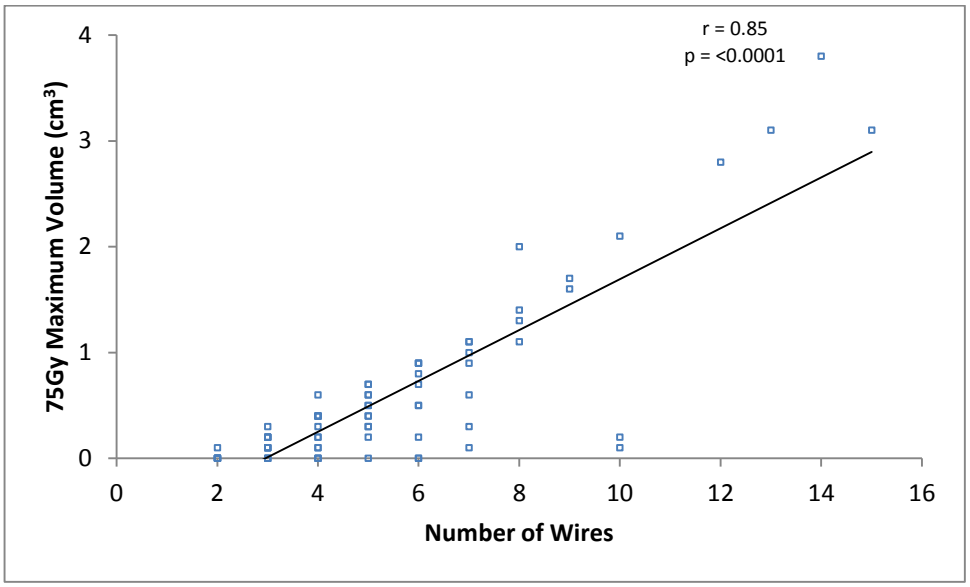


Figure 3.36: 75 Gy (150%) Maximum Volume (cm³) vs Number of Wires

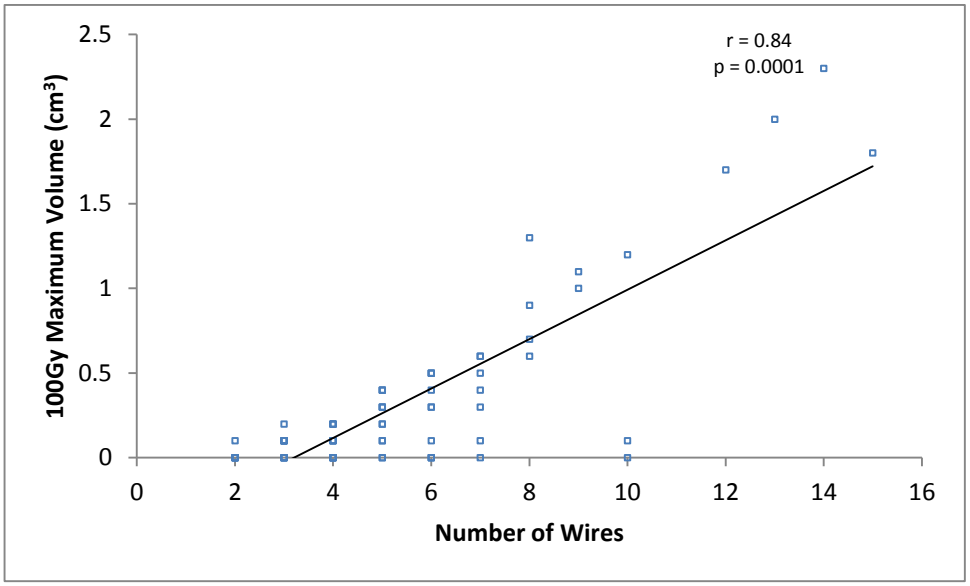


Figure 3.37: 100Gy (200%) Maximum Volume (cm³) vs Number of Wires

The overall Maximums depicted in Figure 3.38 for the 50 Gy Structure Volume ranged from 179.9 Gy to 1215.3 Gy. When analysing the Mean Doses, these ranged from 83.6 Gy to 174.7 Gy with the majority of cases recording a Mean Dose between 83.6 Gy and 143.5 Gy, with the exception of one case recorded at 174.1 Gy (Figure 3.39). Minimum Doses ranged from 28.5 Gy-44 Gy with an average of 37.73 Gy (Figure 3.40).

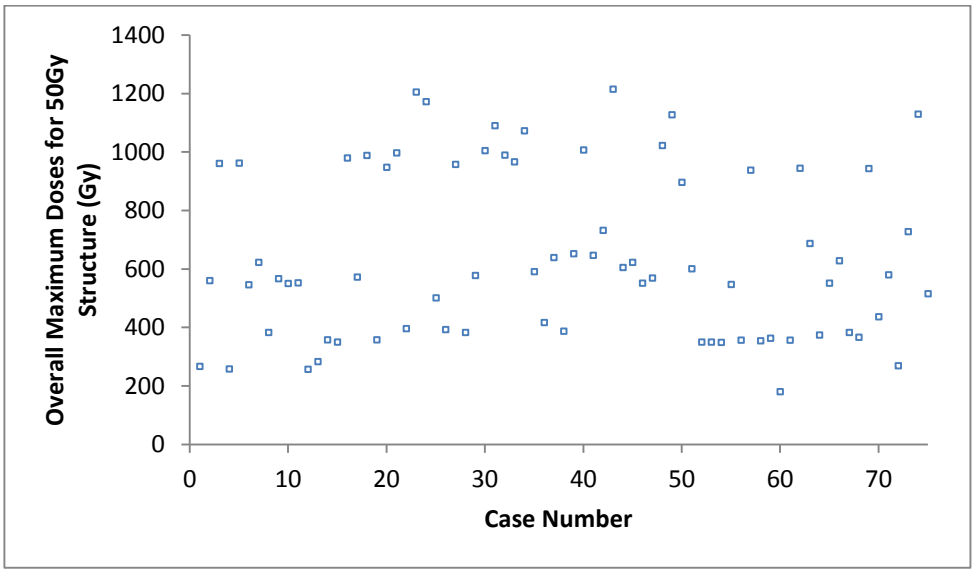


Figure 3.38: Overall Maximum Doses for 50 Gy Structure Volume (Gy)

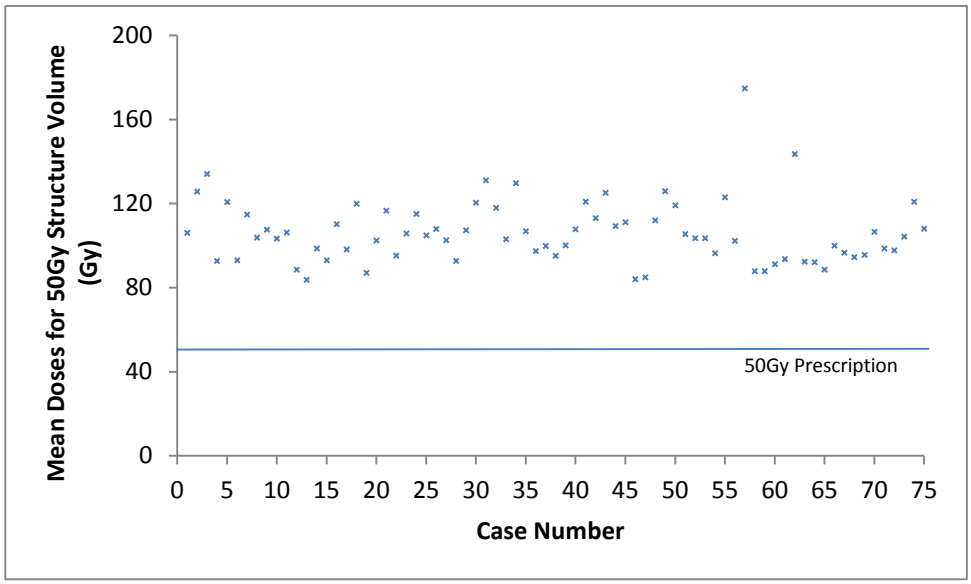


Figure 3.39: Mean Doses for 50 Gy Structure Volume (Gy)

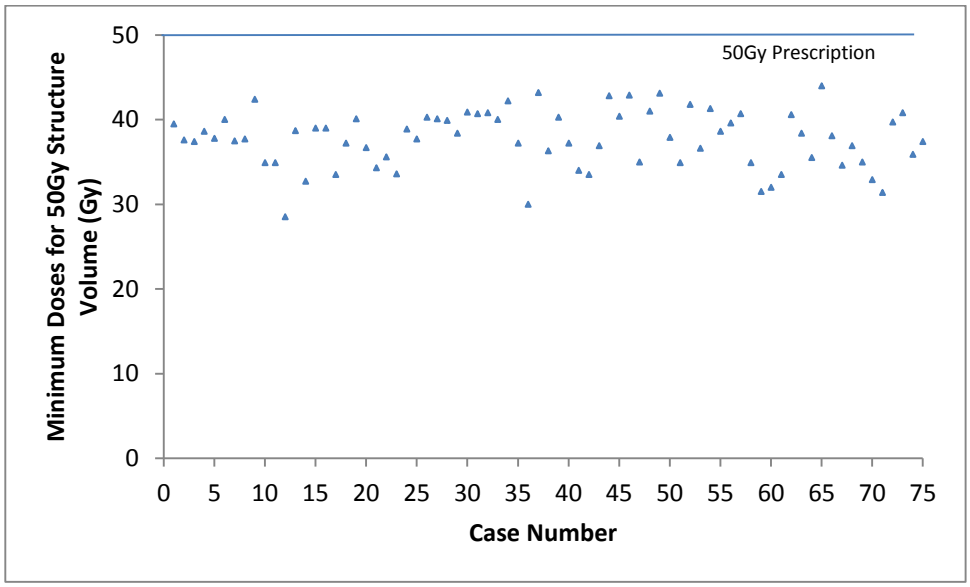


Figure 3.40: Minimum Doses for 50 Gy Structure Volume (Gy)

3.6.8 VARIABILITY IN PLANNING – DVH COMPARISONS

Figure 3.41 illustrates the variability of the plans in this study by displaying a sampling of six different replicated treatments for equine SCC in relation to the Ratio of Total Structure Volume covered by the prescribed 50 Gy. For the purposes of demonstrating a relevant cross-section of results, the six plans depicted by the DVH include those that were identified at the higher and lower dose ends with regard to the Minimum (28.4 Gy-44 Gy) and Mean Doses (83.6 Gy-174.7 Gy) (Case 154: Min=28.4 Gy, Case 226: Min=44 Gy, Case 84: Mean=83.6 Gy and Case 304: Mean=174.7 Gy). Additionally, two randomly selected plans were also included (Cases 329 and 279).

Analysis demonstrates variability in V_{50Gy} coverage in varying degrees for all six plans and ranging from $V_{(50Gy)}$ = 94.6% to 98.3% (Figure 3.41). Table 3.6 identifies the corresponding Volume in cm^3 with each measured $V_{(50Gy)}$ (%) coverage of the Structure Volume along with the 75 Gy and 100 Gy Maximums (and corresponding volumes in cm^3 identified as significant in the reporting of this case series). The variability in results must be observed when reporting on $V_{(50Gy)}$ (%) in view of the variable treatment volumes ranging from 0.02 cm^3 (Case 154) to 5.6 cm^3 (Case 226). For instance, Case 304 records a $V_{(50Gy)}$ of 98.3% which would under normal circumstances be classified as an

optimal coverage of the TV however upon closer inspection it is clear that the area of the TV is in the realm of 0.1 cm^3, a significantly small volume rendering the high coverage as almost insignificant and further adding to the variability encountered within this case series.

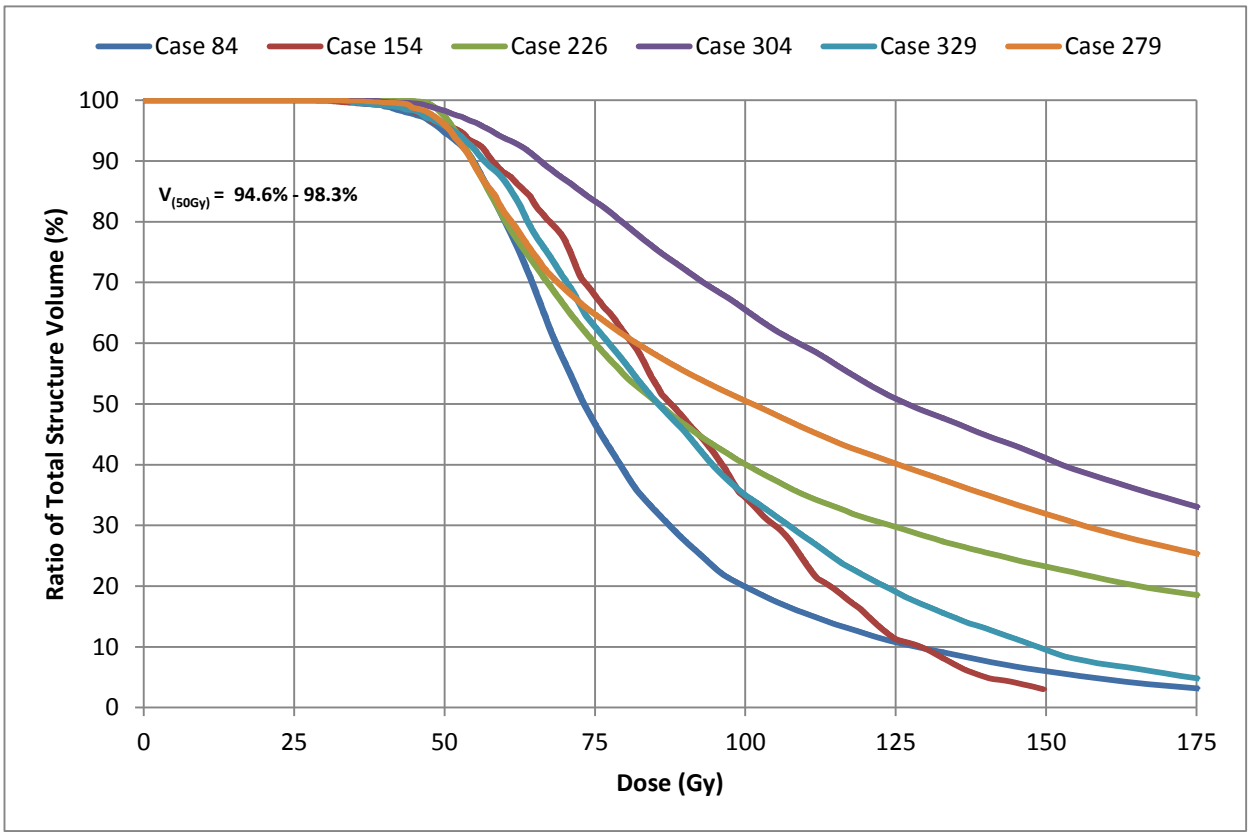


Figure 3.41: Variability in $V_{(50Gy)}$ Coverage

Table 3.6: DVH Analysis for Figure 3.41: Variability in $V_{(50Gy)}$ Coverage

Case	Initial Volume for 50Gy Structure	50Gy Structure Coverage (%, cm^3)	$V_{(75Gy)}$ (75Gy Maximum) (%, cm^3)	$V_{(100Gy)}$ (100Gy Maximum) (%, cm^3)	Number of Wires/Pattern
226	5.6 cm^3	97.3%, 5.45 cm^3	59.6%, 3.34 cm^3	39.5%, 2.21 cm^3	13 wires, clustered, off-set
279	0.5 cm^3	95.8%, 0.48 cm^3	67.3%, 0.34 cm^3	47.9%, 0.24 cm^3	6 wires, planar, 1-line
84	0.2 cm^3	94.6%, 0.19 cm^3	49.0%, 0.09 cm^3	20.0%, 0.04 cm^3	4 wires, clustered, 2-lines
304	0.1 cm^3	98.3%, 0.09 cm^3	84.6%, 0.08 cm^3	63.9%, 0.06 cm^3	3 wires, planar, 1-line
329	0.1 cm^3	95.7%, 0.09 cm^3	61.9%, 0.06 cm^3	34.5%, 0.03 cm^3	2 wires, planar, 1-line
154	0.02 cm^3	95.9%, 0.019 cm^3	70.4%, 0.01 cm^3	32.0%, 0.006 cm^3	5 wires, planar, 1-line

In view of the results in Table 3.6 which demonstrate a slightly better coverage ($V_{(50Gy)}$) for a comparatively larger volume (Case 226), an additional eight plans were analysed in view of their larger volumes (≥1.5 cm^3) and to investigate the effects larger initial volumes has on % coverage of the Target Volume ($V_{(50Gy)}$). The results of the analysis are tabulated below (Figure 3.42 & Table 3.7).

For the cases with initial volumes equal to or greater than 1.5 cm^3, V_{50Gy} coverage ranges from 95.8% - 97.4%. Table 3.7 identifies the corresponding volumes in cm^3 which range from 2.06 cm^3 (initial volume 2.15 cm^3) and 6.56 cm^3 (initial volume 6.75 cm^3). The outcome of this analysis is inconclusive in determining the possible relationship initially questioned between increased volume size and overall isodose (V_{50Gy}) coverage.

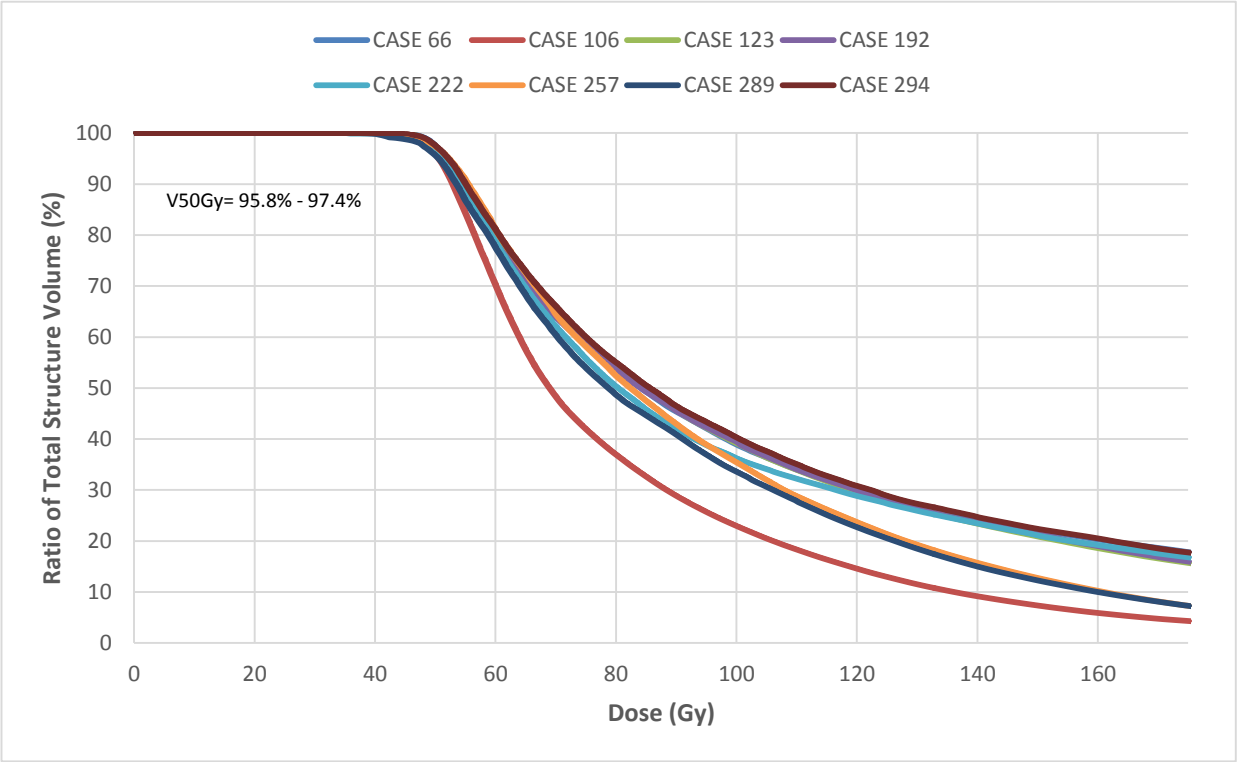


Figure 3.42: Variability in $V_{(50Gy)}$ Coverage for Volumes Greater than 1.5 cms^3

Table 3.7: DVH Analysis for 8 Cases with Volumes >1.5 cm^3

Case	Initial Volume for 50Gy Structure	50Gy Structure Coverage (%, cm^3)	$V_{(75Gy)}$ (75Gy Maximum) (%, cm^3)	$V_{(100Gy)}$ (100Gy Maximum) (%, cm^3)	Number of Wires/Pattern
66	6.75 cm^3	97.4%, 6.56 cm^3	58.6%, 3.96 cm^3	38.9%, 2.62 cm^3	14 wires, clustered, 3-lines
123	5.78 cm^3	96.9%, 5.60 cm^3	57.5%, 3.32 cm^3	36.0%, 2.08 cm^3	15 wires, clustered, 4-lines
222	3.38 cm^3	96.1%, 3.25 cm^3	55.6%, 1.88 cm^3	36.2%, 1.22 cm^3	9 wires, clustered, 3-lines
294	3.61 cm^3	96.93%, 3.49 cm^3	60.8%, 2.19 cm^3	40.2%, 1.45 cm^3	8 wires, clustered, 3-lines
192	2.77 cm^3	95.9%, 2.66 cm^3	58.6%, 1.62 cm^3	39.1%, 1.08 cm^3	8 wires, clustered, 2-lines
106	2.37 cm^3	95.9%, 2.27 cm^3	41.9%, 0.99 cm^3	22.9%, 0.54 cm^3	10 wires, planar, 2-lines
289	2.15 cm^3	95.8%, 2.06 cm^3	53.9%, 1.16 cm^3	33.6%, 0.72 cm^3	7 wires, clustered, 2-lines
257	1.73 cm^3	97.3%, 1.68 cm^3	58.0%, 1.00 cm^3	35.4%, 0.61cm^3	6 wires, clustered, 2-lines

Further analysis was conducted on five cases with known recurrence (n=4) or with 'did not respond' recorded as the reported outcome (Figure 3.43). V_{50Gy} coverage ranges from 91.8%-97.3%. Table 3.8 identifies the corresponding volumes in cm^3 which range from 0.88 cm^3 (initial volume 0.9 cm^3) and 3.07 cm^3 (initial volume 3.2 cm^3). The outcome of this analysis is inconclusive in determining the possible relationship initially questioned between increased volume size and overall isodose (V_{50Gy}) coverage.

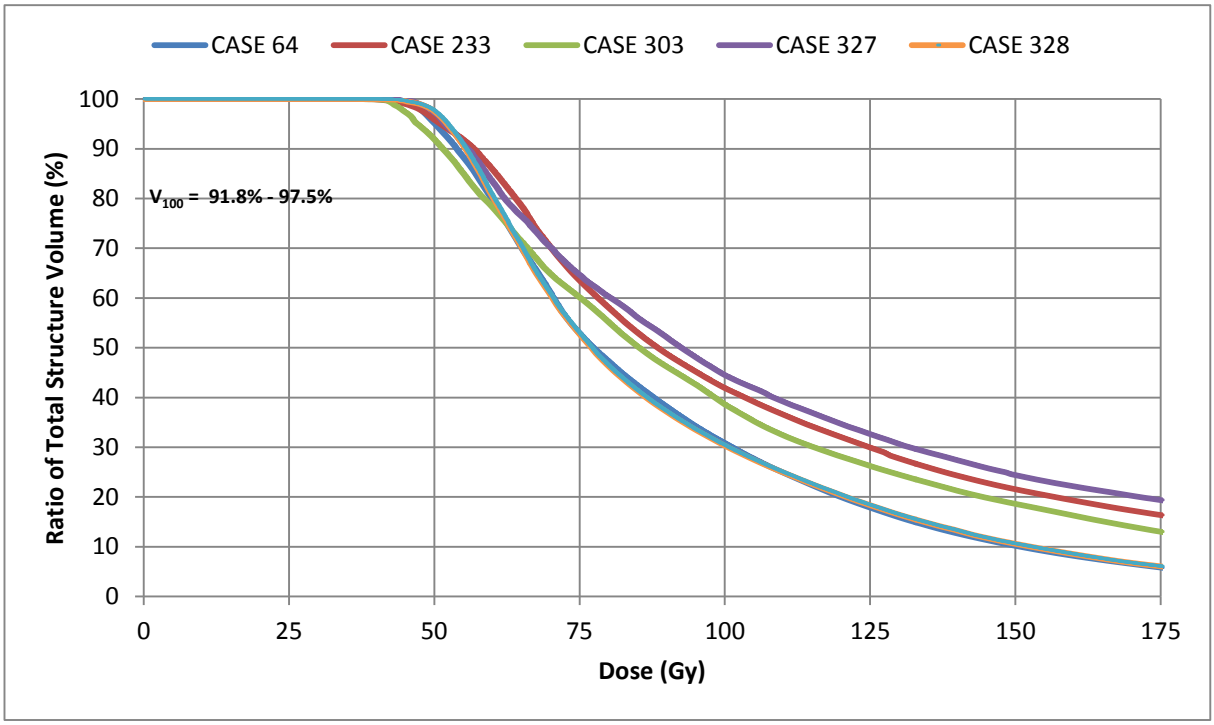


Figure 3.43: DVH for Cases Known to Have Recurrence or 'Did Not Respond' Outcomes

Table 3.8: DVH Analysis for Cases Known to Have Recurrence or 'Did Not Respond' Outcomes

Case	Initial Volume for 50Gy Structure	50Gy Structure Coverage (%, cm^3)	$V_{(75Gy)}$ (75Gy Maximum) (%, cm^3)	$V_{(100Gy)}$ (100Gy Maximum) (%, cm^3)	Number of Wires/Pattern
64	1.4 cm^3	95.0%, 1.32 cm^3	52.8%, 0.73 cm^3	30.8%, 0.43 cm^3	7 wires, planar, 2-lines
233	0.9 cm^3	95.8%, 0.85 cm^3	63.4%, 0.57 cm^3	41.9%, 0.37 cm^3	4 wires, clustered, 2-lines
303	0.9 cm^3	91.8%, 0.88 cm^3	62.8%, 0.58 cm^3	41.6%, 0.38 cm^3	3 wires, clustered, 1-line
327	1.6 cm^3	97.2%, 1.54 cm^3	64.4%, 1.04 cm^3	44.5%, 0.70 cm^3	6 wires, clustered, 2-lines
328	3.2 cm^3	97.3%, 3.07 cm^3	59.3%, 1.87 cm^3	38.6%, 1.21 cm^3	5 wires, clustered, 2-lines

3.6.9 ORGANS AT RISK (OAR)

Organs at risk nearby the treated lesions were identified as the cornea, retina and lens. Doses received by each OAR were recorded and analysed against the accepted tolerance levels for that particular organ. The tolerance levels were based on accepted tolerance doses for human organs surrounding the optical region as adapted by Bentel (1989) and supported by other literature. [34-36] These tolerances describe the levels of tissue dose (cGy) required for there to be an associated 5% (lower threshold) or 50% (upper threshold) injury rate within 5 years (TD 5/5(cGy) or TD 50/5(cGy)), respectively.

Tolerance levels as defined by the literature refer to the *whole* organ. The doses presented below describe the Maximums and Mean Doses as they occur within *partial* volumes inside the organ at risk. Hence the use of 'tolerance levels' and any conclusions regarding overdosing must be interpreted with caution and with full disclosure that the entirety of the organ does not receive the recorded dose. Tolerance levels are based on tolerance doses adapted from a series of human sources and are outlined in the table below (Table 3.9):

Table 3.9: Tolerance Doses for OSCC/POSCC Structures [34-36]

	Tolerance Limits		
Organ	**(Lower) TD 5/5 (Gy)***	**(Upper) TD 50/5 (Gy)****	**Whole/Partial Organ**
Lens of eye	5	12	Whole
Retina	55	70	Whole
Cornea	50	60	Whole

***TD 5/5 (Gy) = tissue dose associated with a 5% injury rate within 5 years**

****TD 50/5 (Gy) = tissue dose associated with a 50% injury rate within 5 years**

Maximum and Mean Doses were recorded for each organ at risk however the reported Maximums must be interpreted with caution due to the inevitable high-dose zone surrounding each source. Analysis of Maximum Doses for the cornea showed a range

between 0.1 Gy to 697.2 Gy. Of the 75 cases, 34 reported the cornea received a dose less than 50 Gy (tolerance lower limit), four cases received a dose to the cornea between 50-60 Gy (tolerance limits) and the remaining 37 cases received a dose above the 60 Gy tolerance (Figure 3.44). In contrast, when analysing the mean doses to the cornea, 100% of the cases (75) maintained a dose to the cornea below tolerance levels ranging from 0.1 to 36.4 Gy (Figure 3.45).

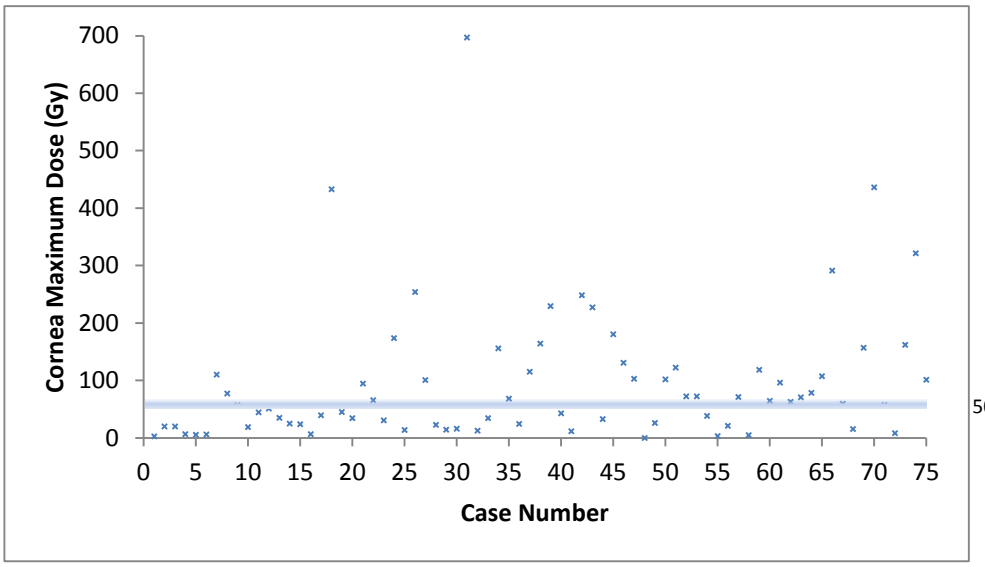


Figure 3.44: Maximum Doses for the Cornea

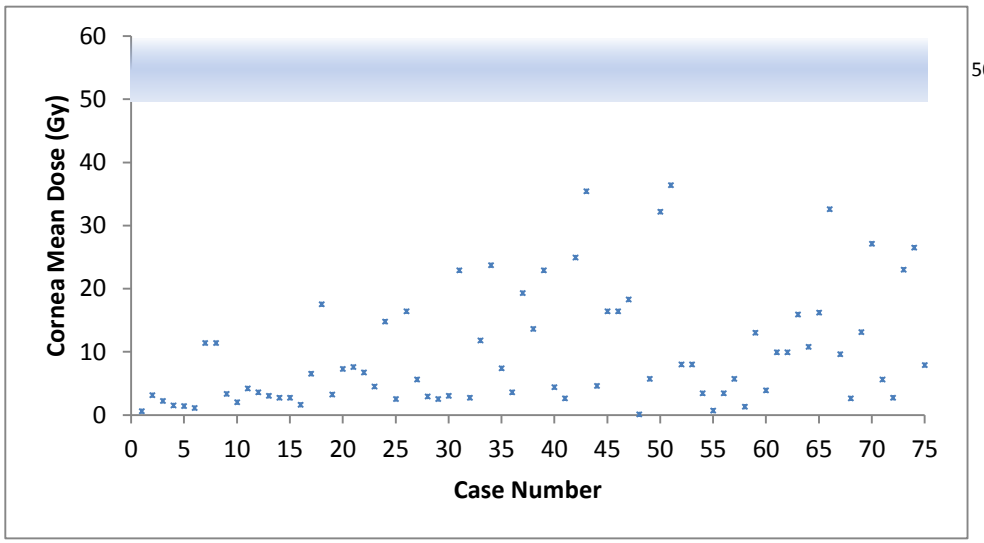


Figure 3.45: Mean Doses for the Cornea

The tolerance range for the lens lies between 5 and 12 Gy for the whole organ. Analysis demonstrated the lens received a Maximum Dose range between 0.1 and 61 Gy. Nine cases received a dose to the lens less than 5 Gy, seven cases received a dose between 5 and 12 Gy and the remaining 59 cases received a dose in excess of the accepted tolerance dose (5-12 Gy). Analysis of the Mean Doses to the lens identified a range of 0.1 to 16.8 Gy. Of the 75 cases, 27 received a dose to the lens less than 5 Gy, 37 received a dose between 5 and 12 Gy and 11 received a dose above 12 Gy (Figures 3.46 & 3.47).

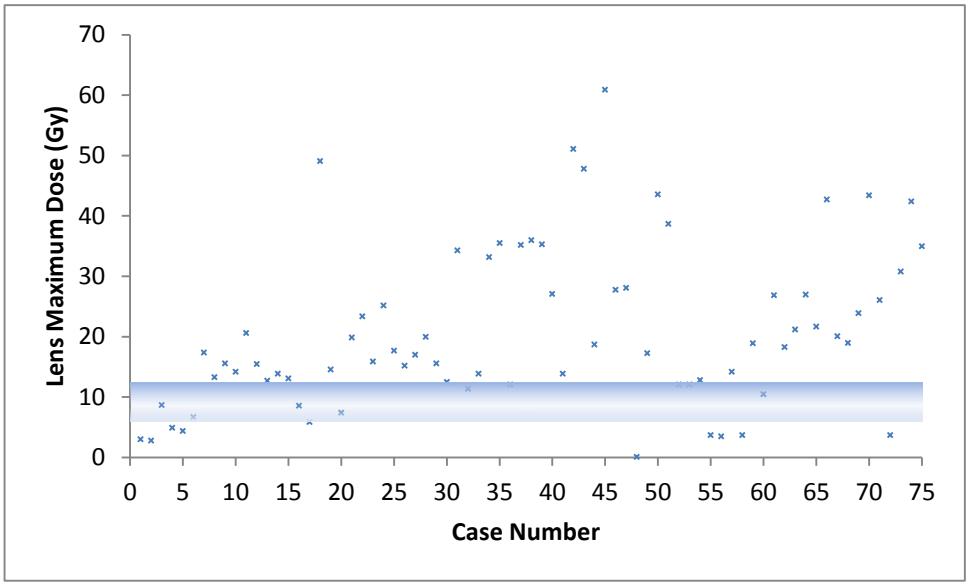


Figure 3.46: Maximum Doses for the Lens

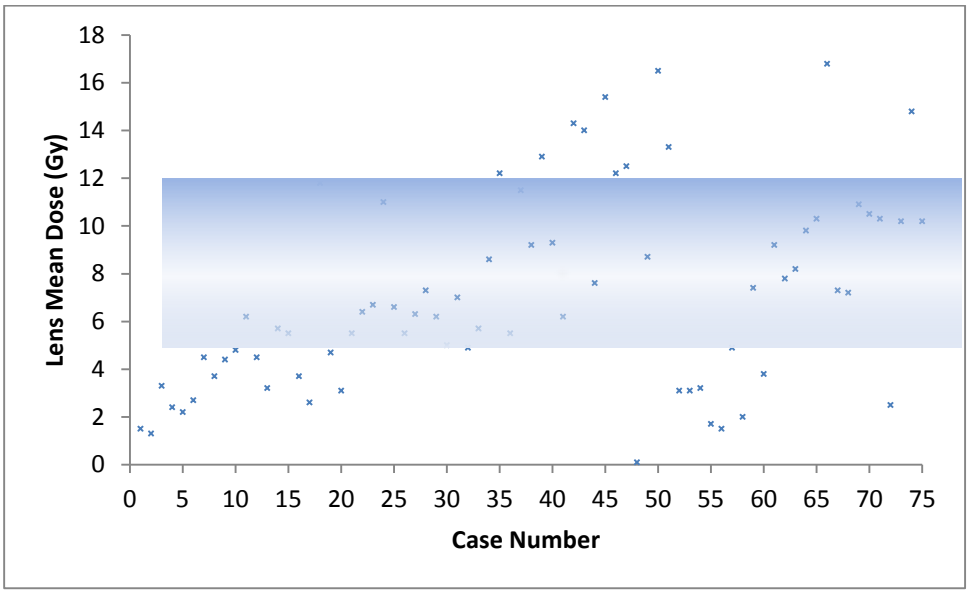


Figure 3.47: Mean Doses for the Lens

Maximum and Mean Doses for the retina were below tolerance (55-70 Gy) for all 75 cases with doses ranging from 0.2 to 25.7 Gy for the maximum doses and 0.1 to 4.2 Gy for the mean doses (Figures 3.48 & 3.49).

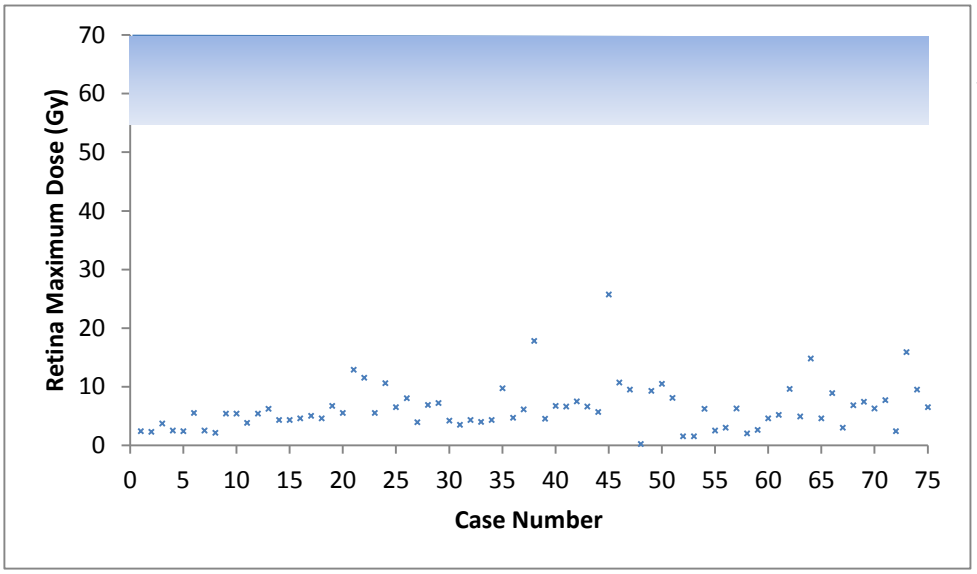


Figure 3.48: Maximum Doses for the Retina

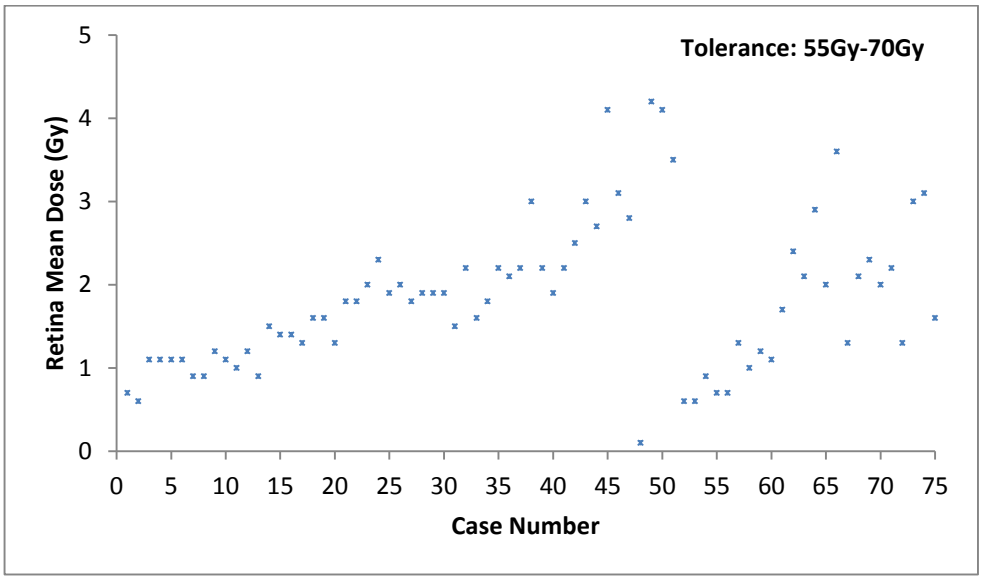


Figure 3.49: Mean Doses for the Retina

3.7 LIMITATIONS

The nature of the information in the medical records is such that there are limitations in the ability to make complete and accurate comparisons regarding compliance with each dose-specification recording systems (ICRU-58) currently used in brachytherapy. Should the records have contained accurate, 3-dimensional representations of volumes (as opposed to 2-dimensional schematic diagrams), 'estimates' would be unnecessary and results may be reported with more confidence and accuracy possibly resulting in better correlations between calculated and estimated diameters and volumes.

Furthermore, without a prescription to guide comparisons, an assumption was made to apply (based on evidence based practice) 50 Gy as the Minimum Target Dose, and 150% (75 Gy) and 200% (100 Gy) as the reportable Maximums for the 50 Gy (100%) prescription.

It must be accepted that treatment results can only be wholly interpreted or replicated if completeness of information is provided regarding the delivery of radiation. This was not the case in this case series. The low numbers in the study add to the complexity of making treatment outcome conclusions. Additionally, the nature of the hand-drawn

schematic representations of treatments leads to the potential for incorrect interpretation of treatment intent. Diagrams do not have a scale by which to guide researchers in identifying exact dimensions resulting in assumptions and estimates. In lieu of information relating to volume (2 dimensional schematic diagrams provided width and length of lesion only), the comparisons made within this study in relation to 50 Gy (Treated Volume) coverage are not reported 3 dimensionally (cm^3). Outcomes (coverage), are reported for 2 dimensional lesions.

The same data set (CT) was used for all planning (n=75). It is acknowledged that the eyes of all horses are not of the same dimensions but research identified average standard sizes for the equine eye and these were in turn transferred to the data sets. Whilst the data set provided a consistent platform for treatment replication, it must be noted that the CT scan was performed on a cadaver, further adding to planning complexities. The horse anatomy was evidently displaced (due to post-mortem changes) hence may not be indicative of true anatomy placement for all conditions.

Researcher 'bias' must be considered when transferring data (from medical records) regardless of quality assurance checks on all plans there is the possibility for misinterpretation of initial treatment intent as a result of incomplete and sub-optimal clinical information for each case.

3.8 DISCUSSION

Isodose distributions were highly variable from plan to plan. Minimums ranged from 28.5 Gy-44 Gy (average 37.73 Gy), whilst Mean Doses ranged from 83.6 Gy-174.1 Gy. Such low Minimum Doses (below expected 50 Gy Minimum Target Dose) indicate potential underdosing of the Target Volume, often associated with recurrence or a reduction in the tumourcidal properties of treatment in those areas. The high Mean Doses could in turn lead to side-effects otherwise not pre-empted by the 50 Gy intended prescription. No strong associations between intended treatment parameters (schematics) and computer-calculated treatment parameters were found, even after conducting multiple statistical analyses with varied data. Several findings, as summarised below, were suggestive of areas for concern and future exploration. Despite

the complexity in extrapolating data for this study, treatment replication was achieved based on various considerations, some of which were assumptions made on the part of the researchers. These assumptions were based on clinical expertise, clinical interpretation of data and supported by human brachytherapy reporting and planning guidelines (ICRU). [1, 31]

3.8.1 SUMMARY OF FINDINGS

A series of findings have been identified;

1. The 50 Gy Structure Volume coverage (V_{50Gy}) showed great variability across all 75 cases.
2. Without a pre-determined prescription and lesion volume, it is difficult to establish how many cases may have been under-dosed or overdosed.
3. Without a biologically significant volume to compare the Maximum Volumes (75 Gy and 100 Gy as well as overall Maximums), it is impossible to establish the potential for side-effects.
4. Treated volumes are unusually small (due to site and nature of cancer) hence maximums are relatively small (volume).

Using brachytherapy as a mode of treatment allows a high radiation dose to be delivered locally to the tumour with good sparing to surrounding normal tissues. The results of this research demonstrate the implantation of radioactive sources for uncalculated periods of time and in haphazard arrangements give rise to wide-ranging outcomes. Additionally, the outcome of this practice is laden with risk to the treating veterinarian and potentially, to the horse. The long-term outcome of the cases treated is largely unknown hence recommendations or assumptions of the benefits of its application cannot be made. In sum, several limitations and weaknesses reduced the ability of the study to conclusively report on the outcomes of the treatment modelling.

One strength of the study, however, lies in the breadth of analyses from the varied data collected, extrapolated and replicated. While acknowledging that many assumptions have been made throughout the study, there were associations of particular interest and

in direct relation to the initial objective of evaluating the efficacy and toxicity of brachytherapy of OSCC/POSCC in equine that lead to a conclusion that the delivery of brachytherapy without training, guidelines and computer planning is disparate in its outcomes as related to coverage and at best, sub-optimal.

The results here cannot be compared directly with other studies. To our knowledge, equine brachytherapy (gold-198) treatments applied manually and without computerised planning have never been replicated and analysed using contemporary treatment planning software and principles. Additionally, dose reference points and techniques of dose calculation vary widely in published brachytherapy reports making cross-study comparisons impossible. [37] RT protocols for previous equine studies have differed extensively in terms of implantation techniques, radiation prescription doses and dose specification. [37] In effect, doses between 32-250 Gy have been used in various studies in the past leaving us with very little ability to correlate between results. [6]

3.8.2 Reporting in Veterinary Oncology

A study conducted between 2005 and 2010 assessed the current status of reporting in veterinary oncology published manuscripts with a view to introducing a standard and globally accepted set of reporting guidelines for future reference. [38] The study outcomes showed that of 46 published manuscripts, 0% met the ICRU dose specification recommendations derived for humans. This result was attributed to a predominance of retrospective studies (variable reporting of information) and the inconsistency in protocols and equipment used in clinics. Without a common ground on which to base treatment protocols and record reported outcomes, the probability of a globally accepted set of protocols is undeterminable. The study recommendations outline the importance of the adoption of reporting guidelines to ensure inter-study comparisons can be made. This in turn leads to clinical decisions based on long-term tested outcomes.

3.8.3 $V_{(50Gy)}$ Distributions

The variability of planning approaches for prostate seed/wire implant brachytherapy in human patients has been identified as recently as 2009. [39] A small study reported in the American Association of Physicists in Medicine (AAPM) Task Group 137 Report (2009)

highlights the variability in treatment outcomes between eight institutions (Figure 3.50). Each institution chose seed placement, planning target volume and strength of sources according to their institutional criteria. The variation among plans was evident and indicative of a patient's considerably different outcomes dependent on each institutions' approach. Planning Target Volume dose varied from V_{100} = 96% to 100% with $V_{(75Gy)}$ in the realm of 32%-92%.

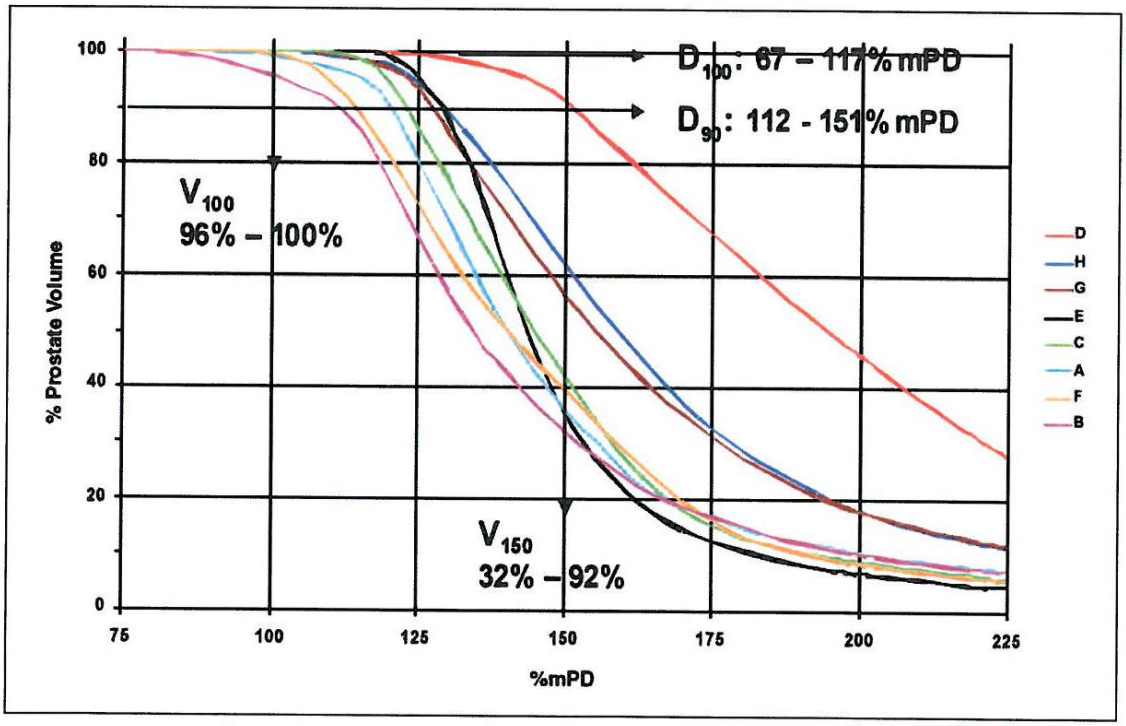


Figure 3.50: Variability in Planning the Same Prostate (Seed Implants) Among Eight Institutions (Reproduced from AAPM Task Group 137 Report) [39]

The study above indicates brachytherapy approaches are still variable and non-standardised. Seed/wire placement is fraught with indeterminate approaches, many of which result in perceived shortcomings to uniform treatment outcomes. The treatment outcomes within this retrospective study mimic many of the currently existing inconsistencies within human brachytherapy using seed/wire techniques.

In reference to the research presented in this thesis, the prescribed dose (Minimum Target Dose) is 50 Gy and is related to the source arrangement and the dose delivered at

the periphery of the TV. The principle behind the application of the treatment dose is that all points of the TV receive a dose (at least) equal to the Minimum Target Dose, in this case 50 Gy. To appreciate fully the dose distribution (volume coverage) within this case series, the Brachyvision function allowing the conversion of the 50 Gy isodose level to a Structure for each treatment was used. This allowed a closer look at the DVH for that particular isodose level. Analyses and interpretation of the 50 Gy coverage allowed us to be able to conclude if the 50 Gy prescription had in fact been met for each individual treatment.

Following analyses of six replicated treatments, variability in isodose distributions as related to the Ratio of Total Structure Volume was identified. Analyses demonstrated a consistent dosing of less than 50 Gy for all plans. Given the varied treatment approaches in this case series, it is not surprising to find none of the cases met Minimum Target Dose Prescription (50 Gy), with a dose spread of $V_{(50Gy)}$ = 94.6%-98.3%. It was identified that larger volumes appeared to result in better % coverage (based on the initial six analysed plans), hence an analyses of all volumes within the series greater than 1.5 cm^3 was performed. This revealed $V_{(50Gy)}$ in the realm of 95.8%-97.4%. Further analysis for all 75 plans demonstrates $V_{(50Gy)}$ coverage variability between 91.8% and 98.2%.

3.8.4 NUMBER OF WIRES & MEAN DOSE

The Mean Dose for the 50 Gy Structure Volume was recorded for each treatment. In interstitial therapy, the dose distribution is non-homogenous. A series of steep dose gradients exist along with regions of high dose around each source.[31] Variations in dose are great and reporting of dose distributions can be complex. Given the fluidity in doses throughout the TV, and the availability of statistical analysis in the form of Dose Volume Histograms for each treatment replication, the Mean Dose for each treatment was recorded and compared to the intended 50 Gy prescription. The correlation between the number of wires and the Mean Dose was statistically insignificant. When Mean Dose was analysed for each case, as expected and irrespective of the number of wires, 0% of the cases, received a Mean Dose of 50 Gy. The lowest recorded Mean Dose began at 83.6 Gy with the highest Mean Dose at 174.1 Gy. The evaluation of dose profiles in complex

plans is difficult. Overestimations of Mean Doses are common in view of the difficulties in calculating local Minimum Doses for each point, however, the accuracy with which doses received by a lesion correlate to the expected dose is of great importance.[1]

3.8.5 MAXIMUMS

High-dose regions around implanted sources are unavoidable. These zones are often small and well tolerated however it is important to correlate radiation dose at these points with late damage by assessing such high-dose volumes. [31] ICRU Report-58 suggests that a dose of approximately 100 Gy is likely to be significant in determining late effects for patients who receive a Minimum Target Dose of 50-60 Gy. [1] In view of the small dimensions of the lesions being treated, analysis was performed on high-dose regions of 75 Gy and 100 Gy as well as Overall Maximums for the entire 50 Gy Structure Volume. A volume of 0-1.5cm^3 received a Maximum of 75 Gy in 67 cases, a volume of 2.0-4.0 cm^3 received 75 Gy in eight cases. Of potential clinical relevance with respect to late damage, as the Maximum increased, the volume within which it occurred decreased. Maximums of 100 Gy occurred in a volume that ranged between 0-0.5 cm^3 and 0.6-2.4 cm^3 in 62 and 13 cases respectively. The exact biologically significant dose and associated volume for interstitial therapy is not yet known however high-dose regions must be reported for future intercomparisons. [31]

The nature of high-dose sources and the high-dose zone surrounding them leads to difficulties when interpreting Overall Maximums for any implant arrangement. Overall Maximum doses were recorded however must be interpreted with caution due to the inevitable high-dose region adjacent to each source. Overall Maximums ranged from 179.9 to 1215.3 Gy. Analysis on Maximums, Overall, 75 Gy and 100 Gy, increased as the number of wires implanted increased demonstrating the impact the number of wires used has on increasing dose and further highlighting the importance of dose computation prior to implantation.

3.8.6 Correlation between Estimated & Computer Calculated Diameters and Volumes

The Treated Volumes (lesions) required to receive 50 Gy were analysed and compared to the estimated volumes, with almost no correlation (r=0.10) between volumes (p-value = 0.3903). That is, the dose coverage for lesions was inconsistent and as a result geographical misses were highly probable. When a tumour or part thereof falls outside of the intended dose zone, a geographical miss is incurred. The result is a lower dose or no dose to an area that was initially prescribed to receive the Minimum Target Dose. This may lead to tumour recurrence or treatment failure. [38, 40] Nine of the 20 horses with follow-up information recorded a recurrence in or around the initial lesion site. Such low numbers make it impossible to correlate the geographical misses recorded with recurrence following treatment replication, however evidence suggests that geographical misses are unquestionably associated with recurrence. [38]

When analysing diameter alone, a weak positive correlation (r=0.28) was established and a trend was evident with a p-value=0.02, signalling a correlation between treatment intention and treatment outcome. The mismatch between diameter correlations and volume correlations make it impossile to conclude on whether the treatment intention was met for all cases and reinforces the importance of computerised planning systems underpinned by completeness of reporting and compliance in meeting dose specification protocols.

3.8.7 Number of Wires vs Computer Calculated Diameters & Volumes

The dose to a point in tissue from a number of radioactive wires can be expressed as the sum of the dose rates to that point from each of the individual wires. [41] This basic algorithm defines dose-rate computation whereby contributions from each source (seed/wire) are summed to reflect dose-distribution. Logically, the greater the number of sources, the greater the dose to a point. In identifying the relationship between the number of wires used in individual cases to the diameter and volume covered by the 50 Gy Minimum Target Dose, it was not surprising to find that as the number of implanted wires increased, the diameter (computer calculated) also increased in a linear relationship. Equally, the computer calculated volume showed a high positive

correlation between the number of wires and the size of the volume. The estimated volume however presented a lesser trend and a low positive correlation was noted. This was in keeping with the inability to relate the estimated volume to any measurement comparison.

3.8.8 Number of Wires, Arrangement & Computer Calculated Volume Increases

Brachytherapy 'systems' for dosimetric calculations encompass a set of rules that take into account source strengths, method of implantation and geometry with the aim of delivering a suitable dose distribution throughout the volume of interest. Many of these systems were developed prior to computed dosimetry being commonplace. A system generally specifies the positioning of the sources with respect to the periphery of the Target Volume and throughout the bulk of the Volume. [31, 41] Uniform source spacing is used in some systems (Quimby System) whilst others are characterised by parallel sources placed at equal distances with the number of planes used correlated to the size of the volume (Paris System).[31] The geometric rules are varied and non-descript, making consistent reporting on outcomes near impossible. Regardless of the systems in place, computer planning has now facilitated complete dose distribution knowledge prior to treatment. Dosimetric calculations can now be based on dose patterns actually achieved rather than the conceptual ideal that underpins non-computer guided systems. The geometric implantation system used in this retrospective study was based on little else other than a previously established (anecdotally) uniform source spacing of ≤0.5 to 1.0 cm between wires. The pattern in which these sources were implanted was decided on during implant and based on the shape and size of the lesion. The method of implantation was performed manually by the treating veterinarian and may have introduced clinican bias. The shape of these arrangements differed and included; clustered, planar or off-set arrangements in varying patterns from a single line to 4 parallel lines to irregular shapes. The reasoning behind the choice of wire placement is not clear however, volume coverage was essentially the expected outcome. Regardless of the distance at which the wires were implanted (≤0.5 or 1.0 cm) or the arrangement of wires, as the number of wires increased, the volume also increased. This held true for

100% of cases and volume coverage increased with increasing wire number for all arrangements, with varied levels of statistical significance.

3.8.9 Arrangement of Wires, Estimated and Computer Calculated Diameters & Volumes

As would be expected, without the pull of accompanying radioactivity, and as a result of dose dropping off markedly with increasing distance from the source, whenever wires were placed in a single line (n=18) a volume large enough to cover the intended lesion size could not be generated. Equally, correlations between estimated diameters and computer calculated diameters (equivalent sphere diameters) were in the weak positive realm. Trends were difficult to establish for the two-line arrangements, and diameter comparisons showed a moderate positive correlation and a statistically significant p-value however no trends could be identified between the generated volumes. Because of high dose gradients, differences in calculated volumes may be observed. [31] The number of cases statistically analysed in the three-four wire arrangement totalled 11, making interpretation of diameter and volume comparisons difficult and possibly invalid due to such low numbers. However, comparisons demonstrated no trends in either dimension. Off-set arrangements (n=21) demonstrated a superior statistical outcome in regard to trends between diameters and volumes. Both sets of analysis (diameters and volumes) resulted in highly significant p-values along with moderate to strong positive linear relationships. The best correlation between the estimated diameters and the calculated and treated volume appeared to be for those arrangements where the wires were implanted in an off-set profile.

Challenges in the distribution of dose are evident in interstitial brachytherapy. [41] To achieve dose uniformity, wire/seed placement is crucial and should involve custom designed wire distribution arrangements for each treated lesion. Commonly used geometry of wires/seeds, whilst individually designed for each patient, includes a set of 'rules' to ensure coverage is adequate and relative geometry effective. [41] There are a number of brachytherapy systems that have evolved into the currently accepted practice. These systems ensure safety based on clinical experience. [31] These rules vary greatly

from system to system and are characterised by specific source spacing and arrangement guidelines. For instance, 1 cm source placement as a sole rule of positioning may not be sufficient to obtain adequate coverage. With regard to the investigated cases, it may be hypothesised that offset profiles appear to offer a good option.

3.8.10 ORGANS AT RISK

Partial or total orbital irradiation may cause a wide range of toxicities, early on-set and late on-set and can range from mild irritations to complete blindness.[36] When analysing the dose received by organs at risk such as the lens, retina and cornea, it became clear that due to the anatomical position of the retina (posterior), and the fast dose fall-off of radioactive Gold-198, the dose received by the retina in 100% of cases (n=75) was well below limits. Both the cornea and lens were calculated to have received Maximum Doses that were substantially beyond the recommended tolerances. The cornea received a Maximum Dose exceeding 50-60 Gy (accepted tolerance) in 49% of cases (n=37), whereas the lens received excessive Maximum Dose beyond recommended tolerance doses (5-12 Gy) in 79% of cases (n=59). Mean Doses for the cornea were below recommended tolerance for 100% of cases however for the lens Mean Doses were identified to fall above 5 Gy for 48 cases (64%).

3.9 CONCLUSIONS & RECOMMENDATIONS

The use of radiation therapy in humans is well documented and reported within the literature. It is a highly effective treatment that stands on a large and robust evidence base. Treatment outcomes have improved significantly with the exploitation of the benefits of combined modality treatments, with a better understanding of radiobiology and with advances in technology. Computerised planning systems have replaced hand-drawn treatment plans and manual implantations of radioactive sources have been superseded with safer alternatives such as after-loading machines. Whilst manual operation (implantation) of sources still occurs, the safety protocols surrounding such techniques are well developed and monitored. Cancer can now be mapped using 3-dimensional computerised tomography imaging and more recently, patient movement can be accommodated through the use of 4-dimensional technologies. Doses are

sculpted to suit each clinical situation allowing for quality assurance to be monitored throughout the entire treatment process. The progression and success of radiation therapy in humans rests in the organised method by which treatments are delivered and recorded for comparative purposes. Treatment protocols and dose-specifications underpin clinical cases for the benefit of the patient and for future reproducibility.

Irrefutably, brachytherapy use in human treatment requires an expert knowledge base. Compliance with dose specifications is crucial to ensure treatment outcomes are beneficial and to reduce possible adverse effects. Purpose-designed planning software used in human therapy allows for treatments to be planned according to constraints and provides a plethora of information in relation to efficacy and toxicity as well as dose distributions to ensure the intended treatment is indeed being delivered.

In comparison and when scrutinising the treatment methods used in this study, it was clear that radiation doses administered in this series did not have associated computer planning. The pattern of implant wire placement was dependent on the size and the shape of the lesion and based on anecdotal information as was described by the treating veterinarian. Each wire was placed approximately ≤0.5-1.0 cm apart to encompass the volume of the lesion. The basis for such arrangements and distances between wires was based on anecdotal knowledge passed down from veterinary surgeon to veterinary surgeon. Wires were implanted manually using a 16 gauge needle with a stylette, a precarious method inevitably leading to undue exposure to the operator's hands. Outcomes of this case series demonstrate that the overall intended dose prescription (50 Gy) was not delivered to any of the lesions if the minimum requirement is 100%. Maximum Doses received by the cornea and lens in a high percentage of cases were above accepted tolerance levels. However, if Mean Doses were to be accepted as a more accurate representation of the doses received by the organs, only the lens received a dose above recommended tolerance levels. It must be noted that tolerance levels for OARs were based on 'whole organ' volumes, whilst this case series received doses to only partial organ volumes.

Follow-up for this case series is limited to 20 cases. Of the 20 horses with follow-up and sufficient information for plan replication, four had recurrence and one did not respond to treatment. Seven did not recur. It is not possible to conclude whether treatment type contributed to the outcomes recorded. It is not possible to conclude whether tumour location influenced the likelihood of recurrence with such small numbers. No side-effects were reported by the clinician in charge of all treatment deliveries. This was ratified by the survey respondents with only one response citing 'loss of hair in small areas'. The lack of follow-up data limits the possibility of making definitive conclusions. Having identified the lack of 50Gy coverage in 100% of the cases does not allow for conclusions on the impact this may have had on overall outcome for the lesions without any further patient follow-up details.

Limitations of the study at hand are common to many retrospective studies and include a dearth of uniformity in the presentation of history, tumour characteristics, adjunct treatments, follow-up and specific details of protocols used. Without a known baseline (established protocols, dose prescriptions/specification), comparisons between studies are impossible. Equally, a lack of conformity treatment approach reduces the ability to make treatment outcome conclusions. Regardless, results of our study indicated that ocular and/or periocular SCCs treated with gold-198 without the use of conventional RT planning principles, the application of constraints and a standardised prescription or protocol, were impossible to be assessed accurately and reported on in relation to success of application.

Despite the limitations of this study, the need for improvement in the establishment of universally accepted treatment recommendations and completeness of reporting within veterinary oncology is clear. The findings of this study provide further support for the development and standardisation of veterinary specific dose guidelines and protocols in the area of brachytherapy. Further study in this area with an emphasis on planning and protocol development in addition to prospective evaluation of clinical trials will help provide a framework for the establishment of best practice in veterinary radiation oncology. Without completeness of reporting of radiation therapy planning, dose and

delivery in veterinary radiation oncology, compliance in meeting dose specification protocols is limited.

Finally, the results of the retrospective study has identified the importance of continuing with the proposed investigations the research set out to accomplish to identify the best approach to the application of brachytherapy for the treatment of OSCC/POSCC.

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CHAPTER 4: SURVEY STUDIES

4.1 CHAPTER OVERVIEW

This chapter describes two separate nationwide surveys.

Following the literature review and retrospective study (Chapters 2 & 3), it became apparent that whilst it was evident that brachytherapy treatment had been used in the past, standardised protocols or best practice approaches were non-existent. To further support the findings and correlate them to present-day evidence, two national surveys were developed and distributed within Australia for the purposes of acquiring data as it relates to current and past practice and radiation compliance within equine clinics.

Cross-sectional studies were considered the most effective way to gather data to investigate radiation safety compliance (Survey 1 - 2011) within the veterinary sphere and to investigate current and past practice in Australia to determine treatment approaches to OSCC and/or POSCC (Surveys 1 & 2 – 2011/2015). The surveys were distributed by the Australian Veterinary Association to their Equine Members.

Chapter 4 consists of one published paper (Paper 4), and one submitted paper (Paper 5). Paper 4 describes the radiation safety compliance results and the submitted paper describes current practice in relation to equine OSCC and/or POSCC in Australia and is based on combined data from surveys 1 and 2.

Relevant information regarding the research methodology for the surveys not able to be included within the papers has been included in Appendix A. This information includes Invitations to Participate, Participant Information Sheets, and the surveys.

4.2 RADIATION SAFETY CONSIDERATIONS AND COMPLIANCE WITHIN EQUINE VETERINARY CLINICS: RESULTS OF AN AUSTRALIAN SURVEY (PAPER 4)

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Radiation safety considerations and compliance within equine veterinary clinics: Results of an Australian survey

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ABSTRACT

Objective: To examine current knowledge and the level of compliance of radiation safety principles in equine veterinary clinics within Australia.
Method: Surveys were sent to equine veterinary surgeons working in Australia. The survey was delivered both online and in hardcopy format; it comprised 49 questions, 15 of these directly related to radiation safety. The participants were asked about their current and previous use of radiation-producing equipment. Information regarding their level of knowledge and application of radiation safety principles and practice standards was collected and analysed.
Results: The use of radiation-producing equipment was evident in 94% of responding clinics (a combination of X-ray, CT and/or Nuclear Medicine Cameras). Of those with radiation-producing equipment, 94% indicated that they hold a radiation licence, 78% had never completed a certified radiation safety course and 19% of participants did not use a personal radiation monitor. In 14% of cases, radiation safety manuals or protocols were not available within clinics.
Conclusions: The study has shown that knowledge and application of guidelines as provided by the Code of Practice for Radiation Protection in Veterinary Medicine (2009) is poorly adhered to. The importance of compliance with regulatory requirements is pivotal in minimising occupational exposure to ionising radiation in veterinary medicine, thus there is a need for increased education and training in the area.

Introduction

Veterinary clinics are equipped with radiation-producing equipment to aid diagnosis of disease, identify relevant pathology, and also for treatment.[1] Radiation-producing equipment commonly used includes plain radiography (X-rays) units and computed tomography (CT) machines. Clinics also use radionuclides in brachytherapy and nuclear medicine.[2] With the use of such equipment comes responsibility to maintain rigid radiation safety standards and practice. There is some evidence, however, of variation in the application of regulated radiation safety standards within veterinary clinics.[3,4]

Veterinary use of radiation in Australia is regulated by the Code of Practice for Radiation Protection in Veterinary Medicine (2009) as implemented by the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA).[2] The code is a platform to increase uniformity of application and interpretation of the requirements of practice across Australia. It provides useful radiation protection information to the veterinary community and stipulates regulations to which practices must adhere. Specifically, the Code stipulates that a 'responsible person' is appointed within each practice; a person with overall management responsibility of the veterinary practice or radiation source. It is also a requirement of the Code that a 'Radiation Management Plan' is actioned within each practice. The plan must incorporate a comprehensive list of actions and procedures (Schedule A: Radiation Management Plan) including: the provision of protocols for procedures, methods to achieve the ALARA principle (As Low As Reasonably Achievable), quarantine provision, personnel monitoring and recording (for each occupational person likely to be exposed to ionising radiation above 1 millisieverts (mSv) annually), protective equipment and staff training and licensing, among other requirements.[2]

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Occupational exposure to ionising radiation endures as a significant and widespread potential risk for veterinarians in view of their current uniqueness of practice.[5,6] This may be partially attributed to the need for veterinarians to engage in a wide range of generalist clinical activities as opposed to a specialist activity.[1,3,5] The requirement for veterinarians to be generalists may compete with their capacity for expert knowledge in areas such as radiation safety, hence impeding the application of crucial radiation safety principles. ARPANSA acknowledges that in veterinary radiography, positioning animals has the potential to increase the magnitude of radiation doses received by veterinary workers – for example, at times members of staff are required to hold the animal during exposures. In relation to horses and adding to the procedural complexities, exposures are usually performed in the field with horses in the standing position. The imaging detector (cassette) is often held by a member of staff whilst the radiograph is acquired, which increases the radiation exposure danger to primary and scattered radiation. The potential hazard in radiation therapy and nuclear medicine imaging with radionuclides is arguably even higher to the operator in view of the ongoing nature of exposure and the higher doses required.[7] In consideration of the extenuating factors potentially contributing to veterinarian exposure to radiation, veterinarians should be aware of the hazards caused by ionising radiation and be compliant with mandatory radiation protection regulations.[8] The practising veterinarian is responsible for the maintenance and correct use of protective clothing and radiation-producing equipment. With this responsibility comes the additional expectation that the veterinarian will be aware of the recommended radiation exposure limits and ways of limiting exposure.[9] Regulated guidelines exist and are underwritten within the Code of Practice for Radiation Protection in Veterinary Medicine; compliance, however, is self-regulated.[2]

The detrimental side effects of radiation exposure have been well documented.[5,10] Adverse effects highlight the need for compliance with radiation safety guidelines and the need for education with respect to the safe use of radiation. Although the precise risk of occupational exposure is unclear, biological effects of low-level exposure to ionising radiation remain a concern.[11] The potential for damaging health effects as a result of occupational radiation exposure in veterinary practice have been acknowledged.[12] The most commonly chronicled effects of radiation exposure include cancer, birth defects and other permanent mutations.[5,8] Published studies in the area of veterinarian exposure to occupational radiation make comparisons to other professions and highlight the potential impact of the limited use of radiation protection equipment and principles. Results of a postal survey of women in veterinary practice found 64% ($n = 1384/2175$) of respondents had been exposed to radiation during pregnancy – an alarming statistic in view of the known dangers of in-utero exposure to ionising radiation and the increased radiosensitivity of the foetus.[1] A separate study reported 82% ($n = 375/457$) of females working in the veterinary field self-reported exposure to X-rays over a period of one year.[12] The maximum reported exposure for this study was in the vicinity of 1.2 mSv per month (14.4 mSv per annum). As a comparison, in Australia, the average dose to diagnostic radiographers and radiation therapists is 0.12 mSv per annum,[13] with the annual limit for radiation workers in Australia being 20 mSv, as recommended by the International Commission on Radiobiological Protection (ICRP).[14]

To investigate and identify current radiation safety considerations and compliance within the equine veterinary field, data was collected on current work practices and compared to the existing Code of Practice for Radiation Protection in Veterinary Medicine (2009) by ARPANSA.[2] The endpoint of this study was to analyse the data and identify significant gaps in knowledge and practice to inform the proposed development of a radiation safety training package designed specifically for veterinary use.

Materials and methods

Ethical approval for this survey was granted by the University of Newcastle Ethics Committee (H-2009-0136).

The survey

This paper reports on data from a survey of equine veterinary surgeons in Australia. The 15 questions on radiation safety included both open and closed questions. The questions aimed at eliciting responses from participants in relation to the requirements stipulated within the Code of Practice for Radiation Protection in Veterinary Medicine.[2] Particular focus was placed on the adherence and knowledge around the 'Radiation Management Plan' requirements including: the provision of protocols, methods to achieve the ALARA principle, quarantine provision, personnel monitoring, protective equipment and staff training and licensing.

The survey was designed using the web-based program Survey Monkey (www.surveymonkey.com, California Office: 640 Oak Grove Avenue, Menlo Park, CA 94025, USA). Details of the survey including a participant information sheet and the link to a web-based survey was sent through the Australian Equine Veterinary Association fortnightly e-mail newsletter followed by a 3-monthly reminder. Details were also sent directly to a group of practitioners identified though the internet and Yellow Pages®. Participants had the option of completing the survey online or hardcopy. A single survey response was requested for each practice.

Results

Data analyses

Data from the online responses were exported into an Excel spreadsheet and combined with the paper-based responses before analysis was undertaken. Data analysis included frequencies and counts. The small number of responses prohibited in-depth statistical analysis to be performed. It must be noted that participants were given the opportunity to choose more than one option in many of the survey questions. This resulted in occasions where the total percentage was more than 100%.

Participants

Veterinarians who work with horses were identified through records accessed via the Australian Equine Veterinary Association (AEVA) public website, through internet searches, and the Yellow Pages®. However rigorous the process of identifying all veterinarians working with horses, it cannot be confirmed that all Australian equine veterinarians were invited to participate.

The radiation safety section was completed by 82 participants, however, results are reported on to reflect the participant sample group that owned radiation-producing equipment; this equated to 77 participants. A wide cross-section of Australia was represented, with responding veterinarians practising throughout all states and territories and some practising in more than one state or territory. Of the 77 responses to the demographics portion of the survey, 39% (30) worked in New South Wales; 22% (17) in Victoria; 19% (15) in Queensland; 9% (7) in Western Australia; 6% (5) in South Australia; 3% (2) in Tasmania; and 1% (1) in the Northern Territory. Additionally, four participants noted they ran clinics in more than one state/territory; these included NSW and Victoria (1), Victoria and Australian Capital Territory (2), and Tasmania and Victoria (1).

Surveyed veterinarians represented a wide range of experience, with 4% (3) having less than 12 months experience; 30% (23) having between 1 and 10 years' experience; 52% (40) between 11 and 30 years' and 14% (11) with more than 30 years' experience.

A total of 70% (54) cited a Bachelor of Veterinary Science (BVSc) or BVSc (Hons) as their highest qualification. A total of 30% (23) cited a higher qualification; Masters 9% (7), and PhD 1% (1), and Membership of The Australian College of Veterinary Scientists (MACVS) 18% (14). Of those, 8% (6) specialised in equine medicine, 4% (3) in equine surgery, and 6% (5) did not report their specialisation. One veterinarian surveyed identified as a Diplomate of the American College of Veterinary Internal Medicine. No respondent reported formal qualifications in the area of radiology or radiation oncology.

Radiation-producing equipment

Of respondents, 94% (77/82) owned radiation-producing equipment, with all of these owning an X-ray machine. Consistent with the aim of the study, which was to investigate current compliance to the radiation safety Code of Practice, data analysis was only conducted on the 77 practices that owned radiation-producing equipment. Other equipment types included nuclear medicine gamma cameras 4% (3) and CT 3% (2) (Table 1). Non-ionising imaging equipment included portable and/or stationary ultrasound machines in 74% (57) and 21% (16) of practices respectively, with two practices owning magnetic resonance imaging machines for large and small animals or for the equine limb. Respondents recorded owning a portable X-ray machine or fluoroscopy unit in two separate cases.

Certified course completion and licensing

Of the 77 participants 78% (60) had never completed a certified radiation safety course. The remaining participants completed a certified course through: in-service (1), conference (1), or a certified course through a university (14). One reported having completed a course through another source but further details were not supplied. No radiation licence was held by 6% (5) of practices (Fig. 1), and 73% (56) of participants reported having a licence although they had not completed a certified radiation safety course. Four respondents did not have a licence and had not completed a course. Sixteen participants reportedly held a licence and had completed a course while one had completed a course and did not hold a licence.

Radiation safety manuals and protocols

Fourteen per cent (11) of participants did not possess or use a radiation safety manual. Radiation protection protocols were present in 80% (61) of the clinics, however, 14% (11) claimed they did not have a protocol. An additional 6% (5) of respondents were unsure if their clinic possessed a radiation protection protocol (Fig. 2).

Table 1
Types of radiation-producing equipment in clinics.

Type	Response percentage	Response count
Ionising equipment		
X-ray machine	100%	77
Nuclear medicine gamma camera	4%	3
Computed tomography	3%	2
Other: mobile X-ray, fluoroscopy	3%	2
Non-ionising equipment		
Portable ultrasound machine	74%	57
Stationary ultrasound	21%	16
Magnetic resonance imaging – large & small animal	1%	1
Magnetic resonance imaging – equine limb	1%	1

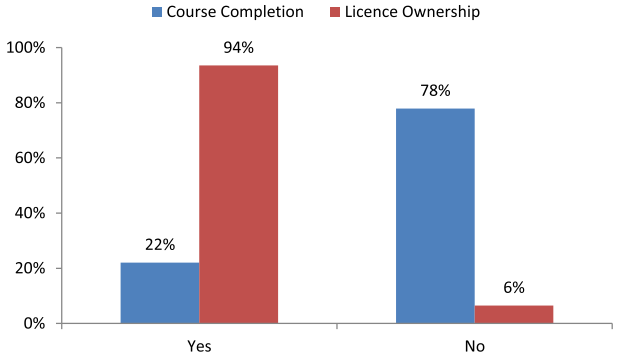

Figure 1. Certified radiation safety course completion and licence ownership.

Staff monitoring

The survey reported staff radiation monitoring was not limited to veterinary surgeons (with 68% (52) reportedly wearing monitors) but also included nursing staff in 64% (49) of responses and when performing procedures requiring radiation. Administration staff were also monitored in 4% (3) of centres (Table 2) Additionally, respondents commented that 'other' personnel (2) who were routinely monitored included veterinary students and staff involved in imaging (1). There were no reports of any veterinarian using the services of a specifically qualified radiographer or technician. Monitoring was not used in 19% (15) of clinics (Table 2).

Types of monitoring

Participants were asked to choose the type of monitoring devices used in clinics; the question allowed multiple choices. Only 73 participants (95%) responded to this question. Photographic film badges were the most commonly used personal monitoring devices 55% (40), followed by body thermoluminescent dosimeters (TLD) 22% (16) and direct reading dosimeters (DRD) 11% (8) (Fig. 3). Two participants (3%) reported a combination of two or three types of monitoring devices within their clinic: photographic film badge, direct reading pocket dosimeter and thermoluminescent dosimeters (1), photographic film badge and finger sachet monitoring (TLD) (1). Nine respondents (12%) noted they used 'other' types of monitoring devices, one of which noted the type was 'to be decided'

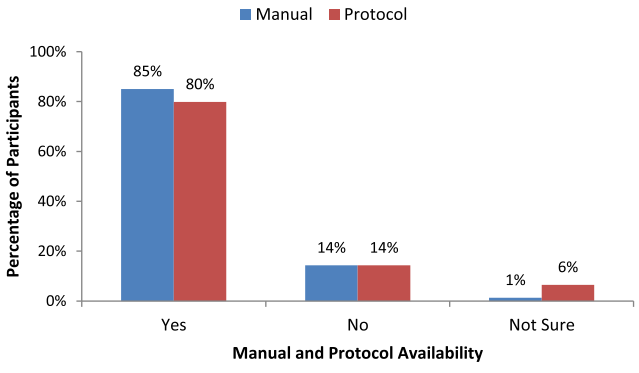

Figure 2. Availability of radiation safety manuals and protocols.

Table 2
Staff within clinic monitored for radiation using personal monitoring devices.

Monitored staff	Response percentage	Response count
Veterinary surgeons		
- Only when performing procedures	68%	52
- Wear them at all times	10%	8
Veterinary nurses		
- Only when performing procedures	64%	49
- Wear them at all times	10%	8
Administration staff	4%	3
No monitoring used	19%	15
Other	4%	3

and another reported 'don't use them, others take images for me'; however, no information beyond 'other' was provided in seven cases. Another participant stated they were to decide what type they would use and another respondent did not know the type they used.

Location of monitors

Seventy-seven participants responded to the question regarding the wearing location of monitors. Monitoring was generally worn at waist level 52% (40), however, some respondents indicated wearing monitors at thyroid level or on fingers 13% (10). The position of the monitors in conjunction with lead gowns varied, though wearing the monitors under the gown and at waist level was the most common response 21% (16), with 4% (3) wearing the monitors at waist level and on top of the gowns. Of the responses, 18% (14) wore the monitor under the gown in an unknown/unspecified location and 4% (3) wore the monitors in an unknown/unspecified location over the gown (Fig. 4). Three did not specify the location of the monitor in relation to the gown. Of the 15 (19%) participants that reported wearing monitoring devices in positions other than those suggested in the survey, 13 did not describe where they were worn, one was yet to decide where they would wear them, and another did not know where they were generally positioned.

Radiation protection devices

The most commonly used radiation protection devices were aprons and thyroid shields at 99% (76) and 83% (64), respectively. Keeping a distance from the source of radiation was implemented in 66% (51) of cases, and exiting the room, decreasing the time spent nearby radiation, and the use of radiation safety signs was evident in 44% (34), 48% (37) and 39% (30) of cases, respectively. Other responses revealed participants used protective lead-lined gloves in 8% (6) of cases, exited the room whenever possible 3%

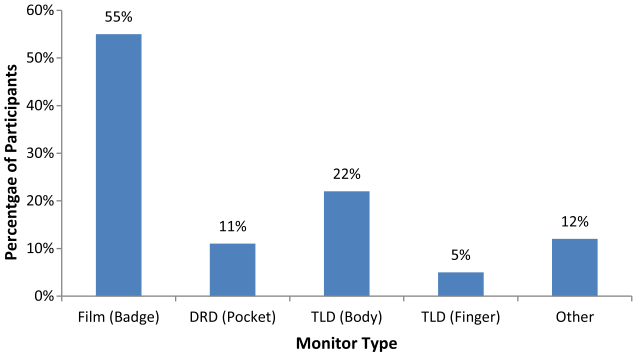

Figure 3. Types of monitoring used.

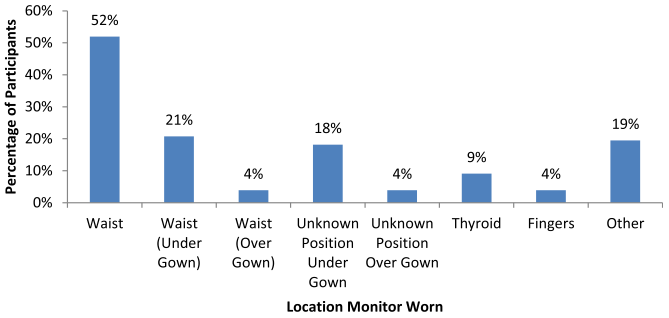

Figure 4. Location of monitors.

(2) (as opposed to every time an animal was exposed to radiation), and another minimised the number of personnel used during the procedure 1% (1).

Storage, preparation and implantation of brachytherapy sources

Participants were asked a series of questions in relation to the implantation of radioactive sources. Only 15 practices responded to this section. In view of the requirement to prepare radioactive sources prior to their use, participants were asked to identify the space within which they prepared sources in their clinic. Of the 15 respondents, 20% (3) used the operating theatre as a preparation area and 47% (7) had a specifically designed space with a leaded glass window. In one (7%) case, a participant used 'any space available'. The implantation system used for radioactive seeds attracted responses from 13 participants, of which 23% (3) reported manual implantation. A further 23% (3) reported the use of a seed gun. Fifty-four per cent (7) of participants reported using 'other' implantation systems, but a description of these was not provided. Responses on the general storage systems for sources included: a room specifically designed for the storing of radioactive sources in two cases (15%), and a lead storage container in five cases (40%). Sixty-nine per cent (9) of participants reportedly stored their sources in 'other' spaces, however, 61% (8) of these did not specify where this area is located. A single response commented: 'would not store these at the clinic', however did not indicate where they would store the sources.

Post-treatment quarantine procedures

Participants were asked to describe their quarantine procedure when using brachytherapy, 10 responded to this section. The response to the question in reference to horses revealed that 60% (6) of respondents kept the horse in the clinic until exposure was minimal, 30% (3) quarantined the horse in a paddock, and 20% (2) allowed the horse to return to the owner's property following implantation with advice to the owner to 'keep their distance from the treated area'. The quarantine period was dependent on the half-life of the source in 70% (7) of cases, while the remaining 3 respondents answered '3–4 days', 'determined by estimate of half-life and evaluation with Geiger counter', and 'a specialist determines this'.

Participant perceived radiation safety knowledge

With respect to radiation safety knowledge, of the 76 who responded to this question, 43% (33) believed their knowledge was well developed and 50% (38) described their knowledge as 'somewhat' well developed. A more specific question regarding their familiarity with the principles of time, distance and shielding

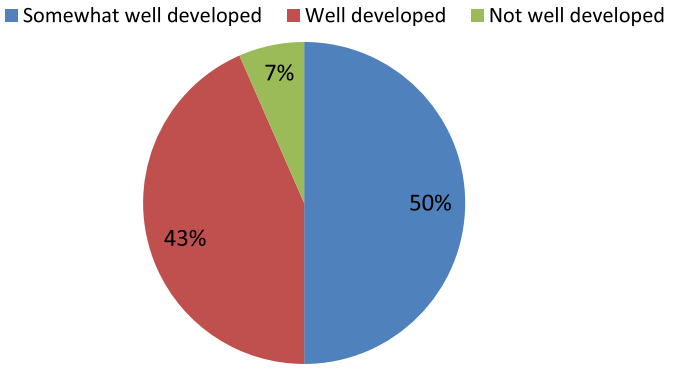

Figure 5. Self-reported radiation safety knowledge.

elicited 74 responses and a higher positive response rate of 73% (54) with 24% (18) 'somewhat' and only 3% (2) definitive 'nos' (Figs. 5 and 6).

Discussion

Veterinary practice has unique differences compared to the human medical applications of ionising radiation. A number of factors specific to veterinary practice may increase radiation dose, these include animal restraining during procedures, the generalist role of veterinarians, and possibly a lack of training and education in radiation safety giving rise to low familiarity with mandatory regulations.[6] Excessive exposure to ionising radiation is a serious occupational health hazard.[5] Every time a radiographic or fluoroscopy unit is activated, or a radioisotope is used, there is the potential for genetic damage or carcinogenic effects, and therefore, all practitioners need to be educated in the methods and procedures that minimise radiation exposure.[10]

Although the exact risk of low-dose occupational exposure to ionising radiation is uncertain, the underlying radiation protection principles should never be challenged.[8] A study by Ackerman et al. (1988) investigated the radiation exposure received by various personnel during equine radiography.[9] The data demonstrated that the exposures measured were within 'acceptable limits' for occupational workers with average doses ranging from 0 to 6 m rads (0.06 mSv). It should be noted that since the effects of exposure to low levels of radiation over long periods of time are not well quantified, these results do not provide justification for complacency. Given the difficulties of quantifying 'safe limits', prudency must be observed when recording radiation exposure values in personnel and reporting them to be within 'safe' levels in accordance with dose limits of 20 mSv per annum as per the ICRP.[14]

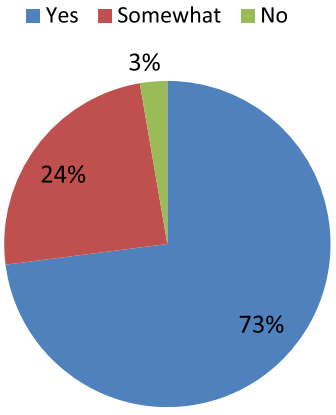

Figure 6. Familiarity with radiation safety principles knowledge of time, distance and shielding.

Certified radiation course completion and radiation licensing

Under the Radiation Control Act and the Environment Protection Authority (EPA), radiation licence conditions must be met and adhered to by the licensee. The criteria for licensing varies slightly in different states within Australia, however, a licence is not granted unless the applicant holds a recognised qualification (inclusive of radiation safety content) or is registered with the Australian Health Practitioner Agency (AHPRA), passes an examination administered by the EPA or has passed a certified radiation safety course approved by the EPA. The completion of the above conditions demonstrates to the EPA that the applicants have appropriate knowledge of the principles and practices of radiation safety protection.[2,15] Clinics are prohibited from operating radiation-producing equipment without current licensing. The current research results reveal that radiation licences were not held by all participants. Additionally, the majority of respondents indicated that they had not completed a certified radiation safety course. It is recognised, however, that the person completing the form may not be the licensee, and therefore not required to complete a certified safety course.

Radiation safety manuals and protocols

Radiation safety manuals were not evident in all centres. For the purposes of this research, the manuals were equated to the 'Radiation Management Plan', demonstrating poor adherence to a mandatory regulation from the ARPANSA Code of Practice. It should be acknowledged, however, that some respondents many not have understood the connection between 'manual' and the 'plan', limiting the emphasis that can be placed on the result. Radiation protection protocols were available in most clinics, however, 11 clinics did not possess a protocol, again not meeting mandatory regulations. Indicative of the obvious need for education, one respondent suggested they did not consider there was a need to have a protocol.

Radiation safety knowledge and protective devices

Veterinarians should not be exempted from the ALARA principle – 'As Low As Reasonably Achievable', a recommendation for limiting the dose to individuals as per the International Commission on Radiation Protection (ICRP).[16] When asked about their familiarity with the principle of decreasing the time of exposure, increasing the distance from the source and increasing the shielding, one-quarter of respondents were not familiar with the principle or were somewhat familiar, regardless of the recommendation and the requirement for its consideration in everyday practice. In relation to shielding, lead aprons were used in the majority of cases; however, even though the use of lead aprons offers protection to some radiation-sensitive organs, they do not limit exposure to the eyes and skin. It must be noted that lead aprons and the purchasing of these is fraught with some complexity in view of the different types available rated for varied energies. The initial and ongoing testing (every 12–18 months) of the integrity of these aprons, as is recommended by ARPANSA, also adds to the reliability and effectiveness of their use.[2] Further recommendations for the use of aprons include compliance with Australian standards for light and heavy aprons and for the design and 'lead equivalence' of the apron to meet the needs of the application it is intended for.[13] A study by Tyson et al. (2011)[19] investigated the surface radiation leakage of a typical

portable X-ray unit to measure operator exposure at simulated hand and collar positions during imaging. The results of this study demonstrated that the use of adequate shielding (wearing lead gloves and lead aprons) when using portable X-ray units contributed significantly to the decrease in overall exposure to the personnel (attenuation of the beam). The lead apron and gloves attenuated the primary beam by 96.9% and 99.2%, respectively. However, the study also noted that protective shielding is not always used as it often proves an impediment for the user in performing the study as a result of the weight and comfort of the protective gear.

Steyn et al. (2005) documented the radiation exposure rates during nuclear medicine imaging and observed the usefulness of wearing a lead apron to reduce personnel exposure. Given that the dose to technologists working with horses is higher than in human practice, the use of lead aprons proved a significant reduction in personnel exposure with mean dose reduction factors ranging from 3.6 to 5.7.[11] It must be noted that radiation protection regulations stipulate that radiation shielding is employed for persons involved in the use of radiation.[2] A study by Morgan (1991)[18] described the experiences of pre-veterinary students in relation to radiation safety practice. The research reported that of those having experience in large animal practices, 69% ($n = 163/236$) regularly used hand-held cassettes during radiographic studies. The necessity for this type of procedure may be circumnavigated with the use of cassette holders (holding poles), which allow for the person to remain as far as practicable from the edge of the primary beam.

Monitoring

The Code of Practice stipulates that if the provisions of the Safety Guide are applied carefully and with consistency, the risk of radiation damage will be slight.[2] It also alerts practitioners to the requirement of radiation monitors to ensure a record of doses is available. Recommendations suggest the monitors should be worn on the trunk, between the waist and the shoulder, and under any protective garments to ensure measurements are representative of the dose received by the person. Requirements mandate personal radiation monitoring to be worn by persons likely to be exposed to ionising radiation in excess of 1 mSv in any one year.[2] The probability of exposure beyond the accepted 1 mSv/yr for veterinarians and those associated with veterinary procedures is increased during large animal radiography. Nuclear medicine potentially exposes personnel to radioactive contamination and inhalation or ingestion risks and the comparably high doses in radiotherapy create a potential hazard to the operators.[2] Within this study it was demonstrated that staff monitoring was not used in at least one-fifth of clinics. The study demonstrated at least six participants practised the wearing of the monitors on top of their aprons, hence recording a measurement of exposure as would be received by the apron and not the exposure that would be received by the individual. Demonstrating a pattern in the failure of veterinarians to consistently include monitoring for potential radiation exposure, a study conducted in 1989 by Wiggins et al. discovered that of 375 veterinarians who reported taking X-rays, 41% did not wear monitoring badges.[12] Additionally, large animal practitioners were found to be less likely to wear monitors ($p < 0.05$).[12]

Storage

Specific requirements for the storage and preparation of radioactive sources are stipulated by the Code of Practice (ARPANSA).[2] These requirements include a locked source container with strict access control and labelled with a notice displaying the radiation hazard warning. Survey results suggest the general storage for sources involved a lead container in some cases. The position for storage of this container was not identified, nor was the use of labelling. Some responses identified a 'specifically-designed room' to have been used for the storage of radioactive sources, however, the properties of this space were not specified.

In view of the potential dangers associated with the use of radioactive materials, the preparation of these requires rigorous attention to safety procedures. The space within which these radioactive sources are prepared and ultimately administered or implanted needs to be specifically designed for the purposes, and those conducting the procedure must be adequately trained.[2] As far as practical, preparation of sources should be carried out in a defined room that contains radiation-shielding provisions for each person and which has restricted access. However, survey results suggest that whilst the majority of clinics comprised a specifically-designed space, one practitioner noted using 'any space available'.

Quarantine

In reference to the quarantine of animals post-implantation of radioactive sources, regulations stipulate the animals must be housed under regular supervision and within a space equivalent to a stall that reduces the likelihood of an escape by the animal.[2] The location of the quarantine stall should be at least 3 m from a walk-through area. Furthermore, animals with permanent implantation of radioactive sources must be housed until the total radiation activity for companion animals is less than 1.2 GBq (animals in regular contact with humans) and 6 GBq for field animals (animals normally held in a paddock).[2] Results from the survey suggest the majority of the clinics kept the horse within the clinic until the exposure was minimal, however, two of the respondents allowed the animal to return to the owner's property following implantation with the advice to 'keep a distance from the treated area'.

Limitations of current study

A number of limitations must be declared in view of their possible impact on the results. It should be noted that the method used to identify facilities, using a combination of records accessed via the Australian Equine Veterinary Association (AEVA) public website, through internet searches, and the Yellow Pages® did not guarantee that all Australian veterinarians were invited to participate. The relatively low response rate may indicate that results reported here are not fully representative of all equine practices. The low response rate also impeded in-depth statistical analysis that may otherwise have been possible for a greater number of responses. Finally, in view of the link between the Code of Practice for Radiation Protection in Veterinary Medicine and the survey, it must be noted that specific questions regarding the 'Radiation Management Plan' and its implementation within clinics as well as the 'Responsible Person', would have informed our research more comprehensively. Furthermore, explicit questions using terminology used in the Code of Practice may have better informed the research.

Conclusions and recommendations for veterinary workers

In keeping with the acknowledgement that veterinarians are a unique professional body on account of their patient load, the requirement for manual handling, and the generalist capabilities of individuals within this profession, it seems clear that definitive education and a prudent approach to existing regulations and guidelines is required.[17] Such an approach would include honouring the principles of time, distance and shielding and considering the concept of ALARA during every procedure that involves the use of radiation, whether it is for diagnostic or therapeutic purposes.[8]

Regulations and standards are available and mandatory for all practices using radiation, the implementation of these and the recognition of their importance are crucial to ensuring compliance is effected and ongoing. It is accepted that veterinary practitioners are highly educated individuals with a capacity for understanding regulatory requirements. It is our view that provision of detailed information, education and training in relation to regulations and the steps required to adhere to these are required as a platform to generate compliance within clinics.

Complications resulting from exposure to radiation are a real possibility.[19] Whilst the provision of radiation protection devices and regulations have improved greatly over time, it is primarily work practices that remain as a determinant of the amount of personal exposure to ionising radiation received by individuals.[10] It is apparent that in the majority of cases, comprehensive training and education within the veterinary group sampled in this survey in relation to radiation safety would benefit practice. The training program should include guidance towards compliance with regulatory requirements, the adoption of the 'Radiation Management Plan' and the 'Responsible Person' as well as information regarding the effects of radiation and how to best avoid unnecessary exposure through optimal work practices. Underpinning the recommendations of the training program would be the provision of explicit recommendations to alter current practice and align it with the Code of Practice. The ultimate goal would be to increase veterinarian awareness of the importance of radiation safety and to augment compliance by providing easily adaptable alternatives to current practice. Some simple practical applications could include:

- Where possible, the use of cassette holders on poles to increase distance from the source
- Wearing lead gowns during procedures where being at close proximity to the animal is unavoidable
- Wearing TLD monitors for all radiation procedures
- Wearing TLD monitors under gowns
- If restraining animals or holding imaging detectors during radiation procedures, the use of finger TLDs is recommended.

Conflict of interest

None.

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4.3 TREATMENT APPROACHES TO OCULAR AND/OR PERIOCULAR SQUAMOUS CELL CARCINOMA IN HORSES: RESULTS OF AN AUSTRALIAN SURVEY (PAPER 5)

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Treatment Approaches to Ocular and/or Periocular Squamous Cell Carcinoma in Horses: Results of an Australian Survey

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ABSTRACT

Objective: To examine current and past treatment of ocular and/or periocular squamous cell carcinoma (OSCC and/or POSCC) in horses in Australia with a particular interest in brachytherapy use, awareness and practice.

Design: A survey was sent to equine veterinarians working in Australia. The survey was delivered online and comprised 52 open and closed format questions. The participants were asked about their treatment approaches to squamous cell carcinoma in horses with particular emphasis on OSCC and/or POSCC and the use of brachytherapy as a treatment option. The survey was evaluated by a veterinarian working party, led by a veterinary collaborator on the research. Results from the survey were supplemented by previously collected survey data (2011) in the area of brachytherapy for the same veterinarian cohort.

Results: A total 86 surveys were returned from the initial survey (2011) and 24 veterinarians responded to the second survey (2015). Fourty-four percent of respondents suggested they would be willing to learn more about brachytherapy and pursue it as a treatment option. Previous brachytherapy use was reported by 9% of respondents. The surveys did not identify any current users of brachytherapy within Australia. Results from the 2015 survey also identified that the most commonly preferred treatment approach for OSCC/POSCC sites and for sites outside of this classification (ear pinnae, muzzle, lips, nostrils, vulva, penis or prepuce, perianal/perineum and extremities), was surgery followed by cryotherapy.

Conclusion: This study reports on current treatment approaches to Squamous cell carcinoma (SCC) in horses in Australia. Additionally, it investigates current and past use, knowledge and perceptions of Australian veterinarians on brachytherapy treatment. The results emphasise that current treatment approaches to SCC in horses, regardless of site, rely on surgery, with cryotherapy as a secondary preferred treatment type. Investigations have also discovered that brachytherapy in horses is currently not evident in Australia however was used in past years. Veterinarians have noted some interest in the potential for the reintroduction of brachytherapy in Australia.

INTRODUCTION

SCC of the eye and adnexa is the most common non-melanocytic tumour of the eye and adnexa in horses. [1-3] The management of equine OSCC and/or POSCC remains a challenge despite its high prevalence among horses. Literature suggests a number of treatment modalities currently exist; surgery, photodynamic therapy, cryotherapy, carbon dioxide (CO_2) laser ablation, radiofrequency hyperthermia, topical or intratumoral chemotherapy, and radiation therapy (RT), predominantly in the form of brachytherapy (implantation of sealed radioactive sources). [4] Whilst no technique can conclusively be identified as the best approach to the treatment of OSCC/POSCC, successful treatment commonly involves one of the above therapies combined with cytoreductive surgery. Furthermore, the value of combining radiation therapy with

surgery or using radiation therapy alone has been identified in relation to benefits in decreasing cosmetic and functional defects. [5-7]

Whilst there is abundant literature on the various approaches used by individual veterinary practitioners [8-20], reporting of outcomes are diverse and non-standard, making it difficult to conclude on the efficacy of the various options. Without an evidence-based approach supported by guidelines, recommendations and reporting parameters, the treatment techniques for OSCC and/or POSCC have become individualised and based on little else than anecdotal information. In contrast, treatment for SCC in human counterparts is an established and successful therapy, with various possible options including excisional surgery (or Moh's surgery) alone or in combination with cryotherapy or RT (external or interstitial). [21, 22]

Interstitial brachytherapy has been identified as one of the most effective treatment options (in combination with other techniques) for ocular/periocular squamous cell carcinoma in equine with regard to recurrence rates, local control, side-effect profile and logistics. [23] The treatment options used in Australia, however, rarely involve the application of radiation therapy (RT) in any format.[24] Veterinarians presented with animals afflicted by cancer, have employed alternate treatment therapies like surgery alone, that have been demonstrated to be less effective with regard to recurrence and local control.[3, 23, 25]

The brachytherapy method of delivering radiation has a number of advantages over other treatment techniques.[26] These include the application of higher doses to the lesion, less damage to surrounding tissue, and more precise geometrical localisation. The treatment can be administered under sedation (constant rate infusion) and does not require a general anaesthetic (GA) in most cases; a significant advantage in view of the known dangers associated with GAs in horses (morbidity and mortality). [27-29] Additional benefits of RT include significantly better cosmetic results and higher preservation of functions compared to other modalities like surgery.[5-7, 27] Unlike chemotherapy, RT is localised and does not cause systemic toxicity.[27]

This paper reports the results of an Australia-wide survey of veterinarians. It is supplemented with data previously collected from the same cohort of veterinarians and

in reference to brachytherapy use in Australia. It represents the initial phase of an ongoing investigation into the efficacy and value of developing a standardised brachytherapy treatment protocol inclusive of radiation safety parameters for the treatment of horses with OSCC and/or POSCC in Australia.

MATERIALS AND METHOD

Ethical approval for this research was granted by the University of Newcastle Ethics Committee, (H-2009-0136).

The Surveys

Both surveys were designed on the web-based program Survey Monkey (www.surveymonkey.com, California Office: 640 Oak Grove Avenue, Menlo Park, CA 94025 USA). The initial survey (2011) comprised 49 questions however only data directly related to brachytherapy has been included within this manuscript. The second survey (2015) comprised 52 questions, including both open and closed format questions, and was subdivided into four sections (Figure 1): demographics; case presentation and diagnosis; current treatment practices and brachytherapy use and knowledge. The questions sought brief educational and professional background, current treatment practice with regard to anatomical site, presentation of squamous cell carcinoma cases, and the current treatment processes in place for these cases. The same questions specific to past and current brachytherapy use were included in both surveys.

It must be noted that the development and distribution of the second survey (2015) stemmed from the need for more comprehensive data collection with regard to specific delineation of anatomical sites surrounding the eye in horses. The initial questions in the first survey were deemed to be too generic hence warranting a re-write supported by a thorough evaluation by a panel of six veterinarian experts in the field of ophthalmology in horses.

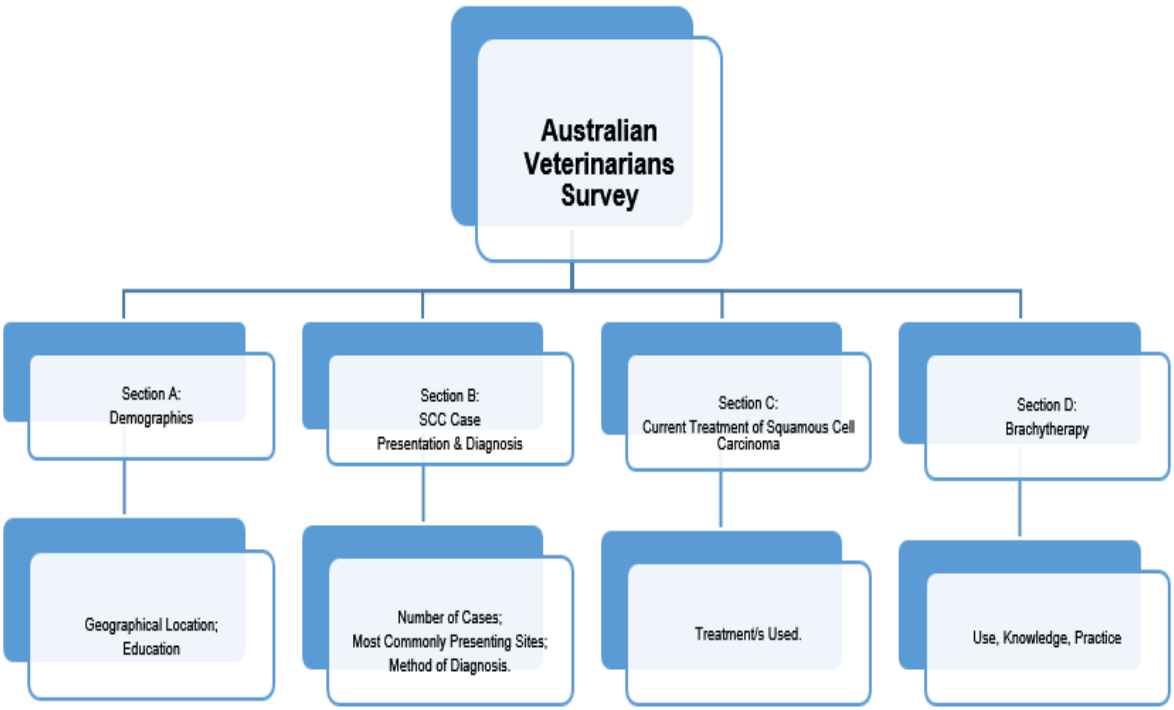

Figure 1: Survey of Australian Veterinarians

Wherever brachytherapy-specific questions were unchanged in both surveys, the responses to these have been reported on collectively. Responses to site specific SCC sites and treatment approaches to these have stemmed from the second survey (2015) only. Much of the data collected from the first survey was related to radiation safety in veterinary clinics and has been published separately. [30]

Participant Group

Veterinarians who work with horses were identified through records accessed through the Australian Equine Veterinary Association (AEVA) public website, through internet searches, the Yellow Pages® and through the AEVA newsletter distributed to their members. However rigorous the process of identifying all veterinarians working with horses, it cannot be confirmed that all Australian equine veterinarians were invited to participate.

The first online survey (2011) was sent to veterinarians identified through the AEVA fortnightly e-mailed newsletter, followed by a 2-weekly reminder email and then sent directly to an additional group of practitioners identified through the internet and

Yellow Pages®. The number of responses received was 86. The second survey (2015) was also sent to veterinarians identified through the AEVA fortnightly e-mailed newsletter, followed by a 2-weekly reminder email. The total number of responses received in 2015 was 24. Responses to the initial survey (2011) gained a higher response rate of 86 however of these, only 9 participants provided information regarding brachytherapy specifically. The brachytherapy data has been amalgamated with the 2011 responses for analyses. The newsletter circulated by the AEVA requested the voluntary participation of its readers in the online survey by providing them with a link and an explanation of the research aims and objectives.

RESULTS

The Respondents - 2011

The number of completed and analysed surveys was 86. A wide cross-section of Australia was represented with responding veterinarians living throughout all states and territories, some reporting to practice in more than one state/territory. Of these, 42% (n=36) worked in New South Wales; 22% (n=19) in Victoria; 20% (n=17) in Queensland; 9% (n=8) in Western Australia; 6% (n=5) South Australia; 4% (n=3) in the Australian Capital Territory; 2% (n=2) Tasmania; and 1% (n=1) in the Northern Territory.

A total of 40% cited a higher qualification beyond a Bachelor of Veterinary Science (BVSc) (90%, n=78), including Masters (9%, n=8), PhD (2%, n=2), Veterinary Scientists Fellowship (7%, n=6) and 'Other' (22%, n=19). Other qualifications included general science and applied science degrees (2%, n=2), toxicology (1%, n=1), equine medicine (3%, n=3), surgery (4%, n=4), dentistry (1%, n=1), anaesthesia, ophthalmology and epidemiology (1%, n=1).

The Respondents - 2015

The number of completed and analysed responses for the 2015 survey was 24. Of these, 11 (46%) worked in New South Wales; 9 (38%) in Victoria; 3 (13%) in Queensland; 1 (4%) in Western Australia; 2 (8%) in South Australia; 1 (4%) in Tasmania; and 1 (4%) in the Northern Territory. There were no respondents from the Australian Capital Territory.

A total of 15 veterinarians (63%) cited a higher qualification beyond a Bachelor of Veterinary Science (BVSc), including Masters (n=3, 13%), (Fellow) Australian and New Zealand College of Veterinary Surgeons (FANZCVS) (n=2, 8%) and (Member) Australian and New Zealand College of Veterinary Surgeons (MANZCVS) (n=6, 25%) and 'Other' (n=2, 8%). Other qualifications included equine medicine (n=1, 4%), equine surgery (n=1, 4%) and American Boarded Specialist in Equine Medicine (n=1, 4%).

Practice Settings - 2011

Of the respondents, 91% reported horses to be one of the main animal types serviced at their clinics. Other animal types included cattle, reptiles, sheep, goats, possums, crocodiles, alpacas and other native wildlife.

Practice Settings - 2015

Of the 24 participants, most cited working in a private/first opinion clinic (n=20, 83%), two classified their work site as a referral clinic only (8%) and another as a university setting (4%). Another participant described their work setting as a thoroughbred breeding stud (4%).

The percentage attributed to horse-related cases ranged between 10-25% (n=7, 29%) and 76-100% (n=15, 63%) with only 2 (8%) clinics reporting to constitute approximately 26-50% of horse cases (Figure 2).

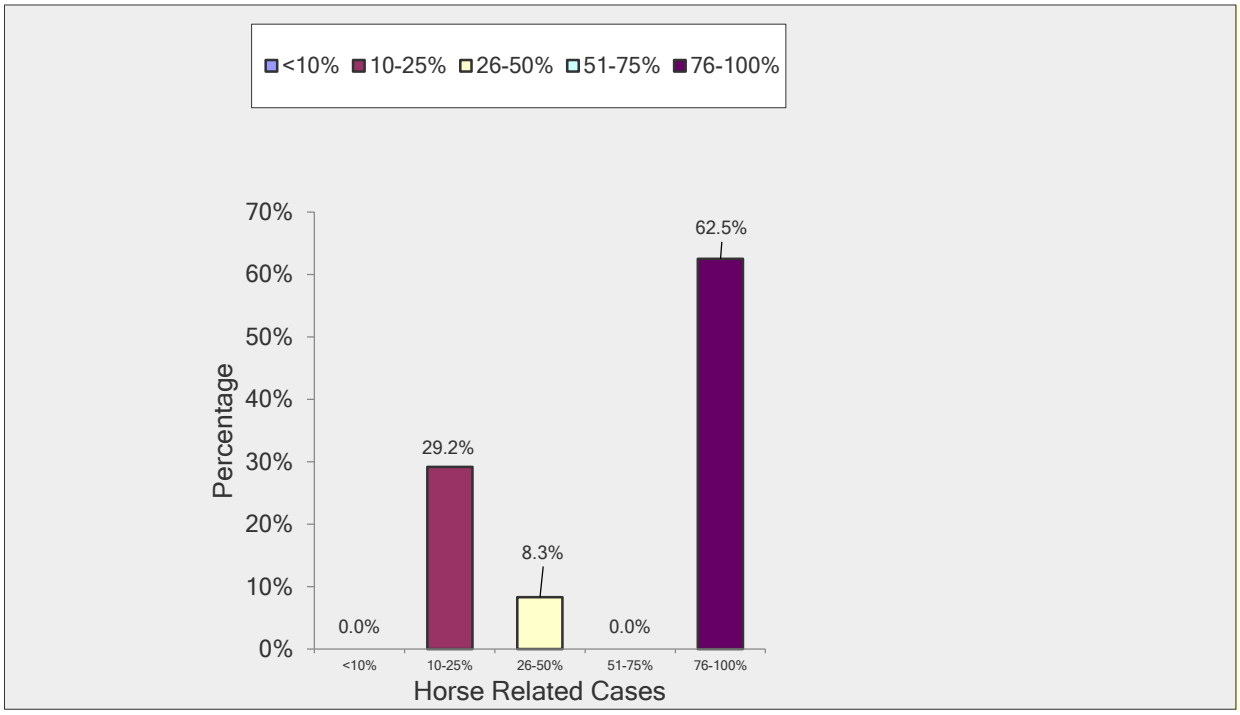

Figure 2: Percentage of Practice Dedicated to Horse Related Cases

SCC Case Presentation - 2011

In relation to the number of cases of SCC (all locations) presenting to a veterinarian on a monthly basis (n=20 responses in total), 14 (70%) noted 1–2 cases, 2 (10%) reported 3-6 cases, and four (20%) reported zero cases. Another four (20%) respondents reported seeing between 1-3 cases per year.

Non-OSCC/POSCC Sites - 2015

Participants were asked to rank the most commonly reported areas of presentation for SCC at sites other than OSCC/POSCC. The ranking system allocated the number 1 as the most highly ranked item, and the results of the ranking were averaged, thus the most common item is expressed by the smallest number. A total of 20 participants answered this question. Rankings show the penis or prepuce to be the most common area for the presentation of SCC followed by the nostrils, muzzle, vulva, the lips, perianal/perineum area, ear pinnae and the extremities (Figure 3).

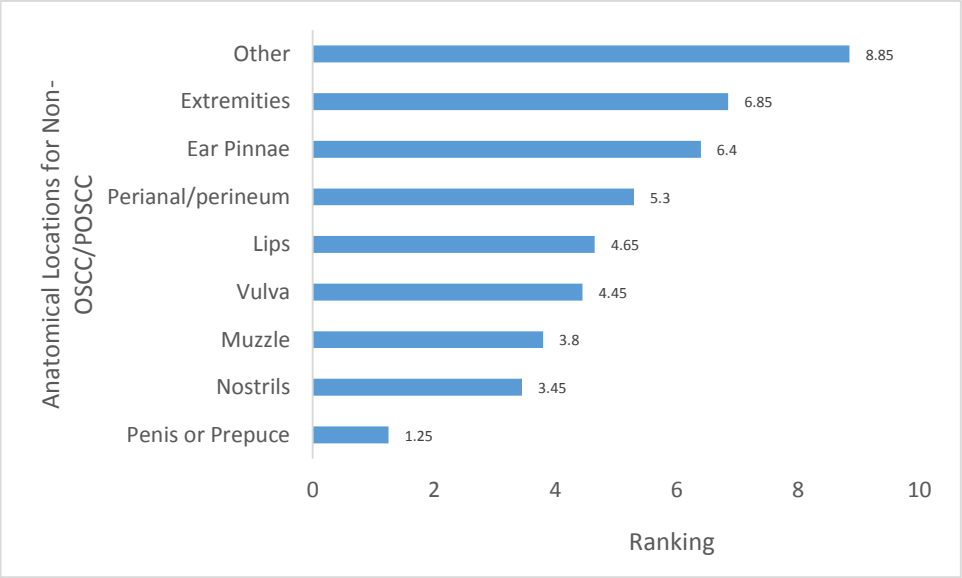

Figure 3: Ranked Anatomical Locations Where Non-OSCC/POSCC is Most Commonly Located

OSCC/POSCC Sites - 2015

In particular relation to OSCC/POSCC cases where OSCC includes the cornea, limbus, and bulbar conjunctiva, and POSCC includes the eyelid, third eyelid and medial canthus, participants were asked to rank the most common to least common areas where they had located SCC. A total of 20 participants responded to this question. The most common area was reported to be within the third eyelid. Ranked in second place was the eyelid (eyelid skin and margin), followed by the limbus, medial canthus, bulbar conjunctiva and cornea (Figure 4).

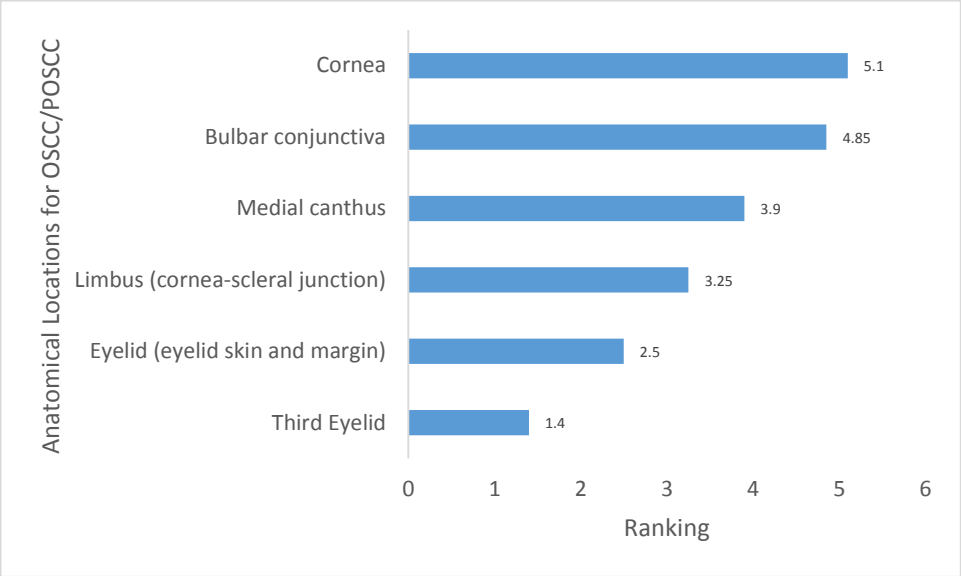

Figure 4: Ranked Anatomical Locations for OSCC/POSCC

Diagnosis - 2015

In relation to the methods of diagnosing SCC, the responses indicated multiple, mixed approaches. Of the 20 respondents, one (5%) based their diagnosis on clinical presentation alone, whilst another (n=1, 5%) based their diagnosis on an incisional biopsy alone. Two other veterinarians (10%) reported establishing diagnosis based on an excisional biopsy, whilst a number of respondents cited using a combination of diagnosis approaches as described below. Six participants (30%) reported their method of diagnosis to include clinical presentation, incisional and excisional biopsies. Another five (25%) referred to a combination of clinical presentation and excisional biopsy whilst only two (10%) reported using clinical presentation grouped with incisional biopsy. Two other participants (10%) selected all available diagnosis approaches as their technique; clinical presentation, incisional and excisional biopsies and cytology. Only one participant (5%) noted using clinical presentation and cytology alone.

When asked if the cost of histopathology services contributed to the decision to make a solely clinical diagnosis, responses varied from 'sometimes' to 'often' in 60% (n=12) and 35% (n=7) of cases respectively and 'never' in 5% of cases (n=1).

Current Treatment of SCC in Areas Other Than OSCC/POSCC - 2015

Participants were asked to nominate their preferred treatment options for specific sites as related to areas other than OSCC/POSCC. A total of 16 participants responded to this question. Treatment options included; surgery, RT, brachytherapy, strontium-90, plaque RT, cryotherapy, carbon dioxide CO_2 laser ablation, photodynamic therapy, immunotherapy (topical or intralesional) or chemotherapy (topical or intralesional). The areas identified as 'all other' beyond OSCC/POSCC included; ear pinnae, muzzle, lips, nostrils, vulva, penis or prepuce, perianal/perineum and the extremities.

Surgery alone was noted to be a preferred treatment approach for 15 participants (94%) for the ear pinnae and the penis or prepuce. The vulva was identified by 14 respondents (88%) as a site where surgical intervention was preferred whilst 13 participants (45%), noted surgery alone was their treatment option for the muzzle, lips and nostrils, respectively. With reference to the perianal/perineum or extremities, 12 respondents (75%) cited surgery as their chosen approach.

RT was chosen as the preferred option by one respondent (6%) for the treatment of all 'other sites' whilst another respondent (n=2, 13%) also noted the penis or prepuce would be a suitable site for the application of RT. Brachytherapy was only identified as a treatment option in the treatment of the nostrils or extremities by one respondent. Cryotherapy obtained eight respondents (50%) in agreement with the approach being a preferred treatment for the muzzle and lips, whilst six participants (38%) cited cryotherapy as a treatment choice for the nostrils, vulva, perianal/perineum and the extremities. Cryotherapy was also named as a favoured treatment approach to the ear pinnae in seven cases (44%) whilst five (31%) noted it would be favourable in the treatment of the penis or prepuce. Carbon dioxide CO_2 laser ablation was categorised as a preferred treatment option in the treatment of the nostrils by a single participant (6%).

All sites were identified by a single participant (6%) in each case to be appropriate areas for the application of immunotherapy (topical) whilst two participants (13%) noted the penis or prepuce would benefit from the application of immunotherapy (topical) as a preferred option. Similarly, one respondent (6%) per site noted immunotherapy

(intralesional) would be a preferred choice for the muzzle, lips, nostrils and the extremities.

Chemotherapy (topical) was noted by three participants (19%) to be the preferred treatment for the ear pinnae and the lips, respectively, whilst four participants (25%) named topical chemotherapy as the preferred treatment approach for the muzzle, nostrils, penis or prepuce and the extremities. Five respondents (31%) chose topical chemotherapy as the treatment choice for the vulva and perianal/perineum, respectively. Intralesional chemotherapy was noted as one of the prime treatment approach by four participants (25%) for the muzzle, lips, nostrils, perianal/perineum and the extremities. Five participants (31%) noted intralesional chemotherapy as their choice for the treatment of the penis or prepuce, whilst three respondents (19%) indicated they would use intralesional chemotherapy to treat the ear pinnae and the vulva. Strontium-90, plaque therapy and photodynamic therapy were not selected by any respondents as a preferred treatment option for any of the sites (Figure 5).

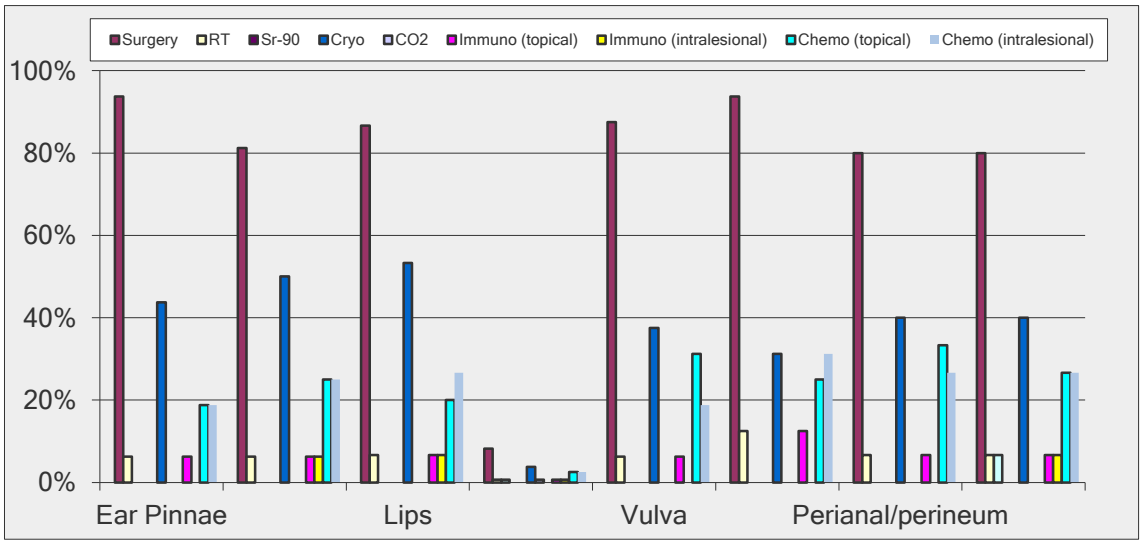

Figure 5: Preferred Treatment Options for Sites Other Than OSCC/POSCC

Current Treatment of OSCC (cornea, limbus, bulbar conjunctiva) - 2015

When participants were given the opportunity to record their preferred treatment approaches for the OSCC sites (cornea, limbus and bulbar conjunctiva), interestingly a

number of treatment options received no responses as a possible preferred treatment, they included; brachytherapy, plaque RT, carbon dioxide CO_2 laser ablation, photodynamic therapy and immunotherapy (topical and intralesional).

The most commonly selected preferred option for the cornea and bulbar conjunctiva was surgery with 15 (94%) respondents selecting this as one of their preferred options (Figure 6). All participants (100%) selected surgery as their preferred treatment approach for the limbus (corneo-scleral junction). RT was selected for each site, by one respondent. Cryotherapy was identified by seven participants (44%) as one of the preferred approaches to the treatment of the cornea and the bulbar conjunctiva. Eight participants (50%) also selected cryotherapy for the treatment of the limbus. Topical chemotherapy for the cornea and limbus was identified by seven participants (44%) as a preferred technique, whilst five (31%) noted they would use it for the treatment of the bulbar conjunctiva. Intralesional chemotherapy was chosen by four participants to be a preferred approach in the treatment of the limbus and bulbar conjunctiva, respectively whilst only two opted for this treatment method with reference to the cornea (Figure 6).

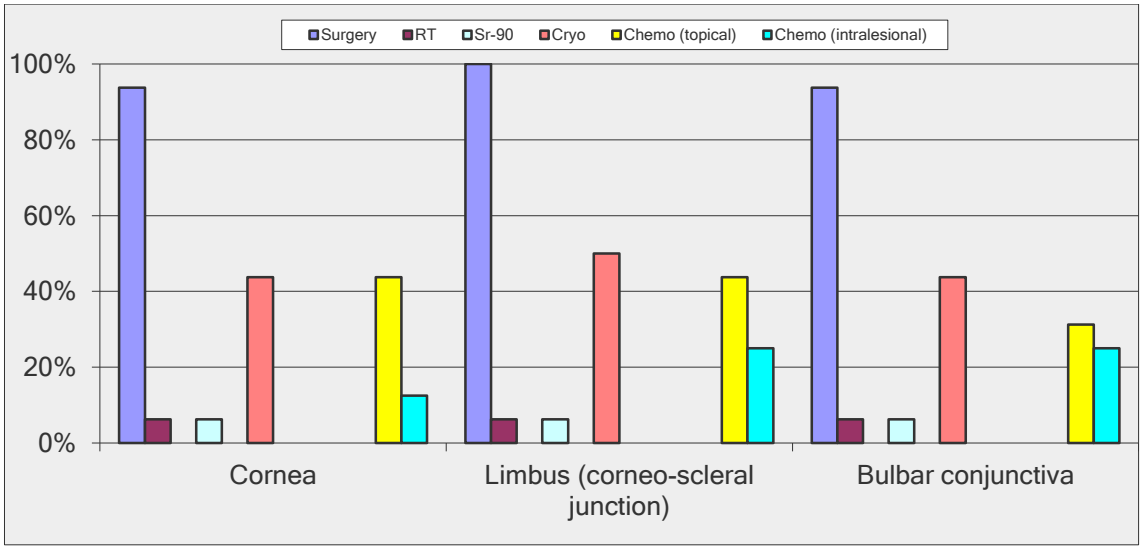

Figure 6: Preferred Treatment Options for OSCC Sites

Current Treatment of POSCC (eyelid, third eyelid, medial canthus) - 2015

The eyelid, third eyelid and the medial canthus are all classified as POSCC. Once again, a number of treatment options received no responses with reference to possible preferred treatments, these included; strontium-90, plaque RT, carbon dioxide CO_2 laser ablation and photodynamic therapy (Figure 7). The most widespread treatment choice with reference to all three sites for POSCC was surgery with a total of 16 participants (100%) selecting it as their preferred approach to treating the third eyelid, another 15 (94%) choosing it for eyelid treatment and 12 (75%) selecting surgery as the preferred treatment for the medial canthus.

Radiation therapy was selected as a preferred treatment approach for all three sites by a single participant, whilst brachytherapy was selected for the treatment of the eyelid and medial canthus but not the third eyelid, by another respondent.

Six participants (38%) chose cryotherapy as a favoured treatment technique for the eyelid and medial canthus whilst only three (19%) noted they would use it for the treatment of the third eyelid. Topical immunotherapy was elected by a single (6%) participant for each site as a favoured approach, whilst intralesional immunotherapy was selected by three (19%) participants for the eyelid, one (6%) for the third eyelid and two (13%) for the medial canthus.

With reference to chemotherapy (topical and intralesional), two participants (13%) cited its application for the third eyelid as preferable whilst another five (31%) cited the use of intralesional chemotherapy as ideal for the treatment of the eyelid and medial canthus. A further singular (6%) participant chose topical chemotherapy for the eyelid whilst another three (19%) preferred the use of topical chemotherapy for the medial canthus (Figure 7).

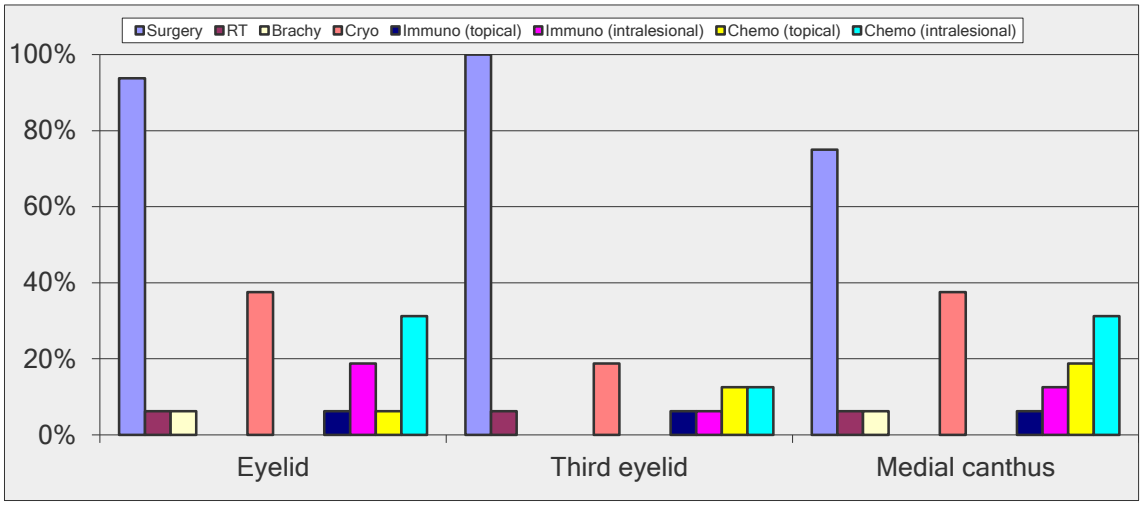

Figure 7: Preferred Treatment Options for POSCC Sites

Surgical Intervention Outcomes – (2011 & 2015)

In reference to the potential outcomes of surgery in and around the eye to provide clear surgical margins, respondents were asked how often this treatment had resulted in the removal of the globe (enucleation). A total of 99 responses were collected. The majority of respondents (65%, n=64) suggested removal of the globe occurred 'sometimes' and 26% (n=26) claimed it occurred 'often'. Nine respondents (9%) replied that it had 'never' occurred.

Brachytherapy Use – (2011 & 2015)

The questions related to brachytherapy use were unchanged for both surveys, 2011 and 2015 hence the responses have been combined and analysed jointly. The majority of respondents (from 38 responses to the question) answered 'no' (n=28, 74%) when asked if they considered brachytherapy to be a well-known treatment method in veterinary science. There was a view that the cost of treatment would be 'prohibitive' in many instances and that licensing was 'hard to get' in Australia with reference to the use of radioactive sources. The availability of radioactive sources and the difficulties associated with this were viewed as major barriers to the use of brachytherapy currently in Australia.

The sub-set of survey questions pertaining to brachytherapy was frequently unanswered. Of the total 110 respondents, 10 (9%) completed this section of the surveys in its entirety and reported having used brachytherapy in the past (three other participants responded to some questions within this section only). The use of brachytherapy was recorded as spanning over three decades. The earliest recorded use was in 1977 and the last of the treatments was applied in 2007 (Table 1). The researchers are also not aware of any brachytherapy treatments being applied since 2007 within Australia. When respondents were asked to comment on reasons for the discontinuation of past treatment, they claimed 'poor availability', 'very expensive', 'problems with radiation licensing', 'cannot get it anymore otherwise would still use it', and 'radiation risk' as their rationale.

Table 1: Brachytherapy Use Amongst Australian Veterinarians

Respondent	Year commenced using brachytherapy	Year ceased using brachytherapy	Total no. of years
64	1977	1980	3
13	1980	2000	20
79	1983	2006	23
77	1987	2004	17
55	1990	2005	15
73	1995	2007	12
75	1998	1998	<1
46	1999	2004	5
60	2000	2005	5
110	unknown	unknown	>4

The application of brachytherapy within the 'active' cohort ranged from once monthly, once 3-monthly, once 6-monthly to once yearly. Other responses were '6 cases in 20 years – only on expensive broodmares', 'every 3 years', and 'twice only' (Table 2).

Table 2: Frequency of Brachytherapy Use

Frequency	No. of respondents
Once monthly	1
Once 3-monthly	1
Once 6-monthly	5
Once yearly	2
Other	3

The most commonly used radioactive source for brachytherapy treatment was gold-198 (10 of 13 responses) followed by iridium-192 (1 of 13 responses), and strontium-90 (1 of 13 responses). One response cited, 'I don't know what it was'. The use of radioactive sources in the form of seeds (9 of 12 responses) was most common, with wires also being used in the remaining 3 cases. No respondent had used brachytherapy in plaque form.

Brachytherapy Application

An open question was asked on the procedures that veterinarians perform in relation to the application of brachytherapy and in direct reference to the dose delivery parameters including dose and time. The calculation of dose and time in each individual case was reported to be 'decided at the time of implantation based on clinical observation of the lesion' in 36% (n=4) of cases. Two respondents claimed their calculations varied each time depending on the size of the lesion. Two respondents claimed the use of a 'treatment plan using radiation therapy software and principles', and another used 'the same for each treatment based on previous observed rates of local control'. Another respondent preferred to vary the treatment time depending on the amount of source remaining, whilst another respondent used the same approach for each treatment based on a standardised protocol applied to all lesions (Table 3).

Table 3: Calculation of Dose and Time

Calculation of amount of dose and time to be applied to lesion	No. of respondents	%
Pre-determined by a treatment plan using RT software & principles	2	18
Decided at time of implantation based on clinical observation of lesion	4	36
Same for each treatment based on previous observed rates of local control	1	9
Same for each treatment based on standardised protocol applied to all lesions	1	9
Varies each time depending on amount of source remaining	1	9
Other	2	18

With reference to the preparation of sources, the participants were asked to describe the methods they most commonly implemented. Six (6) respondents used pre-prepared seeds and calculated the number used based on the half-life of the radioactive source at the time of implantation. Of the respondents, one (1) cut the wires to the same length in every instance and based their approach on 'what has worked in the past and without the use of a dose calibrator'. Reponses to 'Other' included 'don't know' (n=1), 'left to specialist' (n=1), and 'rely on radiotherapist to do calculations' (n=1) (Table 4).

Table 4: Preparation of Sources

Preparation of sources	No. of respondents	%
Cut wires to same length every time based on what has worked in the past WITHOUT the use of a dose calibrator	1	10
Used pre-prepared seeds, the number used is dependent on the radioactivity (half-life, dose) at time of implantation	6	60
Other	3	30

The veterinarians were presented with a list of four (4) choices in reference to the positioning of sources and the calculation of this positioning. Of the respondents, four decided on the position of the sources at the time of implantation and as a result of the size of the lesion, whilst one (1) respondent placed the sources 1cm apart regardless of any other parameters including size. Three of the respondents considered the shape of the lesion in their decision-making with regard to positioning of the seeds or wires and another calculated the position of the sources using a predetermined RT plan (Table 5).

Table 5: Calculation of Position of Sources

Calculation of Position of Sources	No. of respondents	%
As per predetermined treatment plan designed using radiation therapy software and principles	1	8
Approximately 1cm apart	1	8
Depends on the shape of the lesion	3	25
Decided at time of implantation based on SIZE of lesion (clinical examination)	4	33
Other	3	25

The use and application of brachytherapy requires modality-specific equipment. Participants were asked to itemise the type of equipment they owned and used in the application of brachytherapy within their clinic. Five of the respondents indicated that they owned and used a radiation survey meter/Geiger counter, seed gun and lead shield.

Brachytherapy Interest Amongst Respondents

The response to the question, 'Given the benefits of brachytherapy treatment in SCC, would you be interested in introducing/recommencing this type of treatment in your practice?' revealed that (44%) of respondents (n=48 from a possible 110) would be interested. Another 32% (n=35) noted they 'needed more information' before they could make a decision. A total of 16 comments were made in addition to the responses noted above. Some of those comments are listed below.

P5: 'Probably wouldn't want to use – (most staff are of child bearing age) – wouldn't want to expose staff to any increased risk of radiation exposure.'

P15: 'Need logistical information and costing and proof of effectiveness compared to other methods.'

P21: 'I would need direct hands-on exposure to techniques in the hands of an experienced operator before deciding whether the skill etc had a role within our practice.'

P27: 'Depending on cost.'

P53: 'Would have used it already but find it difficult to acquire and use peri-ocular not well studied.'

P68: 'If it were readily available, I would definitely consider it.'

P73: 'Strongly, I feel it is a very worthwhile treatment.'

Participants were given the opportunity to finalise the survey with any further comments they wished to note. Comments included, 'brachytherapy sounds like a good idea', 'as always, cost will be the main factor' (P59), and 'it would be worthwhile for your group to check licensing laws and regulations for the different states and territories in Australia and New Zealand with regard to the feasibility of this practice' (P9).

Limitations of Study

A major limitation within this study is that this research is confined to Australia and therefore generalised to Australian equine veterinarians and their practices. It cannot be guaranteed that all equine veterinarians were included within the initial invitation to participate or the follow-up survey due to the logistics of survey distribution therefore all veterinarians with relevant expert knowledge may not have had the opportunity to contribute to the research. It may be possible that those that completed the survey may not have had expert knowledge in the relevant fields however there may have been others within the clinic who had but did not contribute to the answers. Low response rates for both surveys adds to the issue of completeness of reporting on current practice. The low number of respondents and the weakness in the initial questions related to anatomical sites in the 2011 survey instigated the development and distribution of a

second round of surveys with the aim of collecting a valid number of responses on which to report and further distinguish anatomical structures. Once again, low numbers of respondents in the second survey have led to the limitations in terms of the validity of the analyses. As a result of the anonymity of participants, it may be that the same person who contributed to one of the nine responses in 2011 also contributed to the 2015 survey. Additionally, statistical analysis is limited to respondent counts due to the low number of participants making comparative analysis not possible.

Discussion

This study explored general current treatment practice as well as the use, knowledge and perceptions of Australian veterinarians on the varied aspects of brachytherapy treatment for OSCC and/or POSCC. The paper reports on data derived from responses to two separate surveys about OSCC and/or POSCC and forms part of a larger research project aiming to identify the tools needed to reintroduce brachytherapy within Australia.

Brachytherapy Interest

Whilst a moderate number of veterinarians reported an interest in the brachytherapy modality, their perceived need for more substantial information and training was evident. Limitations identified by participants in this survey highlighted barriers to using brachytherapy – including licensing and accessibility to purchasing of radioactive sources – have contributed to its current low use and application. In addition, the costs associated with not only the application of brachytherapy but other relevant procedures such as histopathology associated with making a diagnosis and post-treatment care required, add to the difficulties of adopting this treatment as mainstream. In some cases, respondents noted concern for the potential radiation risk related with such a treatment and the requirement for more education and training in this area.

Preferred Treatment Approaches

The responses identified the current treatment modalities most commonly used to be surgery in most cases regardless of location, closely followed by cryotherapy and topical or intralesional chemotherapy drugs, or a combination of any two or more of these

modalities. Literature suggests, the use of surgery often results in the requirement for extensive margin resections as a consequence of unknown tumour infiltration. Such extensive surgery can result in the need for enucleation. [31] Although sole surgical resection of equine OSCC/POSCC may be adequate as long as the margins are consistently clear and the tumours are small or identified as carcinomas in situ, tumour recurrence as a result of inadequate surgical excision are commonly reported. [5, 32] Studies investigating the efficacy of surgery as a sole treatment for OSCC/POSCC agree that tumour recurrence is significantly high without the use of a combination of treatments. [3, 25] Regardless of this evidence, surgery remains the most commonly used treatment modality as a sole therapy or in combination with other regimes.

To maximise the benefits of the application of brachytherapy, it is essential that the treatment is delivered proficiently. This proficiency requires the accurate delivery of the technique inclusive of dosimetric specifications, radiation safety considerations and a substantial follow-up. It became evident from those veterinarians who had used brachytherapy in the past, that the methods of application, protocols, equipment and follow-up procedures lacked a systematic or common approach. Individuals demonstrated varied ways of calculating the dose and time of implantation, preparation of sources and positioning of seeds or wires for treatment within the lesion. This variation of approach and the lack of transferable evidence between treatments reduce the likelihood of relevant data collection for the purposes of identifying an evidence-based best practice treatment system.

Conclusion

The results demonstrated a wide and varying approach to the treatment of OSCC/POSCC in horses across Australia however, regardless of the limitations of this study, it is clear that surgery was a preferred treatment approach to OSCC/POSCC for most of the respondents. However, literature affirms the use of surgery in the OSCC/POSCC region has been largely associated with tumour recurrence as a result of incomplete surgical resection.[5, 32] Furthermore, enucleation is not uncommon due to the need for broad margin resections in some cases. [31] In view of the evidence, and the moderate interest indicated from veterinarians in recommencing or introducing

brachytherapy within their practice, it may be proposed that further investigation into the benefits of brachytherapy treatment in OSCC/POSCC in horses would be valuable in contributing to the current knowledge base. In addition, and based on known human treatment benefits, the technique may potentially limit the requirements for extensive resection and potentially reduce the need for enucleation. [23]

Acknowledgments

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CHAPTER 5: TREATMENT PROTOCOL

5.1 CHAPTER OVERVIEW

This chapter is the second last phase in the research and includes a developed **Protocol** for equine OSCC/POSCC treatment with interstitial brachytherapy (gold-198). The Protocol, describing the recommended treatment process, is supported by known ICRU recommendations for brachytherapy treatment in humans, and has been developed in line with accepted Code of Practice regulatory recommendations related to Radiation Protection and Safety in Veterinary Medicine. [1, 2]

To better explain the development of the **Protocol** and as a means of comparison, the initial treatment approach used for the SCC brachytherapy cases in the retrospective case series (1999-2007, Chapter 3), has been included. Both approaches (initial treatment process and developed protocol) are presented in chart-form and referred to as Process-Flows. Gaps identified in the initial treatment approach (1999-2007) have been resolved to better align with accepted brachytherapy treatment procedure, (human), dose reporting requirements and overall regulatory recommendations, resulting in the **'Protocol'**. [1]

Each 'Process' has been described as follows;

1. **Retrospective Treatment Process (1999-2007)** (Figure 5.1).

   A flow-chart describing the initial treatment process used for OSCC/POSCC brachytherapy between 1999-2007 (retrospective).

2. **Recommended Treatment Protocol** (Figure 5.2).

   A flow-chart describing a best-practice approach to the treatment process.

The ***initial*** **Retrospective Treatment Process (1999-2007)** (Figure 5.1) has then been compared to the **Recommended Treatment Protocol** (Figure 5.2).

3. **Retrospective Treatment Process** versus **Recommended Treatment Protocol** (Figure 5.3).

   A flow-chart comparing the initial treatment process (1999-2007) and the recommended treatment process.

In effect, three separate Process-Flows are included within the first section of this chapter to help guide the reader identify the initial treatment approach as compared to the recommended approach (Figures 5.1-5.3).

5.2 PLAN COMPARISONS

Following on from the Process-Flow Charts, and to illustrate their use, comparisons between the treatment process used in the **Retrospective Treatment Process (1999-2007)** are made against the developed **Recommended Treatment Protocol** through the replication of a total of nine treatment plans. The cases chosen for replication are representative of the nine different sets of conditions identified in the retrospective medical reports. Dose reporting has been recorded for each initial plan as per the retrospective approach and again as a 'replan' using recommended planning principles.

In effect, the developed **Recommended Treatment Protocol** is used to replicate a series of treatments (optimised plans), dose reports are then compared to those resulting from the initial retrospective plans (un-optimised plans).

5.3 TREATMENT PLANNING PRINCIPLES

Radiation treatment planning systems calculate and display 3-dimensional dose distributions of radiation beams/fields, arranged around the body/tumour using a mathematical model of the radioisotope's radiation field. Each plan displays a dose distribution in relation to the target volume (tumour) and the OARs surrounding the target volume. The treatment planning process results in a custom plan for each patient that enables the radiation dose to be applied. Brachytherapy treatment planning consists of many individual steps (see Chapter 2), and like planning for EBRT, it is the beginning of the QA process to ensure treatment delivery is maintained within specified parameters required for an optimal treatment outcome. It is generally the role of the radiation therapist to produce an 'optimum' plan which is then approved by the radiation oncologist. The term 'optimum' may be best described as the selection of a best constituent or in the case of RT, a best 'plan' (with regard to some criteria) from a set of available alternatives. [3] Clinical requirements for a plan are translated from the

prescription for the patient, with the intention of the plan driving the complexity of the optimisation. [4]

Treatment planning computers offer a diverse number of tools which aid in localising treatment volumes and calculate dose distributions around these. Modern treatment planning is a complex process and has been constantly evolving over the past two decades. It provides a definitive base from which to develop highly complex treatment plans to deliver optimal treatments. The importance of treatment planning in the delivery of optimal radiation treatments cannot be understated.

5.3.1 TREATMENT PLANNING IN BRACHYTHERAPY

Whilst brachytherapy has the advantage of giving a localised dose to tumours, it is also associated with a number of disadvantages which must be overcome for successful application to occur. Disadvantages (as discussed in Chapter 2) include; the hazard of radiation exposure, the requirement for restriction or hospitalisation/quarantine of patient, the sharp fall-off of brachytherapy which can result in under-dosing if the implant does not adequately cover the tumour and the lack of suitability for large tumours due to its localised capabilities. [5] The clinical application of brachytherapy is therefore fraught with a number of potential difficulties. Treatment planning is perhaps the most important component in overcoming the dosimetry related difficulties and ensuring a successful brachytherapy procedure. Treatment planning involves clinical and physical elements; clinical evaluation, tumour volume and target volume determination, implant and radioisotope selection, amount of radioisotope, arrangement of radioisotope in tumour and overall dosimetry evaluation. Treatment planning in brachytherapy has historically involved X-ray films (localisation of tumour) and has now transitioned to the use of 3-dimensional data sets in most instances (derived from CT). If you consider the placement of seeds is determined during one procedure and that the entire dose is then delivered in this configuration, then optimal determination of seed placement to define the most effective dose distribution is a significant factor in the effectiveness of treatment as seeds remain in-situ for the entirety of treatment. [6]

5.4 DEVELOPMENT OF PROTOCOL

Chapter 3 provides a comprehensive analysis of the retrospective study conducted on 75 horse cases treated with brachytherapy in an Australian clinic. The initial treatments were performed without the use of a treatment planning system (computerised). Implantations occurred manually and wire placement and dose calculations were also conducted manually. Recording of OAR doses was not evident in any of the cases. The process followed by the clinic in the application of brachytherapy for OSCC/POSCC in 75 horses was analysed and recorded as a Flow-Chart (Figure 5.1), referred to as **'Retrospective Treatment Process (1999-2007)'**, this is referred to as the **Retrospective Process** from this point on. The process was scrutinised and compared to currently accepted human brachytherapy planning/treatment processes as recommended by ICRU-58 and further supported by the GEC Handbook of Brachytherapy (based on ICRU recommendations for all brachytherapy procedures). [1, 7] As a result, a second Flow-Chart was developed based on current accepted practice and referred to as the **'Recommended Treatment Protocol'**, this is referred to as the **Protocol** from this point on (Figure 5.2).

To further better understand the potential gaps in the approach used at the clinic (1999-2007), and the accepted human evidence-based processes in brachytherapy, the **Retrospective Process** and **Protocol** were formatted side-by-side (Figure 5.3). Any areas where the **Retrospective Process** did not meet the **Protocol** conditions have been highlighted in red.

Further to the flow-charts provided in Figures 5.1-5.3, it was considered prudent to test the **Protocol** against a number of treatment cases. The cases chosen for replication (using the **Protocol**) are representative of the nine different sets of conditions identified in the treatment applications and include the following treatment methods (Table 5.1):

Table 5.1: Treatment Cases Tested in Protocol

Item Number	Treatment Method
1	Clustered, 1 line
2	Clustered, 2 lines
3	Clustered, 3 lines
4	Clustered, 4 lines
5	Clustered, off-set
6	Planar, 1 line
7	Planar, 2 lines
8	Planar, 3 lines
N/A	Planar, 4 lines – Nil available for planning
9	Planar, off-set

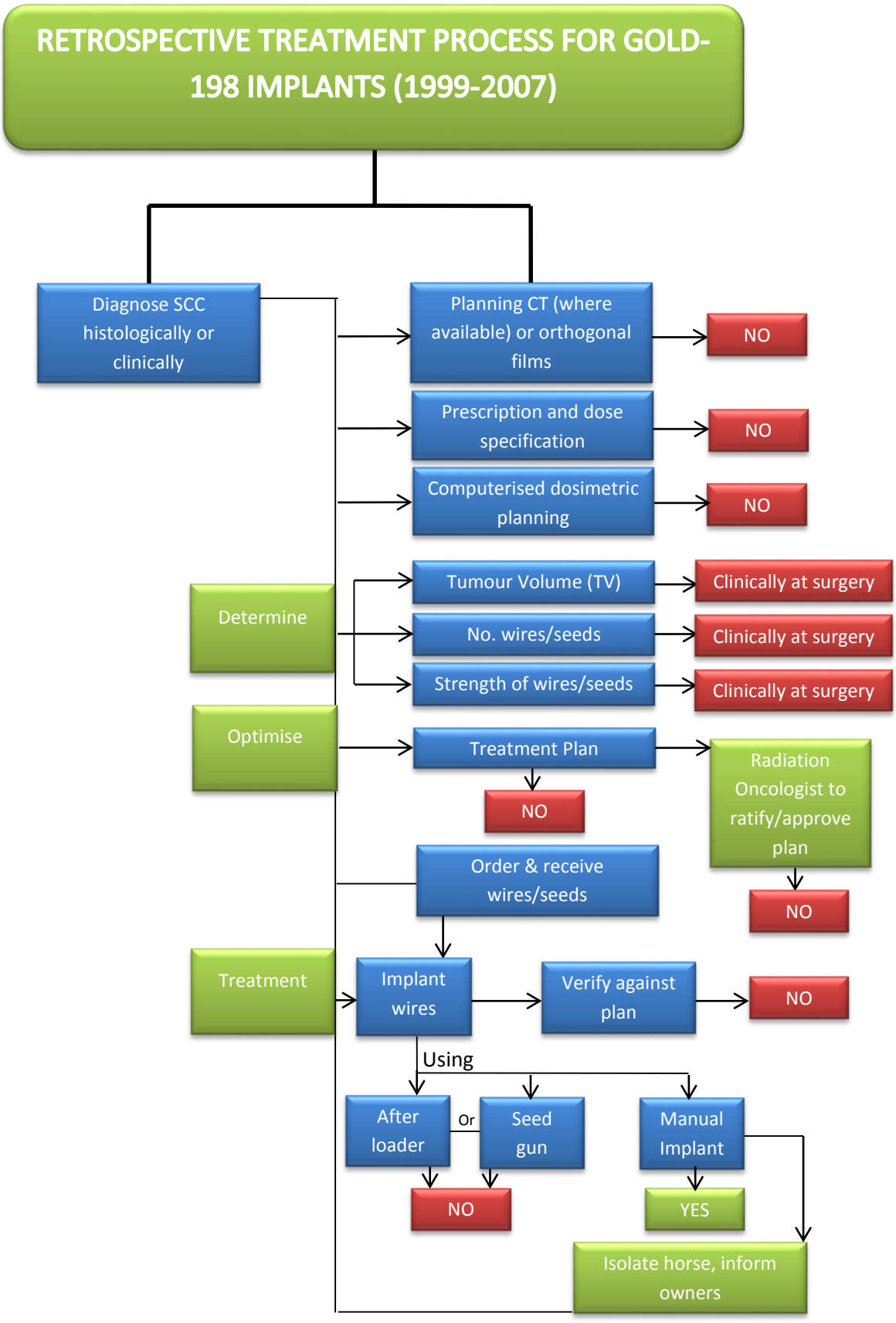


Figure 5.1: Retrospective Treatment Process for Gold-198 Implants (1999-2007)

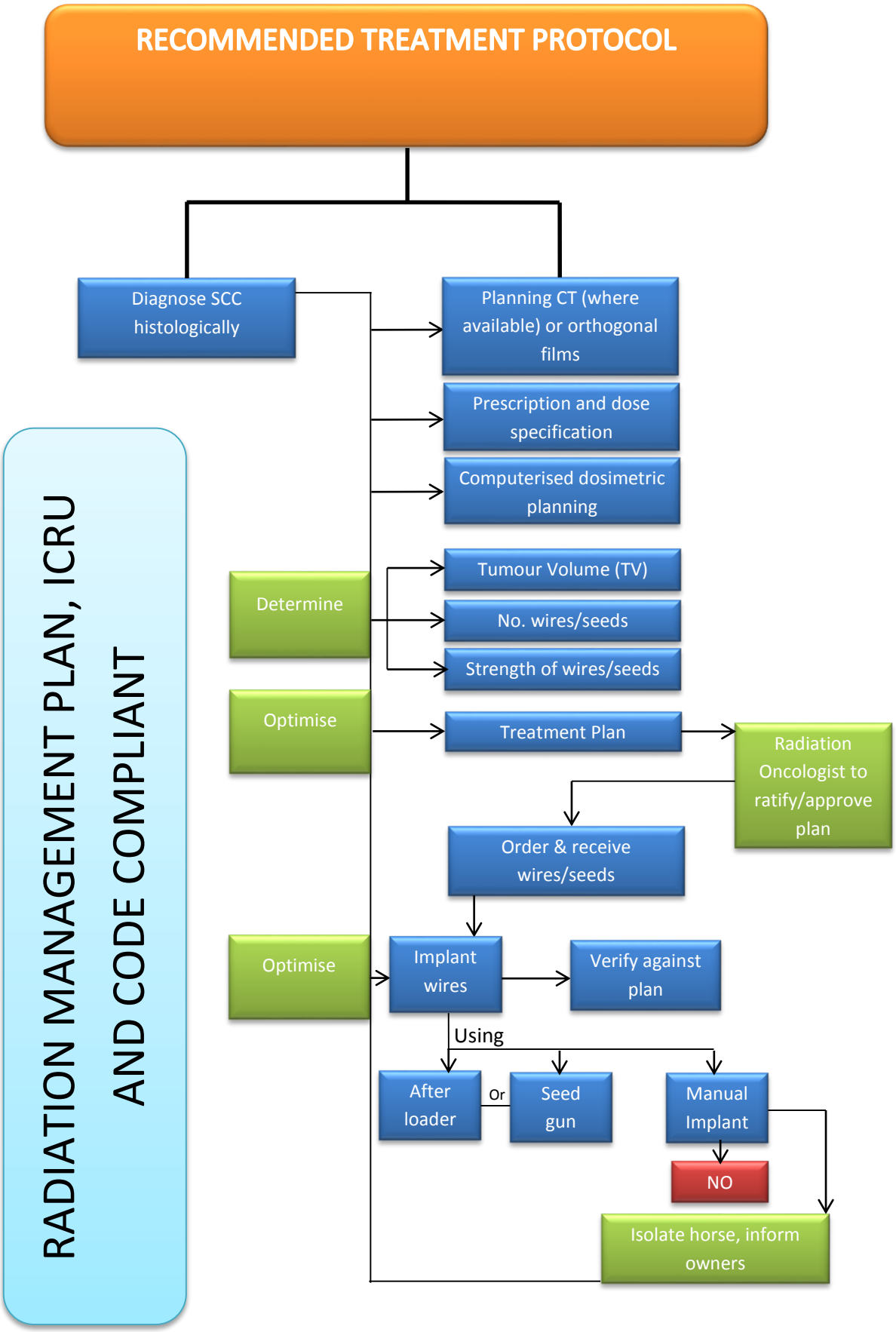


Figure 5.2: Recommended Treatment Protocol for Gold-198 Implants

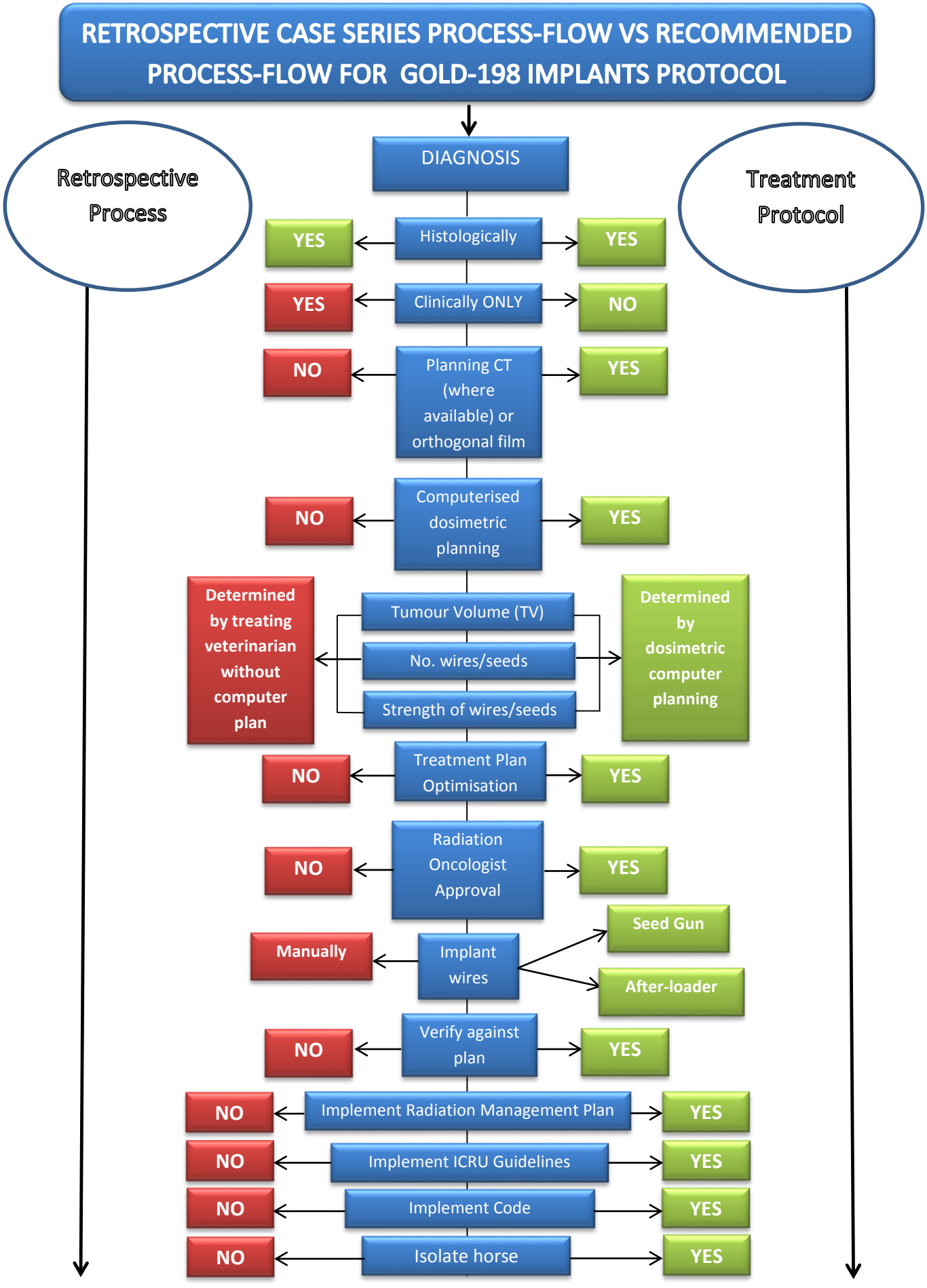


Figure 5.3: Retrospective Treatment Process (1999-2007) vs Recommended Treatment Protocol for Gold-198

COMPARISON PLANS

5.5 COMPARISON PLANS; PROCESS DESCRIPTION

The following plan comparisons (n=9) are used to highlight treatment outcomes for the retrospective treatment approach (1999-2007) in terms of dose reporting parameters against dose reporting parameters for the same cases, using an optimised approach. The optimised approach includes the advantage of access to planning software to allow multiple treatment configurations to be produced in order for the most appropriate plan to be selected. The retrospective plans for a series of treatments (n=9) have been reported (left-side flow chart, Figures 5.4, 5.7, 5.10, 5.13, 5.16, 5.19, 5.22, 5.25, and 5.28) in terms of the method used and known outcomes, where available. These have been compared to the optimised plan for the same cases (right-side flow-chart, Figures 5.4, 5.7, 5.10, 5.13, 5.16, 5.19, 5.22, 5.25, and 5.28). The plans have been chosen to be representative of the cross-section of treatment types used in the retrospective series and are outlined below in Table 5.2:

Table 5.2: Treatment Cases Used in Comparison Plans

Item Number	Case Number	Treatment Method	Outcome	Figure
1	303	Clustered, 1 line	No response	5.4
2	328	Clustered, 2 lines	Recurrence	5.7
3	294	Clustered, 3 lines	No recurrence	5.10
4	123	Clustered, 4 lines	Unknown	5.13
5	233	Clustered, off-set	Recurrence	5.16
6	329	Planar, 1 line	No recurrence	5.19
7	229	Planar, 2 lines	No recurrence	5.22
8	57	Planar, 3 lines	Unknown	5.25
N/A	N/A	Planar, 4 lines – Nil available for planning	N/A	-
9	94	Planar, off-set	Unknown	5.28

5.6 COMPARISON PLAN EVALUATION & DISCUSSION

Plan evaluations and discussion of results can be found at the completion of this Chapter. As a point of reference to support the following dose analysis, a table of OAR constraints (tolerances for organs at risk) is included again within this section (Table 5.3). More comprehensive consideration with regard to accepted tolerances and the potential risks identified should these tolerances be exceeded, can be found in Chapter 3.

Table 5.3: Tolerance Doses for OSCC/POSCC Structures [8-10]

	Tolerance Limits		
Organ	**(Lower) TD 5/5 (Gy)***	**(Upper) TD 50/5 (Gy)****	**Whole/Partial Organ**
Lens of eye	5	12	Whole
Retina	55	70	Whole
Cornea	50	60	Whole

***TD 5/5 (Gy) = tissue dose associated with a 5% injury rate within 5 years**

****TD 50/5 (Gy) = tissue dose associated with a 50% injury rate within 5 years**

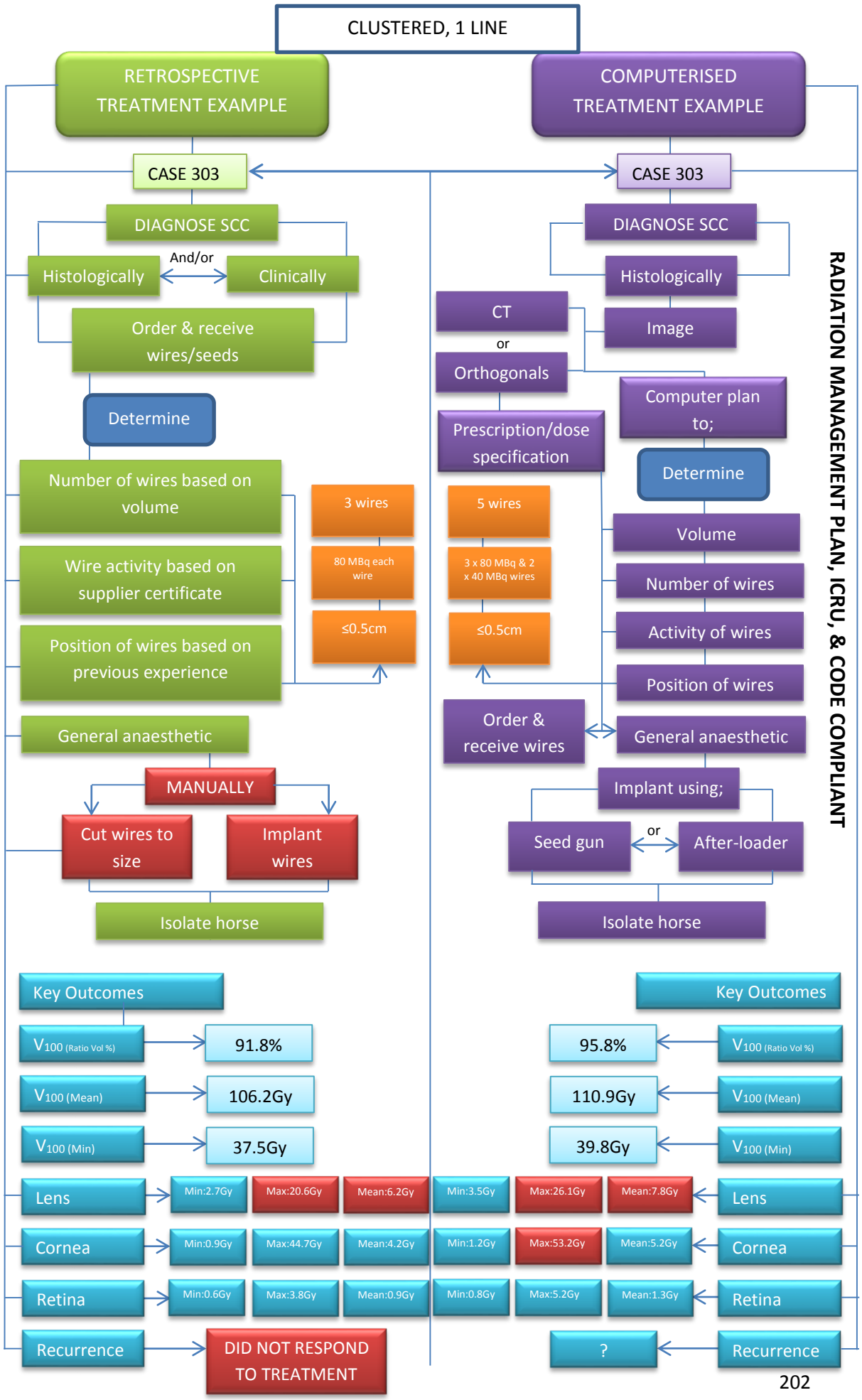


Figure 5.4: Plan Comparison for Case 303
(N.B. Red Highlight denotes over-tolerance parameters)

CASE 303: RETROSPECTIVE DOSE REPORT

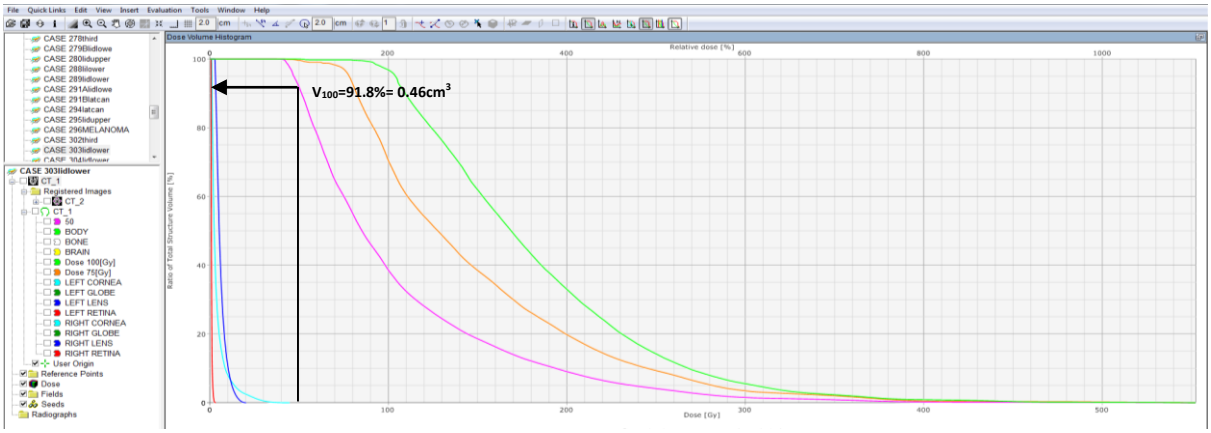


Figure 5.5: Case 303 Retrospective Dose DVH

Table 5.4: Case 303 Retrospective Dose Report

DVH Line	Structure	Volume (cm³)	Min Dose (Gy) & Volume (cm³)		Max Dose (Gy) & Volume (cm³)		Mean Dose (Gy) & Volume (cm³)	
	50Gy Structure Volume (100%)	0.5cm³	37.5Gy		552.4Gy	<0.0001cm³	106.2Gy	0.18cm³
	100Gy Max (200%)	0.1cm³						
	75Gy Max (150%)	0.2cm³						
	Lens		2.73Gy	BT	20.6Gy	<0.002cm³	6.17Gy	0.83cm³
	Cornea		0.95Gy	BT	44.7Gy	BT	4.2Gy	BT
	Retina		0.64Gy	BT	3.8Gy	BT	0.99Gy	BT

BT: Below Tolerance, Red Highlight: Over Tolerance

CASE 303: REPLAN DOSE REPORT

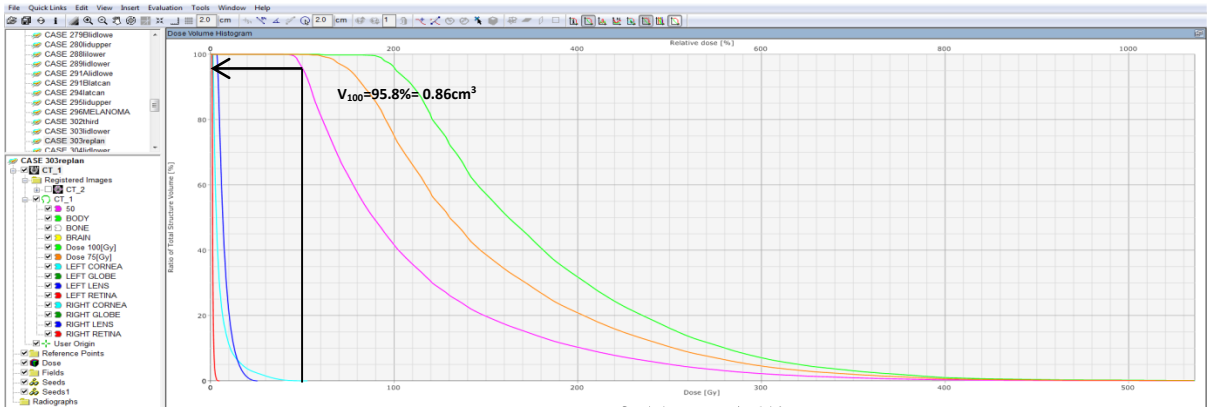


Figure 5.6: Case 303 Replan Dose DVH

Table 5.5: Case 303 Replan Dose Report

DVH Line	Structure	Volume (cm³)	Min Dose (Gy) & Volume (cm³)		Max Dose (Gy) & Volume (cm³)		Mean Dose (Gy) & Volume (cm³)	
	50Gy Structure Volume (100%)	0.9cm³	39.8Gy		564.6Gy	<0.0001cm³	110.9Gy	0.32cm³
	100Gy Max (200%)	0.2cm³						
	75Gy Max (150%)	0.4cm³						
	Lens		3.5Gy	BT	26.1Gy	<0.002cm³	7.8Gy	0.89cm³
	Cornea		1.2Gy	BT	53.1Gy	<0.0003cm³	5.2Gy	BT
	Retina		0.8Gy	BT	5.2Gy	BT	1.3Gy	BT

BT: Below Tolerance, Red Highlight: Over Tolerance

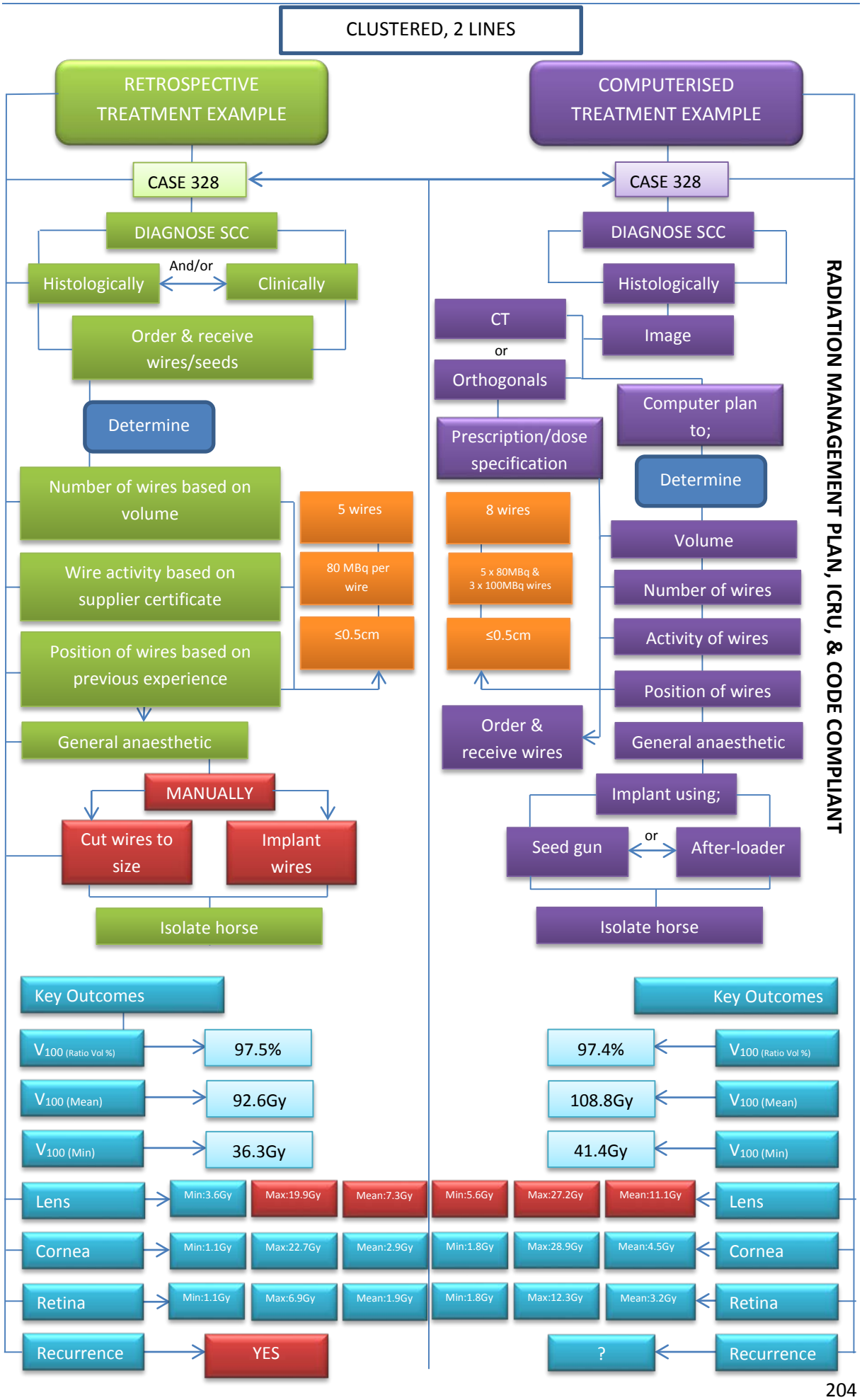


Figure 5.7: Plan Comparison for Case 328
(N.B. Red Highlight denotes over-tolerance parameters)

CASE 328: RETROSPECTIVE DOSE REPORT

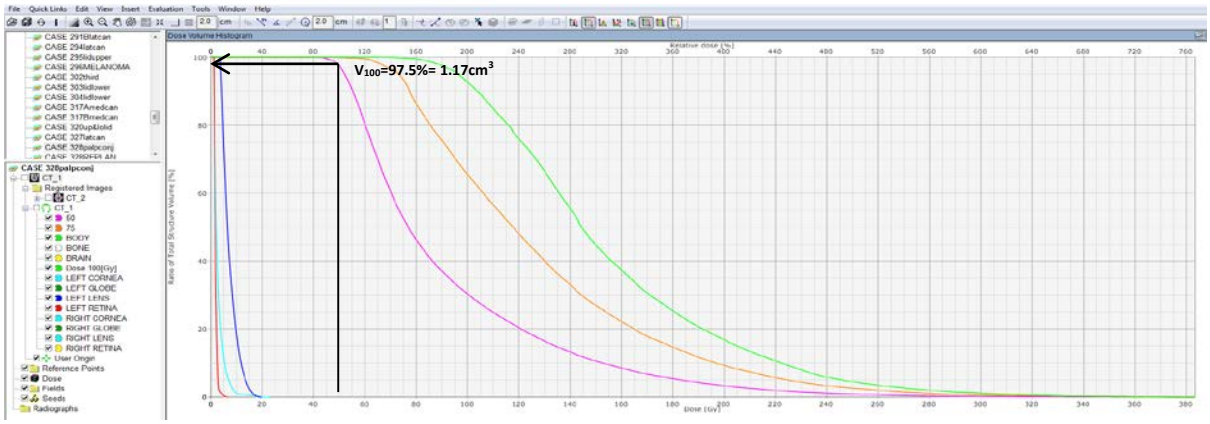


Figure 5.8: Case 328 Retrospective Dose DVH

Table 5.6: Case 328 Replan Dose Report

DVH Line	Structure	Volume (cm^3)	Min Dose (Gy) & Volume (cm^3)		Max Dose (Gy) & Volume (cm^3)		Mean Dose (Gy) & Volume (cm^3)	
	50Gy Structure Volume (100%)	1.2cm^3	36.3Gy		383.4Gy	<0.0001cm^3	92.6Gy	<0.43cm^3
	100Gy Max (200%)	0.1cm^3						
	75Gy Max (150%)	0.3cm^3						
	Lens		3.6Gy	BT	19.9Gy	<0.0004cm^3	7.3Gy	0.93cm^3
	Cornea		1.1Gy	BT	22.8Gy	BT	2.9Gy	BT
	Retina		1.1Gy	BT	6.9Gy	BT	1.9Gy	BT

BT: Below Tolerance, Red Highlight: Over Tolerance

CASE 328: REPLAN DOSE REPORT

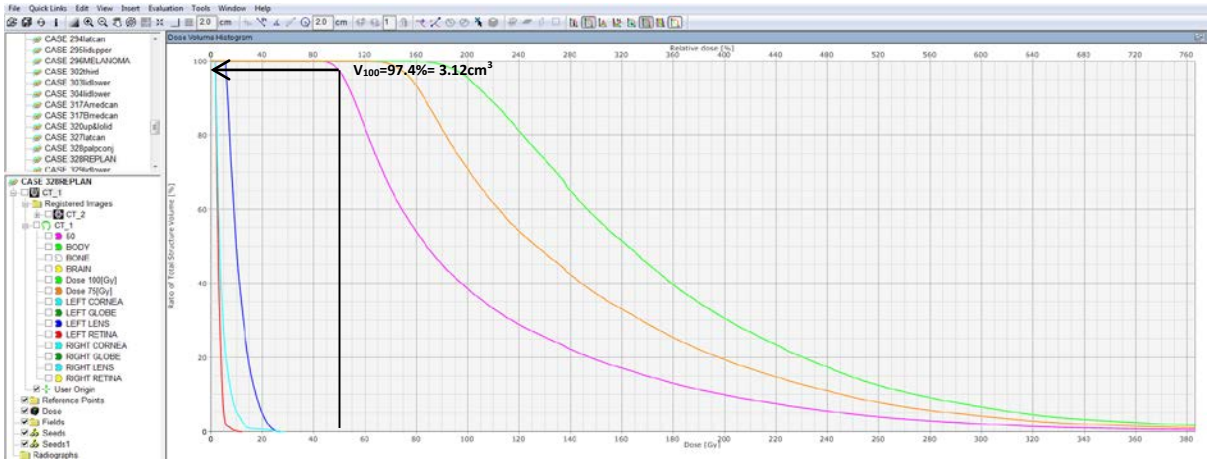


Figure 5.8: Case 328 Replan Dose DVH

Table 5.7: Case 328 Replan Dose Report

DVH Line	Structure	Volume (cm^3)	Min Dose (Gy) & Volume (cm^3)		Max Dose (Gy) & Volume (cm^3)		Mean Dose (Gy) & Volume (cm^3)	
	50Gy Structure Volume (100%)	3.2cm^3	41.4Gy		758.2Gy	<0.0002cm^3	108.8Gy	1.07cm^3
	100Gy Max (200%)	1.0cm^3						
	75Gy Max (150%)	1.5cm^3						
	Lens		5.6Gy	2.4cm^3	27.2Gy	<0.0004cm^3	11.1Gy	0.93cm^3
	Cornea		1.8Gy	BT	28.9Gy	BT	4.5Gy	BT
	Retina		1.8Gy	BT	12.3Gy	BT	3.2Gy	BT

BT: Below Tolerance, Red Highlight: Over Tolerance

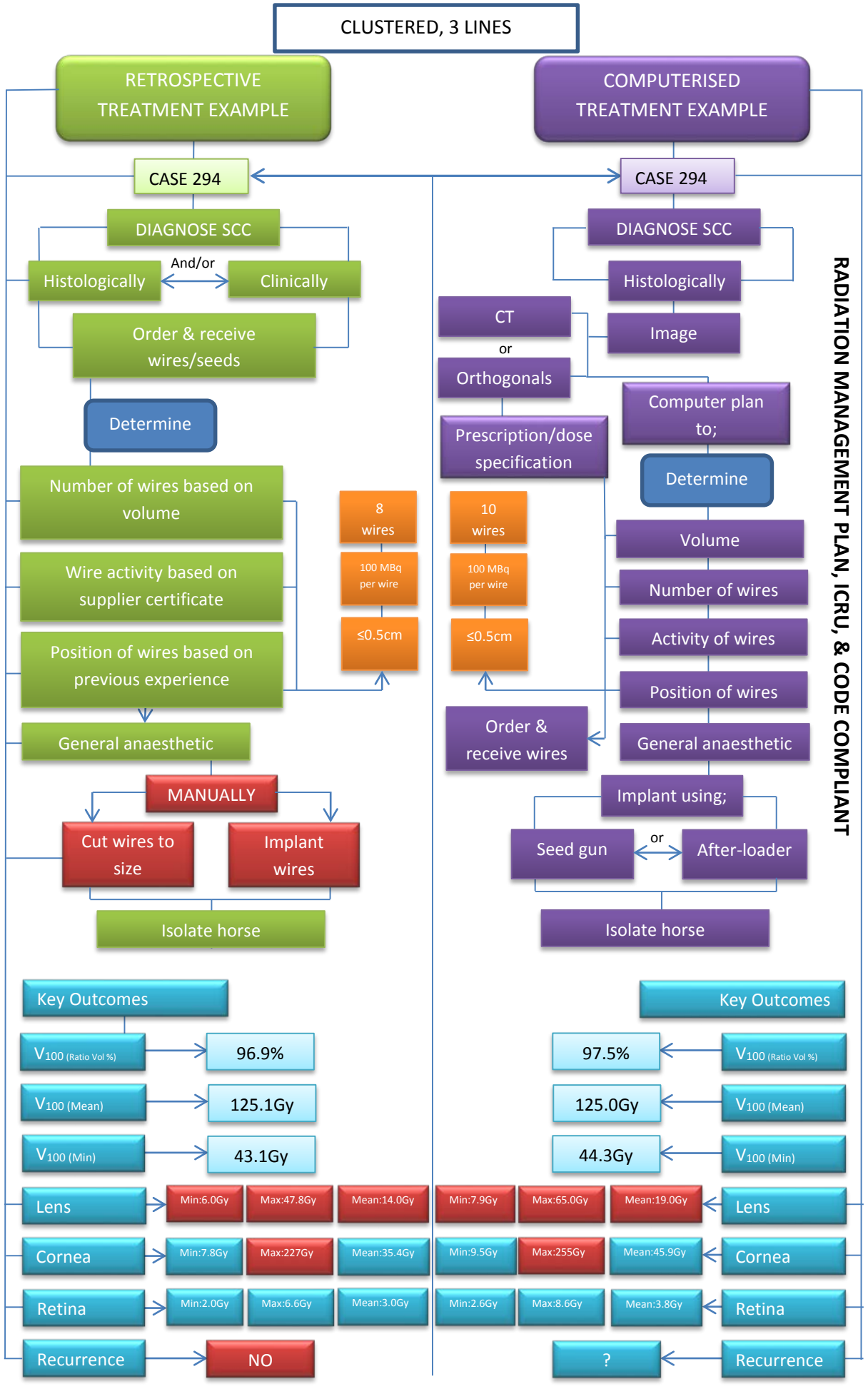


Figure 5.10: Plan Comparison for Case 294
(N.B. Red Highlight denotes over-tolerance parameters)

CASE 294: RETROSPECTIVE DOSE REPORT

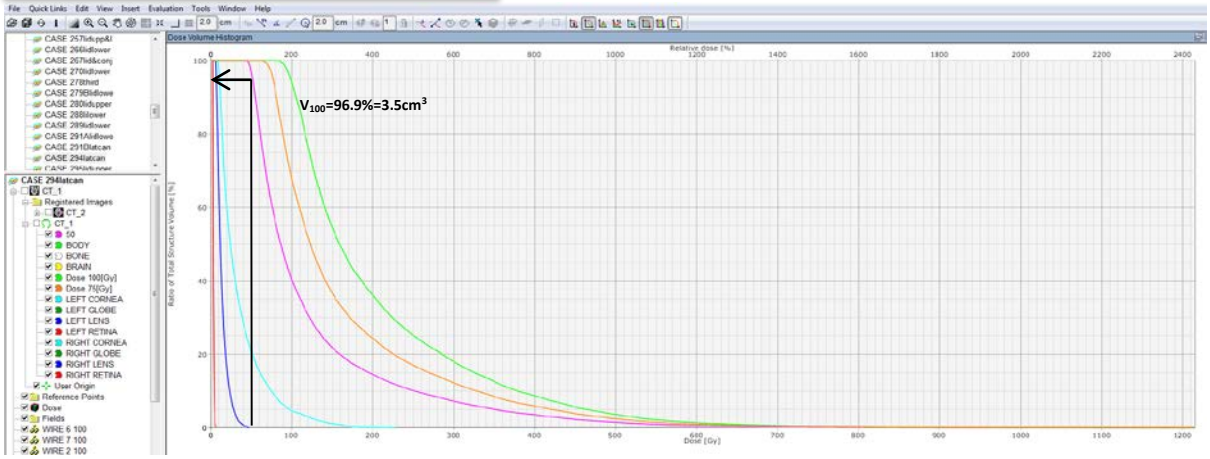


Figure 5.11: Case 294 Retrospective Dose DVH

Table 5.8: Case 294 Replan Dose Report

DVH Line	Structure	Volume (cm³)	Min Dose (Gy) & Volume (cm³)		Max Dose (Gy) & Volume (cm³)		Mean Dose (Gy) & Volume (cm³)	
	50Gy Structure Volume (100%)	3.6cm³	43.1Gy		1215.3Gy	<0.0001cm³	125.1Gy	1.04cm³
	100Gy Max (200%)	1.3cm³						
	75Gy Max (150%)	2.0cm³						
	Lens		6.0Gy	2.39cm³	47.8Gy	<0.0003cm³	13.9Gy	1.001cm³
	Cornea		7.8Gy	BT	227.2Gy	<0.0002cm³	35.4Gy	BT
	Retina		2.0Gy	BT	6.6Gy	BT	3.0Gy	BT

BT: Below Tolerance, Red Highlight: Over Tolerance

CASE 294: REPLAN DOSE REPORT

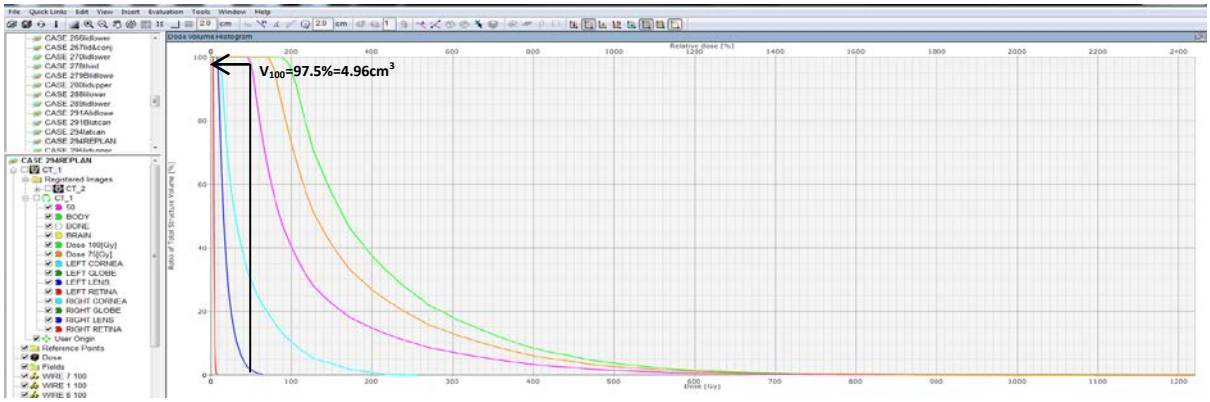


Figure 5.12: Case 294 Replan Dose DVH

Table 5.9: Case 294 Replan Dose Report

DVH Line	Structure	Volume (cm³)	Min Dose (Gy) & Volume (cm³)		Max Dose (Gy) & Volume (cm³)		Mean Dose (Gy) & Volume (cm³)	
	50Gy Structure Volume (100%)	5.1cm³	44.3Gy		1265.7Gy	<0.0001cm³	125.0Gy	1.5cm³
	100Gy Max (200%)	1.9cm³						
	75Gy Max (150%)	2.9cm³						
	Lens		8Gy	2.4cm³	65.0Gy	<0.0004cm³	19.0Gy	0.86cm³
	Cornea		9.5Gy	BT	255.4Gy	<0.0005	45.9Gy	BT
	Retina		2.6Gy	BT	8.6Gy	BT	3.8Gy	BT

BT: Below Tolerance, Red Highlight: Over Tolerance

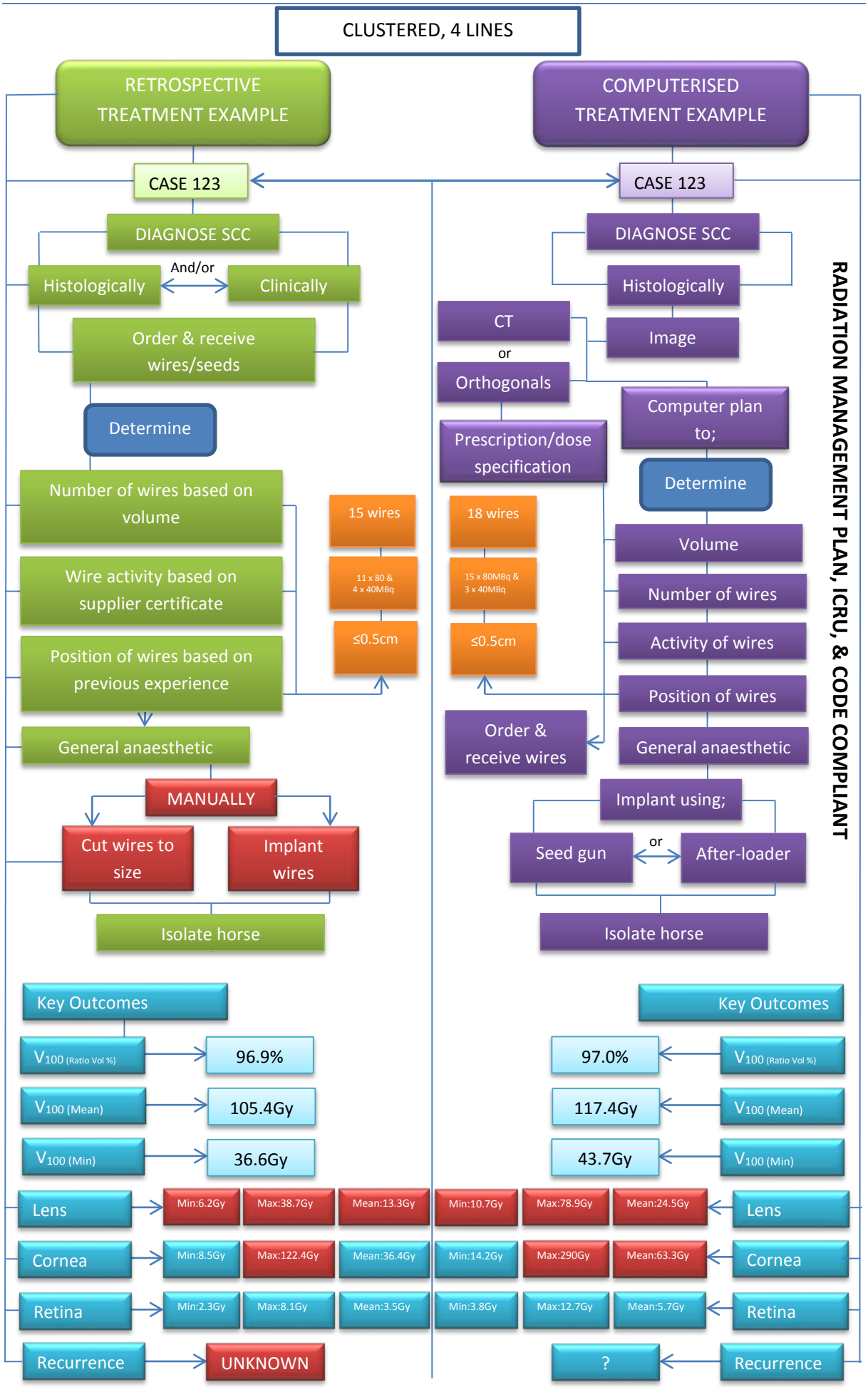


Figure 5.13: Plan Comparison for Case 123
(N.B. Red Highlight denotes over-tolerance parameters)

CASE 123: RETROSPECTIVE DOSE REPORT

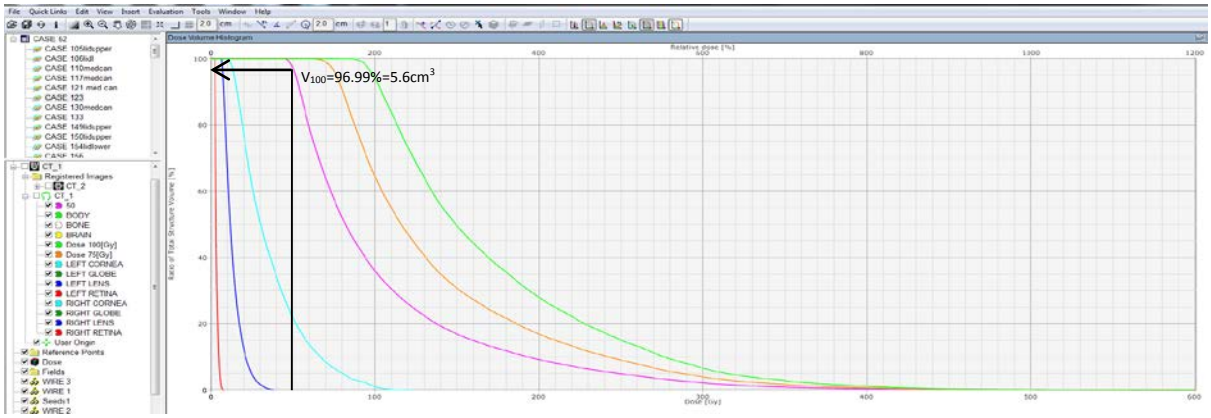


Figure 5.14: Case 123 Retrospective Dose DVH

Table 5.10: Case 123 Retrospective Dose Report

DVH Line	Structure	Volume (cm^3)	Min Dose (Gy) & Volume (cm^3)		Max Dose (Gy) & Volume (cm^3)		Mean Dose (Gy) & Volume (cm^3)	
	50Gy Structure Volume (100%)	5.8cm^3	36.6Gy		600.7Gy	<0.0001cm^3	105.4Gy	1.89cm^3
	100Gy Max (200%)	1.8cm^3						
	75Gy Max (150%)	3.1cm^3						
	Lens		6.2Gy	2.39cm^3	38.7Gy	<0.0003cm^3	13.3Gy	0.91cm^3
	Cornea		8.5Gy	BT	122.4Gy	<0.0002cm^3	36.4Gy	BT
	Retina		2.3Gy	BT	8.1Gy	BT	3.5Gy	BT

BT: Below Tolerance, Red Highlight: Over Tolerance

CASE 123: REPLAN DOSE REPORT

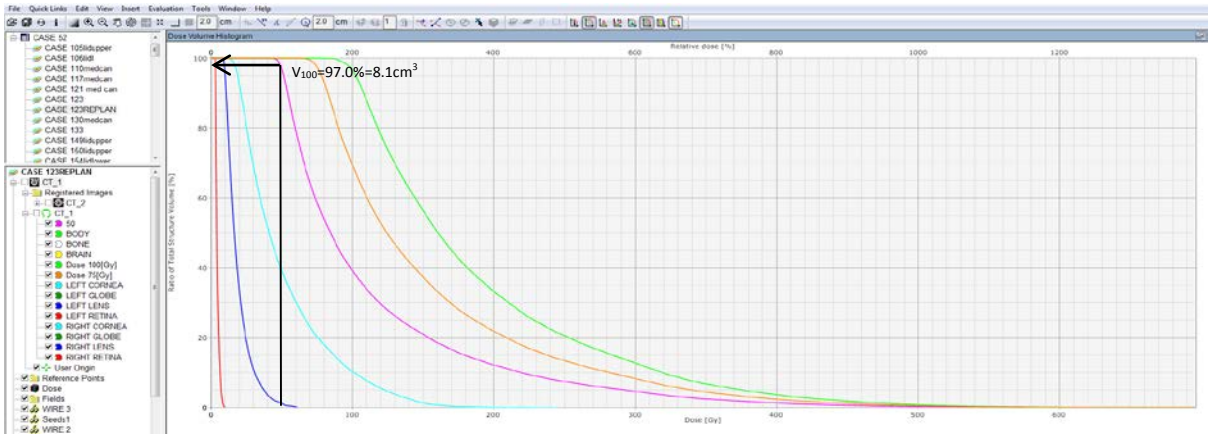


Figure 5.15: Case 123 Replan Dose DVH

Table 5.11: Case 123 Replan Dose Report

DVH Line	Structure	Volume (cm^3)	Min Dose (Gy) & Volume (cm^3)		Max Dose (Gy) & Volume (cm^3)		Mean Dose (Gy) & Volume (cm^3)	
	50Gy Structure Volume (100%)	8.4cm^3	40.3Gy		696.5Gy	<0.001cm^3	114.6Gy	<2.71cm^3
	100Gy Max (200%)	4.0cm^3						
	75Gy Max (150%)	6.3cm^3						
	Lens		8.5Gy	2.4cm^3	61.4Gy	<0.002cm^3	19.0Gy	0.89cm^3
	Cornea		11.4Gy	BT	246.7Gy	<0.0001cm^3	52.1Gy	<0.99cm^3
	Retina		3.1Gy	BT	10.9Gy	BT	4.7Gy	BT

BT: Below Tolerance, Red Highlight: Over Tolerance

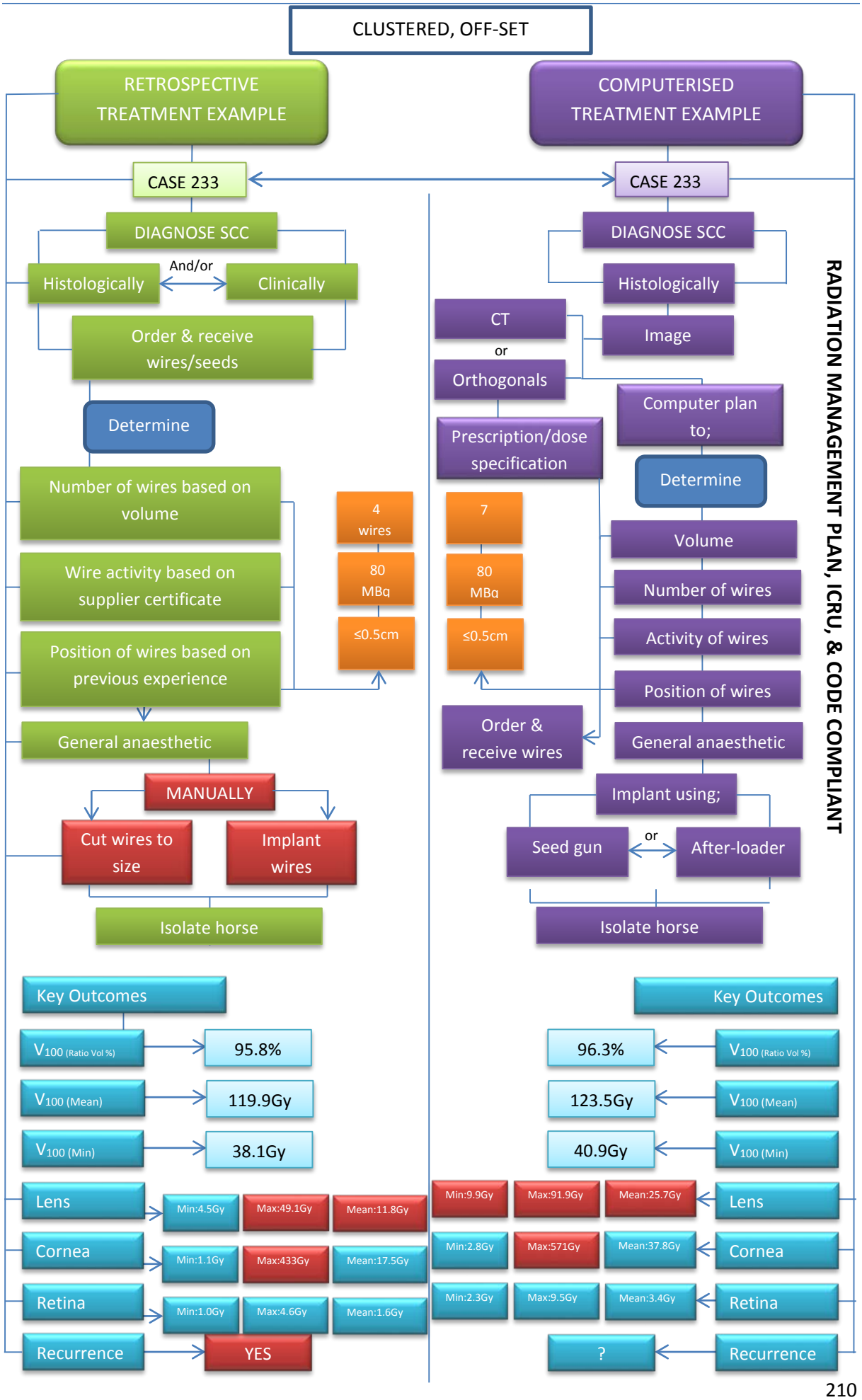


Figure 5.16: Plan Comparison for Case 233
(N.B. Red Highlight denotes over-tolerance parameters)

CASE 233: RETROSPECTIVE DOSE REPORT

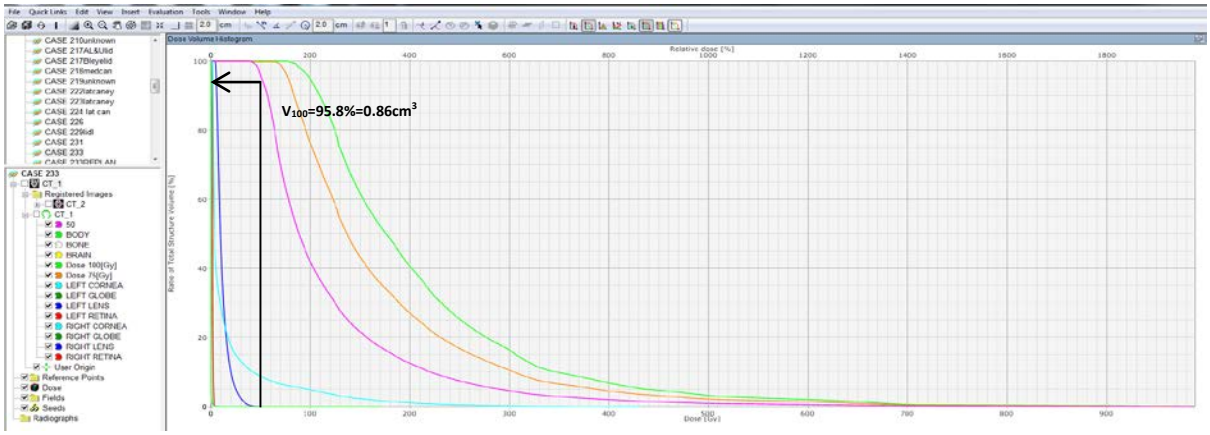


Figure 5.17: Case 233 Retrospective Dose DVH

Table 5.12: Case 233 Retrospective Dose Report

DVH Line	Structure	Volume (cm^3)	Min Dose (Gy) & Volume (cm^3)		Max Dose (Gy) & Volume (cm^3)		Mean Dose (Gy) & Volume (cm^3)	
	50Gy Structure Volume (100%)	0.9cm^3	38.1Gy		988.7Gy	<0.0002cm^3	119.1Gy	<0.29cm^3
	100Gy Max (200%)	0.2cm^3						
	75Gy Max (150%)	0.3cm^3						
	Lens		4.5Gy	BT	49.1Gy	<0.02cm^3	11.8Gy	<0.74cm^3
	Cornea		1.1Gy	BT	432.6Gy	<0.013	17.5Gy	BT
	Retina		1.0Gy	BT	4.6Gy	BT	1.6Gy	BT

BT: Below Tolerance, Red Highlight: Over Tolerance

CASE 233: REPLAN DOSE REPORT

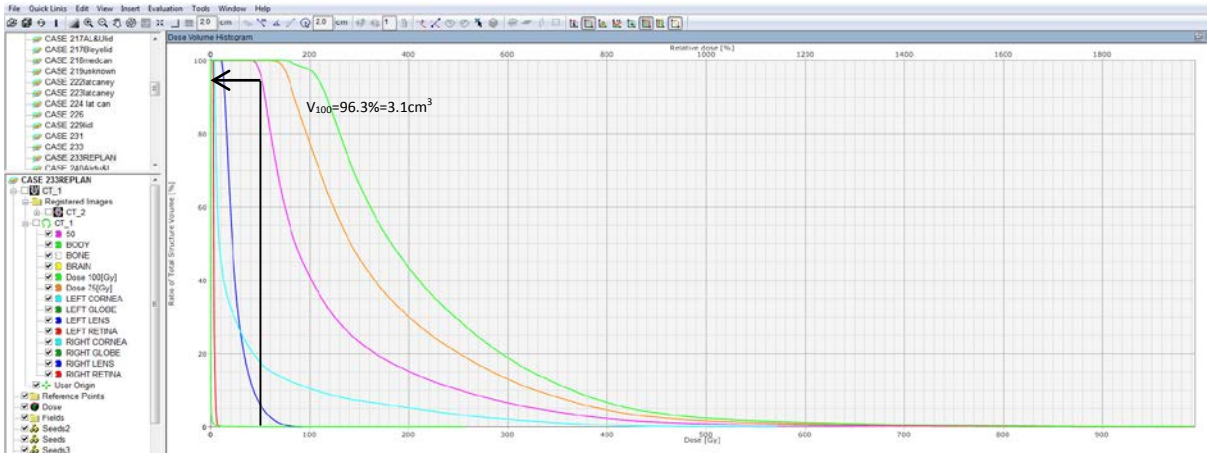


Figure 5.18: Case 233 Replan Dose DVH

Table 5.13: Case 233 Replan Dose Report

DVH Line	Structure	Volume (cm^3)	Min Dose (Gy) & Volume (cm^3)		Max Dose (Gy) & Volume (cm^3)		Mean Dose (Gy) & Volume (cm^3)	
	50Gy Structure Volume (100%)	3.2cm^3	40.9Gy		1153.5Gy	<0.0001cm^3	123.5Gy	0.99cm^3
	100Gy Max (200%)	1.1cm^3						
	75Gy Max (150%)	1.6cm^3						
	Lens		9.9Gy	<2.0cm^3	91.9Gy	<0.0003cm^3	25.7Gy	0.74cm^3
	Cornea		2.8Gy	BT	571.0Gy	<0.017cm^3	37.8Gy	BT
	Retina		2.3Gy	BT	9.5Gy	BT	3.4Gy	BT

BT: Below Tolerance, Red Highlight: Over Tolerance

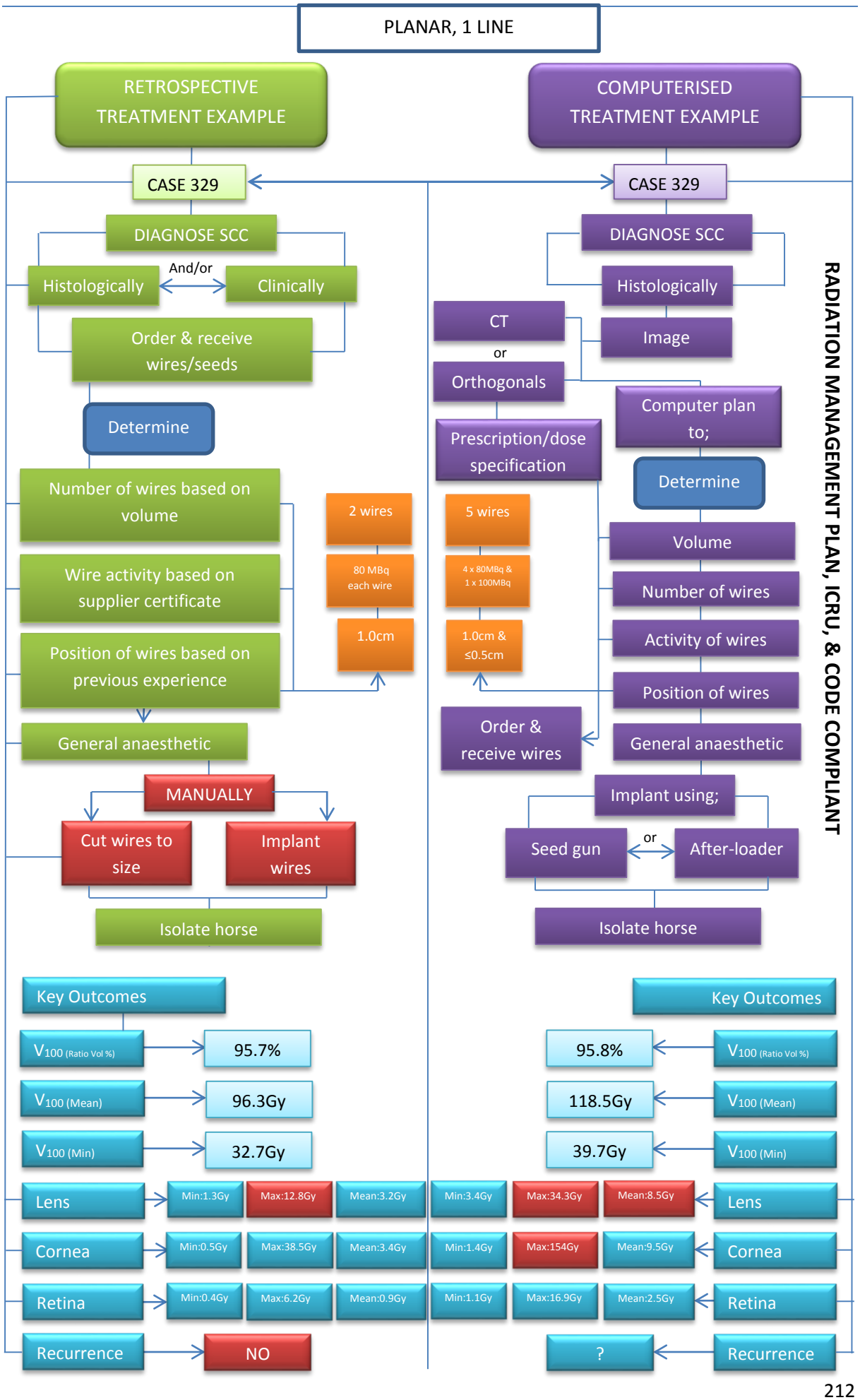


Figure 5.19: Case 329 Plan Comparison
(N.B. Red Highlight denotes over-tolerance parameters)

CASE 329: RETROSPECTIVE DOSE REPORT

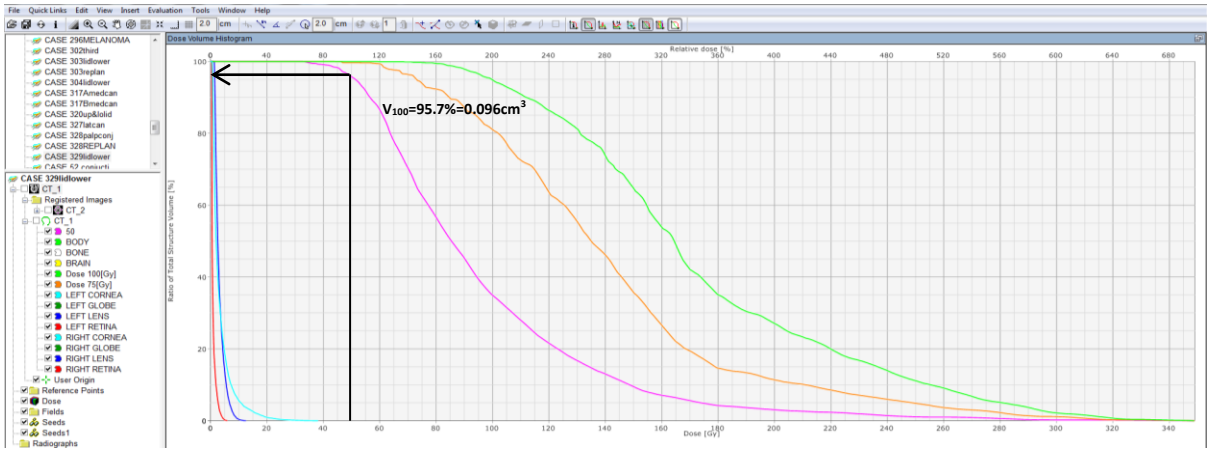


Figure 5.20: Case 329 Retrospective Dose DVH

Table 5.14: Case 329 Retrospective Dose Report

DVH Line	Structure	Volume (cm^3)	Min Dose (Gy) & Volume (cm^3)		Max Dose (Gy) & Volume (cm^3)		Mean Dose (Gy) & Volume (cm^3)	
	50Gy Structure Volume (100%)	0.1cm^3	32.7Gy		349.0Gy	<0.00001cm^3	96.3Gy	0.03cm^3
	100Gy Max (200%)	0cm^3						
	75Gy Max (150%)	0cm^3						
	Lens		1.3Gy	BT	12.8Gy	<0.012cm^3	3.2Gy	BT
	Cornea		0.5Gy	BT	38.2Gy	BT	3.4Gy	BT
	Retina		0.4Gy	BT	6.2Gy	BT	0.9Gy	BT

BT: Below Tolerance, Red Highlight: Over Tolerance

CASE 329: REPLAN DOSE REPORT

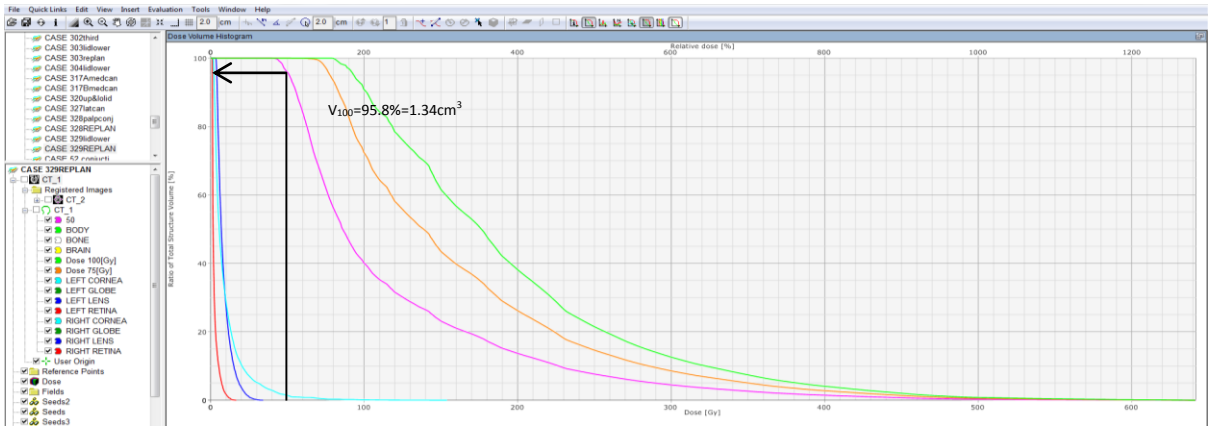


Figure 5.21: Case 329 Replan Dose DVH

Table 5.15: Case 329 Replan Dose Report

DVH Line	Structure	Volume (cm^3)	Min Dose (Gy) & Volume (cm^3)		Max Dose (Gy) & Volume (cm^3)		Mean Dose (Gy) & Volume (cm^3)	
	50Gy Structure Volume (100%)	1.4cm^3	39.7Gy		641.7Gy	<0.0001cm^3	118.5Gy	0.44cm^3
	100Gy Max (200%)	0.5cm^3						
	75Gy Max (150%)	0.7cm^3						
	Lens		3.4Gy	BT	34.3Gy	<0.0005cm^3	8.5Gy	0.73cm^3
	Cornea		1.4Gy	BT	154.3Gy	<0.0001	9.5Gy	BT
	Retina		1.1Gy	BT	16.9Gy	BT	2.5Gy	BT

BT: Below Tolerance, Red Highlight: Over Tolerance

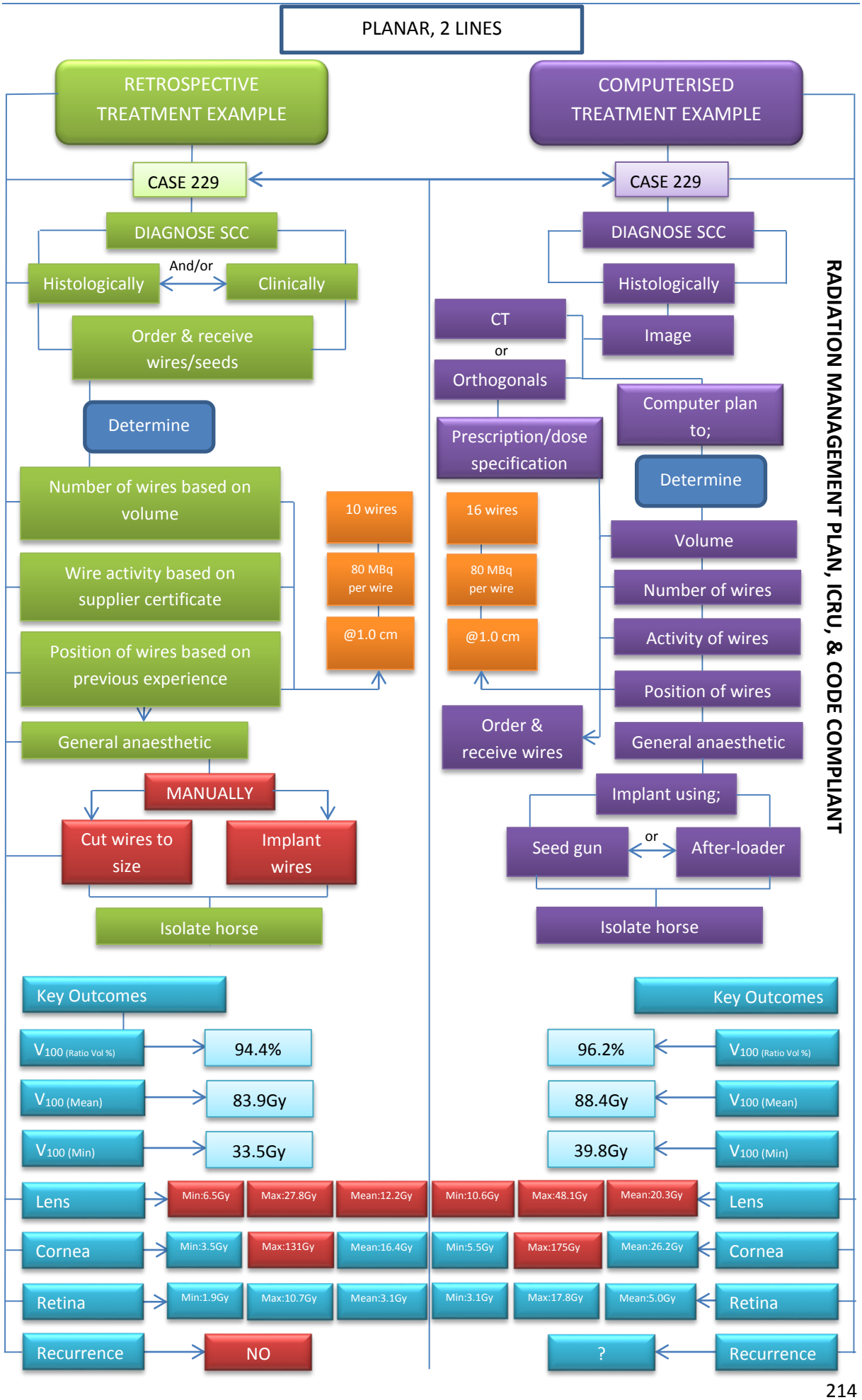


Figure 5.22: Plan Comparison for Case 229
(N.B. Red Highlight denotes over-tolerance parameters)

CASE 229: RETROSPECTIVE DOSE REPORT

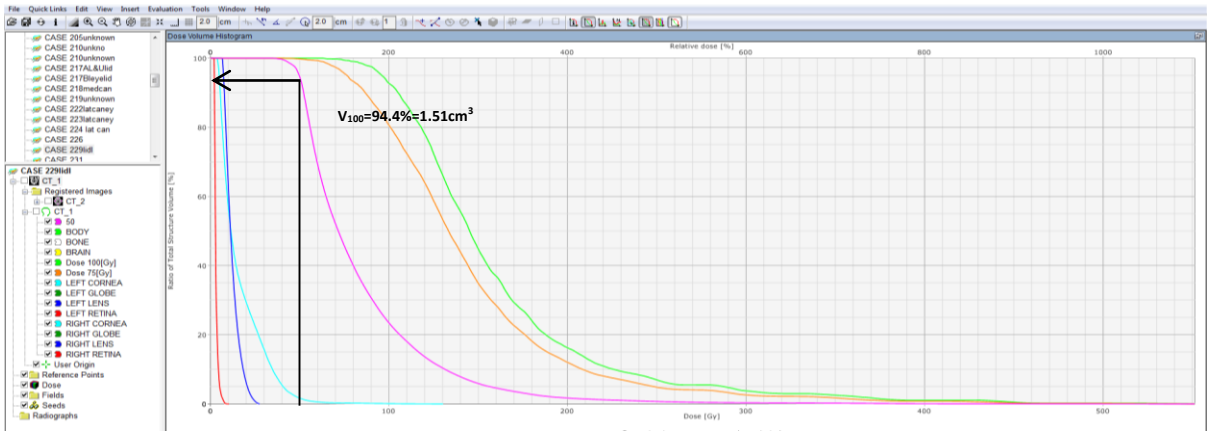


Figure 5.23: Case 229 Retrospective Dose DVH

Table 5.16: Case 229 Retrospective Dose Report

DVH Line	Structure	Volume (cm^3)	Min Dose (Gy) & Volume (cm^3)		Max Dose (Gy) & Volume (cm^3)		Mean Dose (Gy) & Volume (cm^3)	
	50Gy Structure Volume (100%)	1.6cm^3	33.5Gy		551.4Gy	<0.0001cm^3	83.9Gy	0.59cm^3
	100Gy Max (200%)	0cm^3						
	75Gy Max (150%)	0.1cm^3						
	Lens		6.5Gy	2.38cm^3	27.8Gy	<0.0009cm^3	12.2Gy	0.97cm^3
	Cornea		3.5Gy	BT	130.6Gy	<0.0001cm^3	16.4Gy	BT
	Retina		2.0Gy	BT	10.7Gy	BT	3.1Gy	BT

BT: Below Tolerance, Red Highlight: Over Tolerance

CASE 229: REPLAN DOSE REPORT

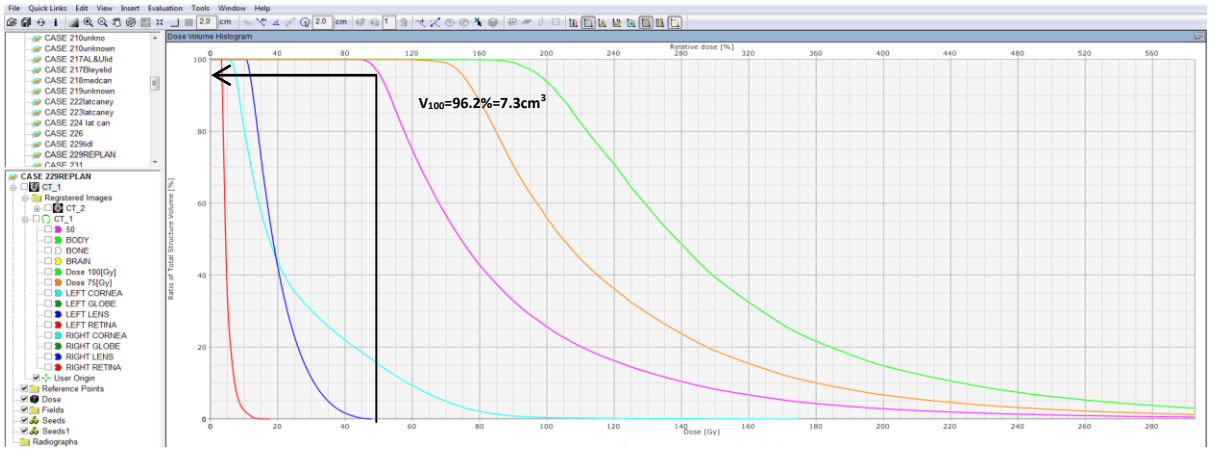


Figure 5.24: Case 229 Replan Dose DVH

Table 5.17: Case 229 Replan Dose Report

DVH Line	Structure	Volume (cm^3)	Min Dose (Gy) & Volume (cm^3)		Max Dose (Gy) & Volume (cm^3)		Mean Dose (Gy) & Volume (cm^3)	
	50Gy Structure Volume (100%)	7.6cm^3	39.8Gy		597.5Gy	<0.0001cm^3	88.4Gy	2.6cm^3
	100Gy Max (200%)	1.2cm^3						
	75Gy Max (150%)	3.2cm^3						
	Lens		10.6Gy	2.3cm^3	48.1Gy	<0.001cm^3	20.3Gy	0.98cm^3
	Cornea		5.5Gy	BT	174.5Gy	<0.0001	26.2Gy	BT
	Retina		3.1Gy	BT	17.8Gy	BT	5.0Gy	BT

BT: Below Tolerance, Red Highlight: Over Tolerance

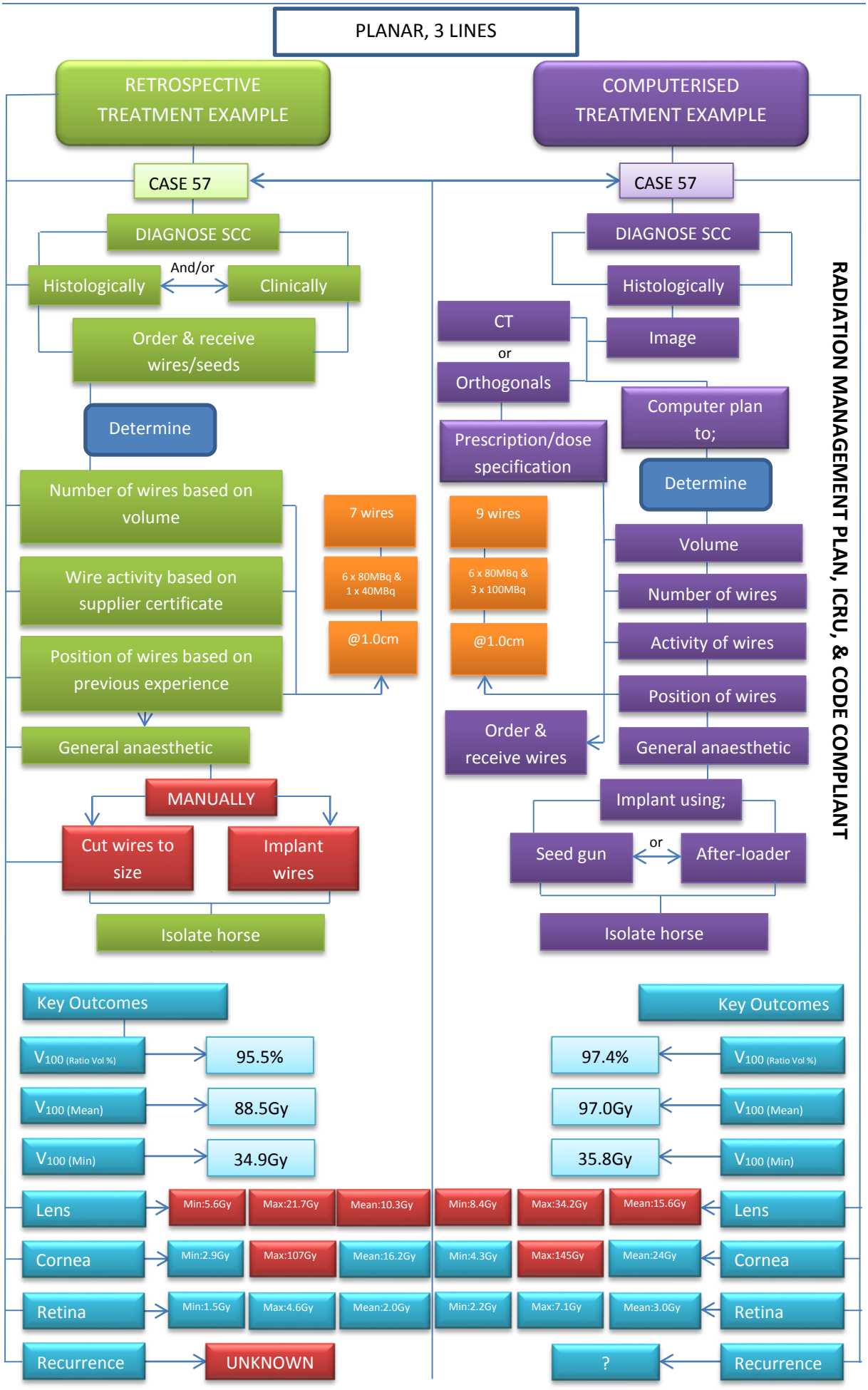


Figure 5.25: Plan Comparison for Case 57
(N.B. Red Highlight denotes over-tolerance parameters)

CASE 57: RETROSPECTIVE DOSE REPORT

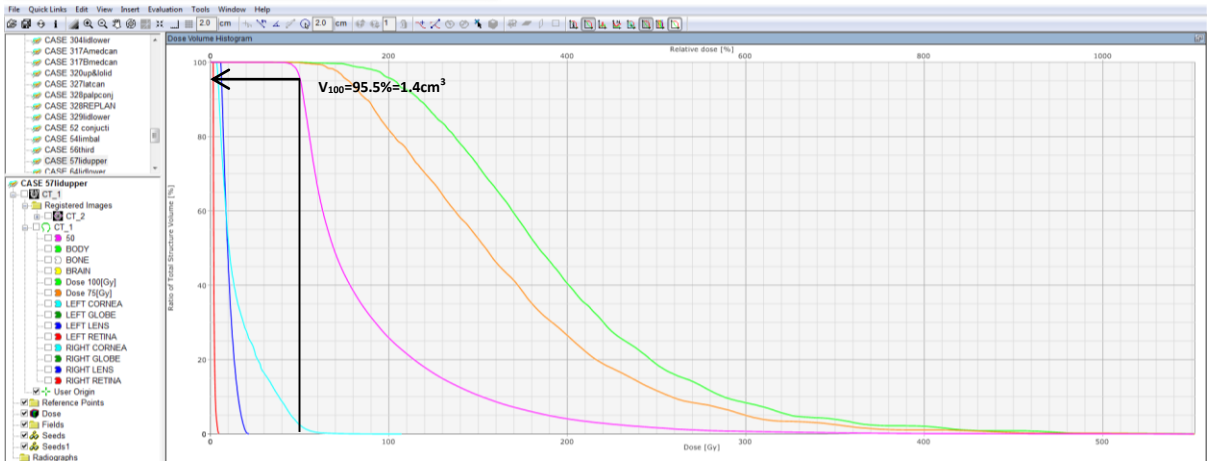


Figure 5.26: Case 57 Retrospective Dose DVH

Table 5.18: Case 57 Retrospective Dose Report

DVH Line	Structure	Volume (cm^3)	Min DoseCase 57 (Gy) & Volume (cm^3)		Max Dose (Gy) & Volume (cm^3)		Mean Dose (Gy) & Volume (cm^3)	
	50Gy Structure Volume (100%)	1.5cm^3	34.9Gy		551.6Gy	<0.0001cm^3	88.5Gy	0.47cm^3
	100Gy Max (200%)	0cm^3						
	75Gy Max (150%)	0.1cm^3						
	Lens		5.6Gy	2.0cm^3	21.7Gy	<0.0003cm^3	10.3Gy	0.86cm^3
	Cornea		2.9Gy	BT	107.4Gy	<0.0001	16.2Gy	BT
	Retina		1.5Gy	BT	4.6Gy	BT	2.0Gy	BT

BT: Below Tolerance, Red Highlight: Over Tolerance

CASE 57: REPLAN DOSE REPORT

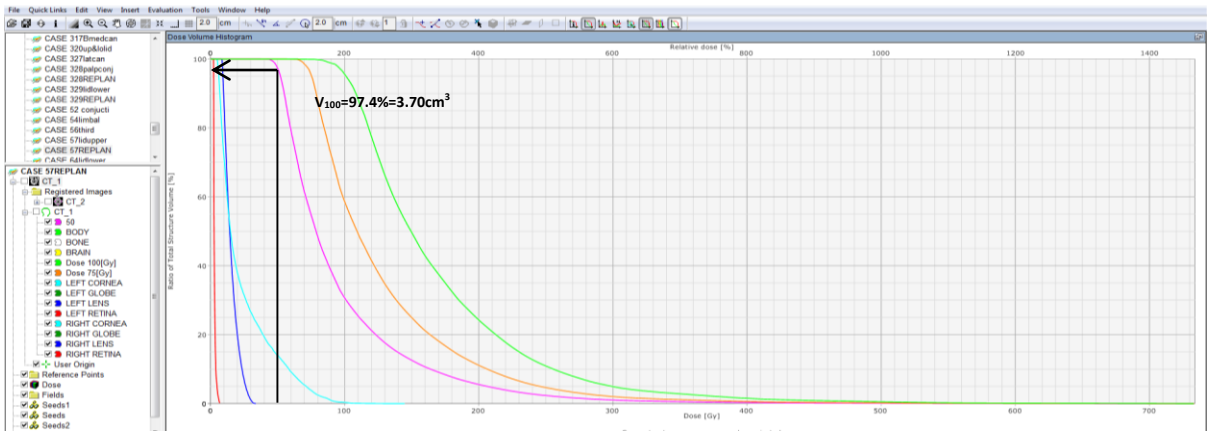


Figure 5.27: Case 57 Replan Dose DVH

Table 5.19: Case 57 Replan Dose Report

DVH Line	Structure	Volume (cm^3)	Min Dose (Gy) & Volume (cm^3)		Max Dose (Gy) & Volume (cm^3)		Mean Dose (Gy) & Volume (cm^3)	
	50Gy Structure Volume (100%)	3.8cm^3	35.8Gy		733.8Gy	<0.0001cm^3	96.6Gy	1.24cm^3
	100Gy Max (200%)	0.7cm^3						
	75Gy Max (150%)	1.7cm^3						
	Lens		8.4Gy	2.1cm^3	34.2Gy	<0.001cm^3	15.6Gy	0.84cm^3
	Cornea		4.3Gy	BT	145.4Gy	<0.0001cm^3	24.1Gy	BT
	Retina		2.2Gy	BT	7.1Gy	BT	3.0Gy	BT

BT: Below Tolerance, Red Highlight: Over Tolerance

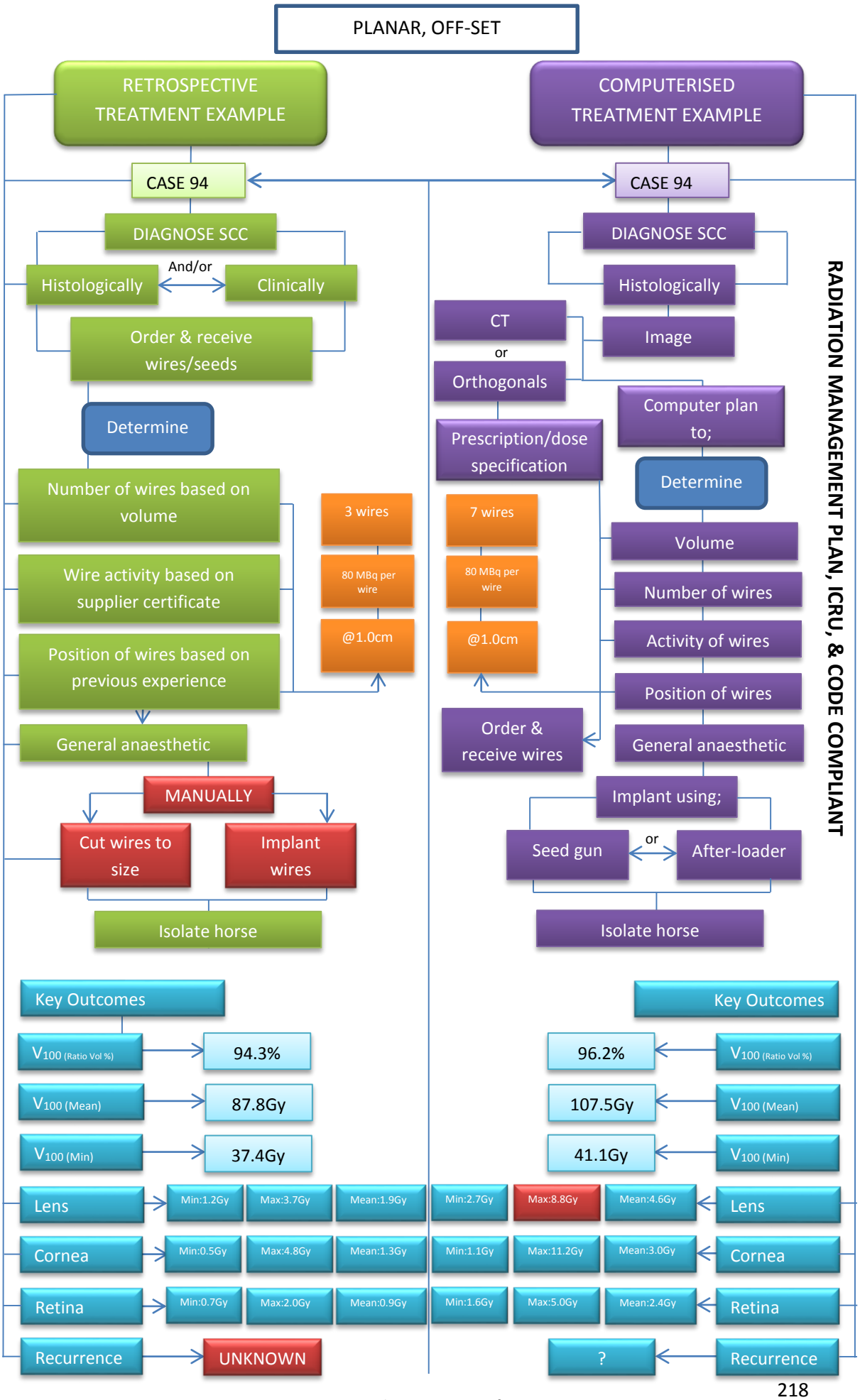


Figure 5.28: Plan Comparison for Case 94

(N.B. Red Highlight denotes over-tolerance parameters)

CASE 94: RETROSPECTIVE DOSE REPORT

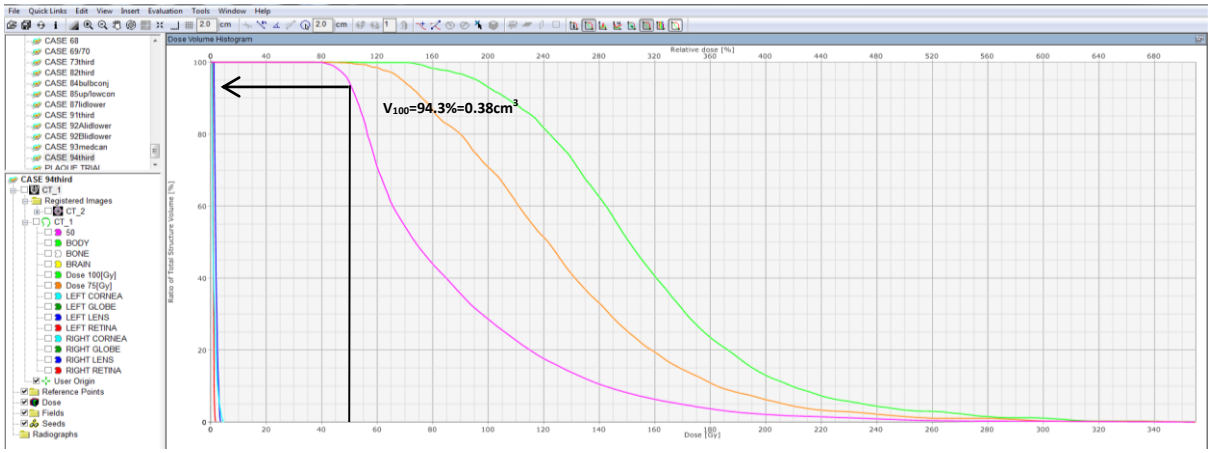


Figure 5.29: Case 94 Retrospective Dose DVH

Table 5.20: Case 94 Retrospective Dose Report

DVH Line	Structure	Volume (cm^3)	Min Dose (Gy) & Volume (cm^3)		Max Dose (Gy) & Volume (cm^3)		Mean Dose (Gy) & Volume (cm^3)	
	50Gy Structure Volume (100%)	0.4cm^3	37.4Gy		354.9Gy	<0.0001cm^3	87.8Gy	0.133cm^3
	100Gy Max (200%)	0cm^3						
	75Gy Max (150%)	0cm^3						
	Lens		1.2Gy	BT	3.7Gy	BT	2.0Gy	BT
	Cornea		0.5Gy	BT	4.8Gy	BT	1.3Gy	BT
	Retina		0.7Gy	BT	2.0Gy	BT	1.0Gy	BT

BT: Below Tolerance, Red Highlight: Over Tolerance

CASE 94: REPLAN DOSE REPORT

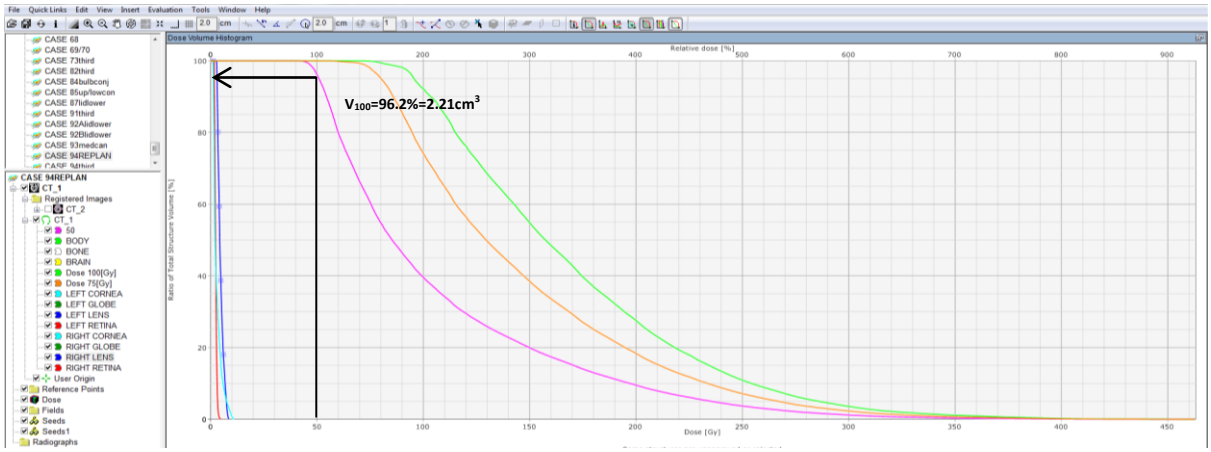


Figure 5.30: Case 94 Replan Dose DVH

Table 5.21: Case 94 Replan Dose Report

DVH Line	Structure	Volume (cm^3)	Min Dose (Gy) & Volume (cm^3)		Max Dose (Gy) & Volume (cm^3)		Mean Dose (Gy) & Volume (cm^3)	
	50Gy Structure Volume (100%)	2.3cm^3	41.1Gy		463.1Gy	<0.0001cm^3	107.5Gy	0.79cm^3
	100Gy Max (200%)	0.7cm^3						
	75Gy Max (150%)	1.1cm^3						
	Lens		2.7Gy	BT	8.8Gy	<0.008cm^3	4.6Gy	BT
	Cornea		1.1Gy	BT	11.2Gy	BT	3.0Gy	BT
	Retina		1.6Gy	BT	5.0Gy	BT	2.4Gy	BT

BT: Below Tolerance, Red Highlight: Over Tolerance

5.7 RESULTS

Optimisation allowed control over dose outcomes to the tumour volume as well as OAR's. Overall outcomes from replanning of cases are presented in Table 3 and described below.

5.7.1 $V_{(50Gy)}$: MINIMUM AND MEAN DOSES

By replanning the initial case series plans, eight from nine have increased $V_{(50Gy)}$ % Structure Volume although four from nine increased only marginally (between 0.1% and 0.6%) – these were cases 294, 123, 233 and 329. Of the cases replanned, nine from nine increased in terms of the Minimum. Increase ranged between 0.9% and 7.1% at its largest. Other increases are as follows; 1.3%, 5.1%, 1.2%, 2.8%, 6.3%, 7% and 3.7%. Logically, if all Minimums increased, the Means also increased for all cases (9 from 9). Range: 4.7%, 16.2%, 0.1%, 12%, 3.6%, 22.2%, 4.5%, 8.5%, 19.7%, (from 0.1%-22.2%).

5.7.2 THE CORNEA OF THE EYE

If the recommended tolerance dose levels for the cornea are less than 50 Gy (for TD5/5(Gy)) and less than 60Gy (for TD50/5(Gy), then the following holds true for the nine cases:

5.7.2.1 CORNEA – RETROSPECTIVE PLAN MAXIMUMS

When evaluating the retrospective cases in reference to retrospective Maximums, five from nine cases are over tolerance, with doses ranging from 107 to 433 Gy. The remaining four cases are below tolerance (4.38 to 44.7Gy, Cases 94, 328, 329 and 303).

5.7.2.2 CORNEA – REPLAN MAXIMUMS

Replan Maximums for the cornea demonstrate under tolerance in only two cases (328 & 94) at 28.9 Gy and 11.2 Gy, respectively. Again, the tolerance levels relate to 'whole' organs and the specified doses in this evaluation are for 'partial' organs only.

5.7.3 THE LENS OF THE EYE

If the tolerance levels for the lens of the eye fall between 5 Gy TD5/5(Gy) (tissue dose associated with a 5% injury rate within 5 years) and 12 Gy TD50/5(Gy) (tissue dose

associated with a 50% injury rate within 5 years) [8-10] then the following holds true for the nine cases;

5.7.3.1 LENS – RETROSPECTIVE PLAN MAXIMUMS

Eight from nine retrospective plans show a Maximum in excess of 12 Gy (ranging from 12.8 to 49.1 Gy). Case 94 is the singular case where the dose to the lens for the retrospective plan remains below tolerance (Maximum = 3.7 Gy). It must be noted that tolerance levels (as per Table 3) refer to 'whole' organs, the doses specified here in this evaluation refer to 'partial' areas of the organ (lens) only.

5.7.3.2 LENS – REPLAN MAXIMUMS

When evaluating the replanned cases in reference to Maximum lens dose, nine from nine cases demonstrate over tolerance dose. Of these, eight are situated above 12 Gy (TD50/5(Gy)), ranging from 26.1 Gy to 91.9 Gy and one remains below 12 Gy but above 5 Gy (TD5/5(Gy)), at 8.8 Gy (Case 94).

5.7.3.3 LENS – RETROSPECTIVE PLAN MINIMUMS

Minimums as they relate to the lens of the eye show four from nine cases are over the 5 Gy tolerance (TD5/5(Gy)) with the remaining five remaining below tolerance.

5.7.3.4 LENS – REPLAN MINIMUMS

Replan Minimums show over tolerance (TD5/5(Gy)) in six cases and below tolerance in three cases (Cases 303, 329, & 94).

5.7.4 THE RETINA OF THE EYE

Retina doses remained well below tolerance levels (55-70 Gy) for all nine cases in both the retrospective plans and replans.

Table 5.22: Evaluation of Retrospective Plans vs Replans

Case Number	$V_{(50Gy)}$ (%)		Mean (Gy)		Min (Gy)		Lens Min (Gy)		Lens Max (Gy)		Lens Mean (Gy)		Cornea Min (Gy)		Cornea Max (Gy)		Cornea Mean (Gy)	
	Retro	Replan	Retro	Replan	Retro	Replan	Retro	Replan	Retro	Replan	Retro	Replan	Retro	Replan	Retro	Replan	Retro	Replan
303	91.8	95.8	106.2	110.9	37.5	39.8	2.7	3.5	20.6	26.1	6.2	7.8	0.9	1.2	44.7	53.2	4.2	5.2
328	97.5	97.4	92.6	108.8	36.3	41.4	3.6	5.6	19.9	27.2	7.3	11.1	1.1	1.8	22.7	28.9	2.9	4.5
294	96.9	97.5	125.1	125.0	43.1	44.3	6.0	7.9	47.8	65.0	14.0	19.0	7.8	9.5	227.0	255.0	35.4	45.9
123	96.9	97.0	105.4	117.4	36.6	43.7	6.2	10.7	38.7	78.9	13.3	24.5	8.5	14.2	122.4	290.0	36.4	63.3
233	95.8	96.3	119.9	123.5	38.1	40.9	4.5	9.9	49.1	91.9	11.8	25.7	1.1	2.8	433.0	571.0	17.5	37.8
329	95.7	95.8	96.3	118.5	32.7	39.7	1.3	3.4	12.8	34.3	3.2	8.5	0.5	1.4	38.5	154.0	3.4	9.5
229	94.4	96.2	83.9	88.4	33.5	39.8	6.5	10.6	27.8	48.1	12.2	20.3	3.5	5.5	131.0	175.0	16.4	26.2
57	95.5	97.4	88.5	97.0	34.9	35.8	5.6	8.4	21.7	34.2	10.3	15.6	2.9	4.3	107.0	145.0	16.2	24.0
94	94.3	96.2	87.8	107.5	37.4	41.1	1.2	2.7	3.7	8.8	1.9	4.6	0.5	1.1	4.8	11.2	1.3	3.0

5.8 DISCUSSION

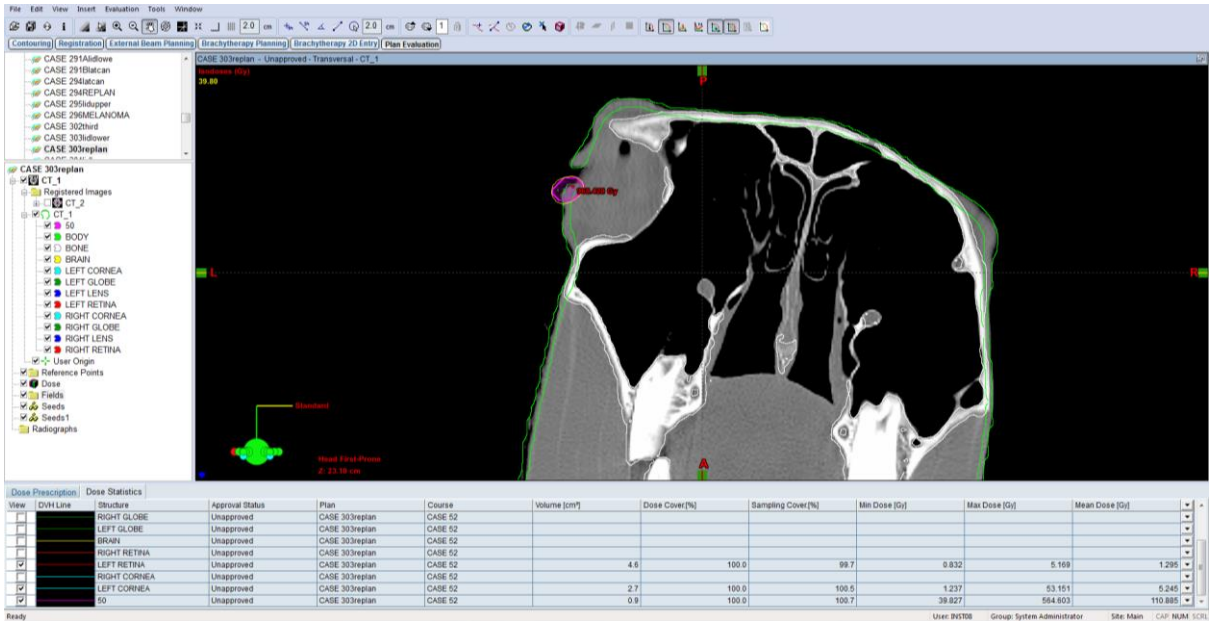
Treatment planning begins with the decision to treat a tumour. This decision is generally made by the Radiation Oncologist and includes defining the volume to be treated, the dose required, the length of treatment to be delivered and is largely supported by medical imaging. This information is used to prepare an optimal plan which results in an uniform dose to the target volume whilst minimising any excess dose to surrounding organs at risk. The availability of a treatment planning computer is pivotal in ensuring an optimal plan is prepared. In lieu of such computerised support, treatment plans can be erratic and sub-standard. [8]

Radiation therapy planning requires an amount of compromise on the part of the specialist in their search for an optimum plan. The goal of delivering the tumourcidal dose to the target volume often results in over-dosing normal surrounding tissues. An equilibrium is often difficult to reach however the development of optimum plans is possible through the use of computerised systems and the expertise and persistence of the operator.

Overall evaluation of the retrospective plans in comparison to the optimised replans demonstrates a number of improvements were possible through the use of computerised planning however some of the improvements were made at the cost of some critical parameters like OAR doses and overall Maximums.

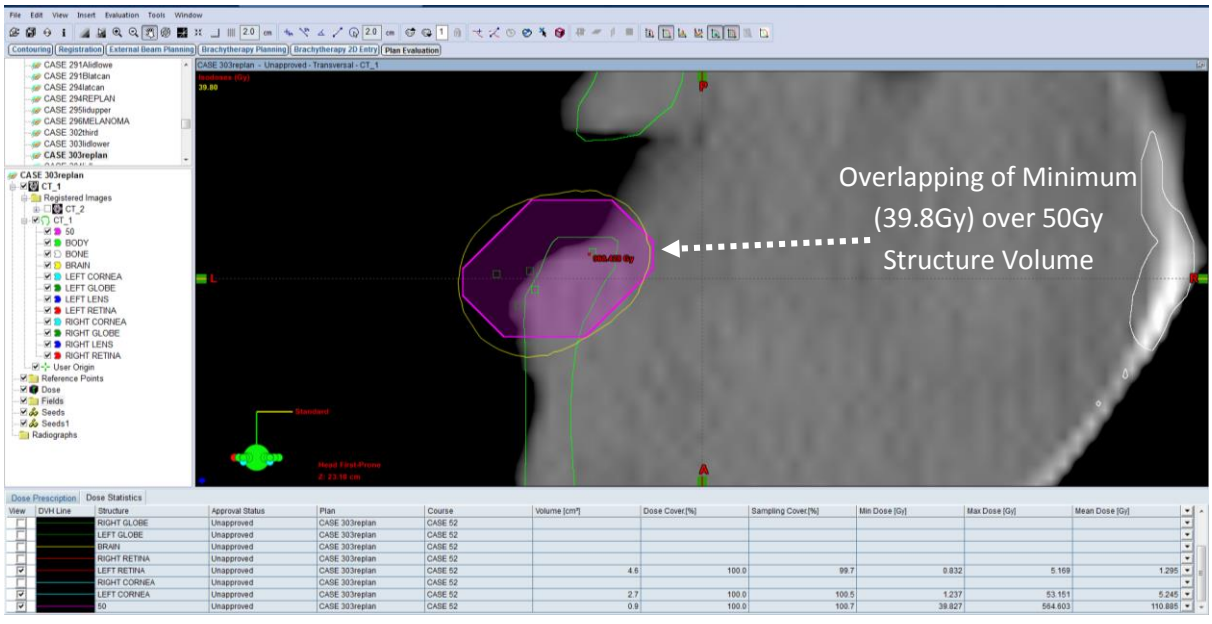
5.8.1 MINIMUM DOSES

Computerised replans largely attributed to the increase of Minimum doses in nine from nine cases however this is largely inconclusive since the original size of the minimum volumes (isodose overlapping the 50 Gy Structure Volume) are too small and calculation too complex to identify conclusively (Figures 5.31 and 5.32).



= 50 Gy Structure Volume = 39.8Gy Minimum Dose (note overlap of 50 Gy Structure Volume)

Figure 5.31: Case 303 Minimum Dose



= 50 Gy Structure Volume = 39.8Gy Minimum Dose (note overlap of 50 Gy Structure Volume)

Figure 5.32: Case 303 Minimum Dose - Zoom

Increased coverage of the 50 Gy Structure Volume was successful in the replans in eight from nine cases however in four of these, the increase was marginal and would ultimately not contribute significantly to the treatment outcome. In evaluating the coverage increase of the 50 Gy Structure Volume in the replans, it must be considered that;

a. The original intended treatment volumes were largely unknown and,
b. The treatment volumes resulting from the replans were significantly small, varying from 0.1 cm^3 at its smallest to 5.8 cm^3 at its largest.

5.8.2 OARs

The resulting increase to the OAR doses from the replans occurred in both the lens and the cornea. The original over tolerance for the lens in the retrospective plans occurred in eight plans, the replans resulted in over tolerance in all nine cases. The over tolerance cases increased from five cases in the retrospective series, to seven cases in the replans for the cornea. These increases highlight the compromise/s made in the pursuit of increasing the Structure Volume (50 Gy) coverage and Minimums. Whilst at face value it appears to be a negative outcome in terms of the increased Maximum doses to both the lens and the cornea, it is prudent to acknowledge the significantly small volumes on which this analysis is based. The position of the wire/s (in relation to the lens) contribute to the dose delivered and it must be considered that in a clinical situation, the placement could be shifted (pre-treatment) and during the planning process by the RO to ensure such doses are minimised; an additional benefit of clinical optimisation. It must also be reiterated that the Mean doses would be a better approximation of side effect assessment. The tolerance doses for both the lens and cornea are specified for the 'whole organ', that is, the whole lens or whole cornea. Literature suggests the dimension of an equine lens of the eye (thickness) is in the realm of 12.30 ± 0.83 mm. Corneal radius (vertical) is 15.02 ±1.09 mm and 15.96 ± 1.28 mm (horizontal). Following analysis it is obvious that the Maximums to these highly sensitive organs are discernible in very small volumes. It is impossible to ascertain the potential biological significance (damage), short term or long term, with the Maximum volumes ranging from <0.0001 cm^3 to 0.02 cm^3 at its largest dimension.

The retina, as a result of its posterior anatomic position (Figure 5.33), remained largely untouched with Maximum doses remaining below tolerance levels for all nine cases, initial retrospective plans and replans.

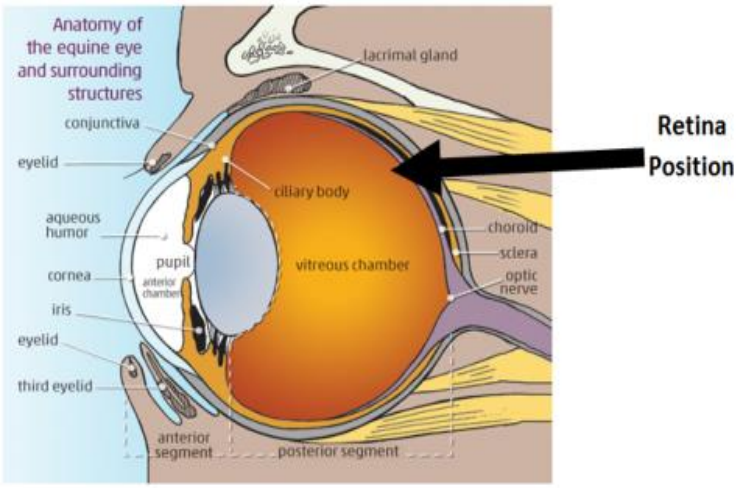


Figure 5.33: Retina Position in the Equine Eye [11]

5.9 CONCLUSION

The opportunity to plan treatment volumes using optimisation tools such as Brachyvision has the potential to enhance planning outcomes. However, this cannot be done unless information such as tumour volume dimension and location, surrounding OAR location, prescription as well as radioactive source properties, are available. Without some form of computerised planning, comprehensive dose reporting is impossible hence basic brachytherapy recommendations cannot be met. Additionally, replication of successful treatment is almost impossible.

The results from the replan identified the ability to improve plan Minimums and in some instances, the $V_{(50Gy)}$ coverage also. However it is not these improvements that illustrate the benefits of using radiation therapy expertise and computerised planning systems, these are highlighted by the ability to record doses to not only the tumour volume but also the OARs. Furthermore, it is the ability given by the optimisation capabilities of the software (coupled with RT expertise) that allows for a 'trial and error' approach to planning prior to the implantation of radioactive sources within a horse. To optimise treatment plans is to derive a best approach to individual cases.

The outcomes of the testing of the Protocol against a total of nine retrospective cases aligned with the expectation that given the expertise and optimisation tools (in the form of Brachyvision) allowed the operator to take time to assess various implantation arrangements to evaluate dosimetry of these arrangements to ascertain a best plan option. Improvements were evident in various areas of dose distribution and can be attributed to the opportunity permitted to the operator (RT) to test a number of different plans to ensure treatment delivery is maintained within the specified parameters for optimal treatment outcomes, both short term and long term.

Finally, and perhaps most importantly, the results from this study show that whilst improvements to dose distributions are possible through the use of optimisation, it is the potential for recording of treatment approaches, source implant patterns and overall dose distribution outcomes that add to the current evidence base. It is through tried and tested methods and repeated application of these that proficiency in clinical treatments develop.

5.1 REFERENCES

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CHAPTER 6: CODE OF PRACTICE FOR RADIATION PROTECTION IN VETERINARY MEDICINE

6.1 FOREWORD

Information contained within this summary and flow-chart is wholly underpinned by ***The Code of Practice for Radiation Protection in Veterinary Medicine (2009)*** and the ***Safety Guide for Radiation Protection in Veterinary Medicine*** – Radiation Protection Series No.17 (RPS17). [1] The Code details the requirements that must be followed in veterinary medicine and for the application of ionising radiation. It is supported by the Safety Guide.

This summary is intended as a ***general guide*** for staff involved either directly or indirectly, with the use of ionising radiation including radioactive sources for the diagnosis and/or treatment of disease in animals. The manual provides a summary of advice and guidance on good radiation practice and on meeting regulatory requirements as they apply and are appropriate for each practice. It is ***not*** intended to be a ***comprehensive*** manual on all aspects of radiation protection. Full radiation protection principles and Australian regulatory requirements can be found at;

http://www.arpansa.gov.au/publications/codes/rps17.cfm

6.2 INTERPRETATION

It must be noted that the use of the word '***must***' within any part of this manual indicates that the requirement to which it refers is ***mandatory***. [1]

The following document includes;

- A summary of key features extracted from the Code of Practice for Radiation Protection in Veterinary Medicine as it pertains to the 'Responsible Person' and the 'Radiation Management Plan', presented in tabulated form.

- A flow-chart summarising the Code of Practice for Radiation Protection in Veterinary Medicine (radiation protection principles, regulatory requirements, roles and responsibilities).

LIST OF ABBREVIATED TERMS

ARPANSA	Australian Radiation Protection and Nuclear Safety Agency
CT	Computed Tomography
ICRP	International Commission on Radiological Protection
mSv	milliSievert
RMP	Radiation Management Plan
RP	Responsible Person
RPS	Radiation Protection Series
RPS1	Radiation Protection Series 1
RPS17	Radiation Protection Series 17
Sv	Sievert

6.3 INTRODUCTION

This document is not intended to be a comprehensive manual on all aspects of radiation protection. It has been developed in response to the known hazardous nature of radiation and the identification via a national survey that the application of radiation protection principles and compliance are not always of a satisfactory standard in veterinary medicine.

6.4 ACKNOWLEDGMENTS

As previously stated, this document is based wholly on the ***The Code of Practice for Radiation Protection in Veterinary Medicine (2009)*** and the ***Safety Guide for Radiation Protection in Veterinary Medicine*** – Radiation Protection Series No.17 (RPS17). Review of this document should be ongoing to maintain currency, ensure alignment with international/national recommendations and guidelines, and should be overseen by the author/s and/or other qualified staff such as medical physicists.

6.5 SOURCES OF IONISING RADIATION

Radiation is energy which can be both ionising and non-ionising. Ionising radiation has the ability to change the chemical structure of atoms and therefore cause biological damage to those exposed to it. [(2)] The main ionising radiation sources from which we are exposed include cosmic, terrestrial, internal and medical imaging and are generally classified as natural or man-made. Naturally occurring radiation has the same ionising effects as man-made radiation. They do not differ in ionising properties and are therefore comparable with one another. [(2)] The average amount of natural radiation that each member of the Australian population receives per year is 1.5 mSv and contributes around 50% of an individual's annual dose (Figure 6.1). [(2)]

Medical imaging and therapeutic technology has advanced greatly over time and is being utilised more frequently resulting in increased radiation dose to patients. [(2)] Common imaging modalities that use ionising radiation include Computed Tomography (CT), general X-rays and fluoroscopy. Today, the medical use of radiation contributes to just over 50% of the total amount of radiation received by the Australian population. [(2)]

6.5.1 BACKGROUND RADIATION

Background radiation exposure is common to everyone and is in addition to any radiation received by individuals as a result of a medical procedure. Most sources of radiation exposure occur naturally and include; cosmic radiation from the sun, terrestrial radiation from the ground and building materials and naturally occurring radiation in food, such as potassium-40. Decay of uranium in the ground releases radon gas and contributes largely to the component of background radiation.[3] Generally, the levels of background radiation are modest, with the world average of natural background radiation dose to an individual in Australia being approximately 1.5 mSv per year. [4] The world average of natural background ionising radiation is represented in Table 6.1.

Table 6.1: World Average of Natural Background Radiation [4]

Source of Exposure	Exposure (per year)
Inhalation (radon gas)	0.2-10 mSv
External terrestrial	0.3-1 mSv
Ingestion	0.2-1 mSv
Cosmic radiation	0.3-11 mSv
Total natural	**1-13 mSv**

6.5.2 ARTIFICIAL SOURCES OF RADIATION

Artificial or man-made sources of radiation include medical diagnostic imaging and treatments. Artificial radiation sources and the ionising radiation emitted from them are no more damaging than radiation emitted from natural radioactive materials. Direct comparisons between natural sources and artificial sources of ionising radiation are feasible. [4]

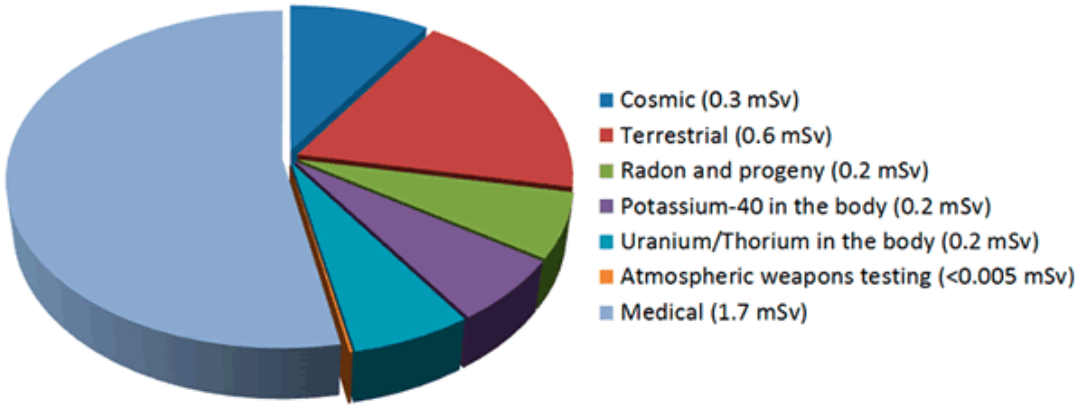

Figure 6.1: Average Yearly Radiation Exposure in Australia [2]

6.6 TYPES OF EXPOSURE

6.6.1 OCCUPATIONAL EXPOSURE

Occupational exposures are incurred as a result of work-related activities and primarily as a result of working directly with radiation. [5, 6]

6.6.2 MEDICAL EXPOSURE

Medical exposure refers to that incurred by patients as part of their own medical diagnosis or treatment; by persons (volunteers) involved in medical research, and doses incurred by persons knowingly while voluntarily helping in the support and comfort of patients. [5, 6]

6.6.3 PUBLIC EXPOSURE

Exposure sustained by members of the public from radiation sources, discounting any occupational or medical exposure and the normal natural background radiation. [5, 6]

6.7 IONISING RADIATION – THE RISKS

The detrimental side effects of radiation exposure have been well documented.[7, 8] Adverse effects highlight the need for compliance with radiation safety guidelines and the need for education with respect to the safe use of radiation. Although the precise risk of occupational exposure is unclear, biological effects of low-level exposure to ionising radiation remains a concern.[9] The potential for damaging health effects as a result of

occupational radiation exposure in veterinary practice have been acknowledged.[10] The most commonly chronicled effects of radiation exposure include cancer, birth defects and other permanent mutations. [7, 11]

Veterinarians engage in a wide range of generalist clinical activities as opposed to a specialist activity. [7, 12, 13] The requirement for veterinarians to be generalists may compete with their capacity for expert knowledge in areas such as radiation protection and regulatory requirements, hence inhibiting the application of crucial radiation safety principles. The Australian Radiation Protection and Nuclear Agency (ARPANSA) acknowledges that in veterinary medicine, positioning animals has the potential to increase radiation doses received by veterinary workers. Restraining of animals is at times necessary during exposures. In relation to horses and adding to the procedural complexities, exposures are usually performed in the field with horses in the standing position.

6.8 RADIATION PROTECTION STANDARDS (RPS)

RPS set necessary requirements for safety. These requirements are regulatory and contain key procedural requirements and are supported by the basis of best international practice standards in radiation protection. The Radiation Protection Series is published by ARPANSA. The premise of the Series is to uphold practices which protect human health and the environment from the potentially detrimental effects of radiation. [1] The Series are published in four different categories;

1. Radiation Protection Standards
2. Codes of Practice
3. Recommendations
4. Safety Guides.

6.8.1 CODES OF PRACTICE

Codes of Practice contain practice-specific requirements that must be met to ensure an adequate level of safety in procedures involving exposure to radiation. The Codes are prescriptive and often referenced by regulations and/or conditions of licence. The requirements listed under the Code of Practice are expressed in ***'must'*** statements. [5]

6.8.2 RECOMMENDATIONS

Recommendations are written in an explanatory style and describe the fundamental concepts and objectives of best international practice. Recommendations provide guidance on elemental principles for radiation protection. (5)

6.8.3 SAFETY GUIDES

Safety guides provide practice-specific direction on achieving the requirements established in Radiation Protection Standards and Codes of Practice. The Safety Guides may recommend good practices in a non-descriptive fashion and are expressed in ***'should'*** statements. These ***'should'*** statements indicate that the measures recommended are habitually necessary in order to fulfil the requirements of the RPS and Codes of Practice. (5)

6.9 ORGANISATION OF RADIATION PROTECTION IN VETERINARY MEDICINE

Radiation principles and regulatory requirements for the safe use of ionising radiation in veterinary medicine apply to;

a) The ***Responsible Person*** - a person with overall management responsibility of the veterinary practice and/or,

b) The ***Veterinary Surgeon*** responsible for prescribing the radiation procedure and/or,

c) The ***Operator*** who exposes animals to radiation.

N.B. The **Responsible Person**, **Veterinary Surgeon** and **Operator** may be the same person in many practices.

6.9.1 RADIATION PROTECTION IN VETERINARY MEDICINE: CODE OF PRACTICE AND SAFETY GUIDE (RADIATION PROTECTION SERIES NO.17)

The Radiation Protection Series Number 17: Code of Practice for Radiation Protection in Veterinary Medicine (2009), establishes the radiation protection principles and regulatory requirements for the safe use of ionising radiation in veterinary medicine. The Code also establishes the specific roles and responsibilities for; the Responsible

Person (RP) and the veterinary surgeon (responsible for justifying and prescribing procedures) along with the technician/operator who exposes the animal to radiation.

The Code also outlines the requirement for a comprehensive Radiation Management Plan (RMP) to be prepared to address radiation protection principles, as well as the management of radiation incidents including mandatory reporting. [5]

6.10 DOSE LIMITS

To limit the potential risk to health from exposure to ionising radiation in the Australian workplace and to develop a common setting for radiation protection requirements for the control of exposure to radiation, the ARPANSA provides a National Standard for Limiting Occupational Exposure to Ionising Radiation (RPS1) (Table 6.2), based on the International Commission on Radiological Protection (ICRP) Recommendations. [5, 6]

Dose limits specified within Australia by ARPANSA (RPS1) are as follows; [5]

Table 6.2: Dose Limits for Ionising Radiation (RPS1 – based on ICRP) [5]

Application	Occupational Dose Limit	Public Dose Limit
Effective Dose	20 mSv per year, averaged over a period of 5 consecutive calendar years	1 mSv in a year
Annual Equivalent Dose in:		
The lens of the eye	20 mSv	15 mSv
The skin	500 mSv	50 mSv
The hands and feet	500 mSv	-

6.11 RESPONSIBILITIES OF THE RESPONSIBLE PERSON

The ***Responsible Person*** is responsible for the management of radiation safety within their facility. Each facility using irradiating apparatus or radioactive materials has a responsibility for organising safety procedures according to regulatory requirements.

Table 6.3: Responsibilities of the Responsible Person

RESPONSIBILITIES OF THE RESPONSIBLE PERSON	
In relation to the Radiation Management Plan (RMP) the Responsible Person must ensure that;	
1	A RMP is developed, implemented and regularly reviewed
2	The RMP incorporates components listed in The Code of Practice
3	The staff affected by the RMP are compliant in its requirements
In relation to protocols and procedures, the Responsible Person must ensure that;	
1	The need to carry out the procedure is taken into account
2	Procedures are approved by the veterinary surgeon and are in keeping with RMP provisions and The Code of Practice
3	Radiation dose is justified by the veterinary surgeon in accordance with the RMP and The Code of Practice
4	Radiation exposures are optimised by the veterinary surgeon in accordance with the RMP and The Code of Practice
5	The potential detriment to the operator, assistants and carer or owner of the animal is taken into account
6	The benefits and risks and efficacy of alternate procedures are taken into account

7	Treatment planning procedures for RT are followed
8	Treatment planning equipment for RT is tested
9	A qualified expert in the field of RT checks basic data for each RT software program used
In relation to radiation doses, optimisation and limitation of exposure the Responsible Person must ensure that;	
1	Radiation doses to occupationally exposed persons and members of the public do not exceed dose limits
2	Doses are maintained as low as reasonably achievable (ALARA)
In relation to radiation monitoring, the Responsible Person must ensure that;	
1	A personal radiation monitoring device is provided to each occupationally exposed person
2	Internal and biological monitoring are carried out for each occupationally exposed person likely to be exposed to internal radioactive material
3	A radiation dose record is kept for each occupationally exposed person
4	Investigation and review is carried out whenever an occupationally exposed person receives a dose in excess of dose constraints
5	Adapt working conditions for pregnant workers to ensure the embryo/foetus is afforded the same level of protection as a member of the public
In relation to the veterinary radiation facility, the Responsible Person must ensure that;	
1	It is designed, constructed, shielded, maintained and used ensuring the dose constraints are within the relevant regulatory authority requirements
2	Dose to members of the public and to occupationally exposed persons are limited
3	A Radiation Source Register is updated and maintained

In relation to radiation incidents, the Responsible Person must ensure that;	
1	The radiation incident is investigated
2	The radiation incident is reported
3	Preventative action to avoid recurrence is implemented
In relation to the veterinary radiation facility training and authorisation requirements, the Responsible Person must ensure that;	
1	Only persons who are appropriately authorised operate irradiating equipment or handle radioactive sources/waste
2	Each occupationally exposed person has training or instruction in the work being done
3	Each occupationally exposed person has training or instruction relating to the source and equipment used
4	Each occupationally exposed person has training or instruction in the associated hazards
5	Each occupationally exposed person has training or instruction in the required protection and minimisation of dose
6	Each occupationally exposed person has training or instruction in required compliance with RMP
7	A qualified expert is used to advise on matters relating to radiation protection
In relation to radiation shielding, the Responsible Person must ensure that;	
1	Shielding is used appropriately in close proximity to the source
2	Shielding is compliant with RMP requirements
3	Shielding is well documented at time of installation and at time of modifications

In relation to warning notices, the Responsible Person must ensure that;	
1	A visible warning sign is evident at each access point into a radiation area
2	An illuminated sign reading 'IONISING RADIATION – DO NOT ENTER' is positioned at any entry point to a room with radiation producing equipment or machines or sources
3	The illuminated sign is illuminated instantly when radiation producing equipment is in preparation mode and/or as the source emerges its shielded housing
In relation to the death of an animal, the Responsible Person must ensure that;	
1	The dose to any person handling the corpse is minimised
2	Sources or applicators are removed
3	The level of activity remaining in the corpse is calculated and documented
4	Instructions (written) regarding the handling of the corpse in the case of it having radioactive material, is provided to all involved persons
In relation to the provision of advice to owners/handlers, the Responsible Person must ensure that;	
1	Written information must be given to owners/handlers of an animal that is discharged with an implanted source or radiopharmaceutical
2	The written information includes details on the risks associated with ionising radiation
3	The written information includes details on restricting exposure to persons
4	The written information includes details on storage or disposal of sources (dislodged)
5	The written information includes details on contamination prevention
6	The written information includes details on course of action in the case of contamination

6.12 RADIATION MANAGEMENT PLAN (RMP)

The responsible person is responsible for the development, implementation, and review of the Radiation Management Plan. To ensure currency, arrangements for obtaining expert advice in relation to radiation protection and any other requirement that may impact on radiation safety within a practice/facility must be obtained.

The Radiation Management Plan must address the following:

Table 6.4: Radiation Management Plan (RMP)

RADIATION MANAGEMENT PLAN (RMP)	
The Radiation Management Plan must address the following;	
1	Protocols and work practices for all procedures that involve ionising radiation
2	Protocols and work practices to ensure the correct animal is undergoing correct procedure
3	Protocols and work practices to ensure the correct planning and delivery of treatment
4	Protocols and work practices to ensure optimised shielding
5	Protocols and work practices to ensure proper action is taken if radiation doses to occupationally exposed persons or members of the public exceed dose constraints
6	Animal supervision throughout procedures where movement could affect outcome
7	Provision of isolation within facility for animals undergoing treatment using radioactive sources
8	Roles and responsibilities of staff including qualifications, training and supervision where appropriate

9	Licensing
10	Radiation monitoring provisions for all personnel exposed to radiation
11	Provision of radiation protective equipment for all personnel
12	Provision of appropriate ancillary equipment, animal restraints and safety devices
13	Procedures necessary to manage radiation incidents and emergencies
14	Procedures necessary for reporting radiation source faults
15	Provision for source storage and transport
16	Provision for waste management (radioactive)

6.13 RADIATION PROTECTION FLOW-CHART FOR VETERINARY MEDICINE

The following is a flow chart summarising the range of responsibilities pertaining to the Responsible Person, inclusive of the Radiation Management Plan (RMP) (Figure 6.2). The chart has been developed as a supporting feature to the summarised Tables (6.3 & 6.4) and as a one-stop document to guide veterinarians at the commencing stages of any radiation procedure. As per the summaries found in Tables 6.3 and 6.4, it is not intended as a comprehensive, stand-alone document but rather as the impetus towards establishing best-practice approaches in the area of radiation protection. It has been based wholly on the Code of Practice for Radiation Protection in Veterinary Medicine (2009) and the Safety for Radiation Protection in Veterinary Medicine (RPS17).[1] It is recommended that the following flowchart and Tables are reviewed in conjunction with RPS17 (http://www.arpansa.gov.au/publications/codes/rps17.cfm).

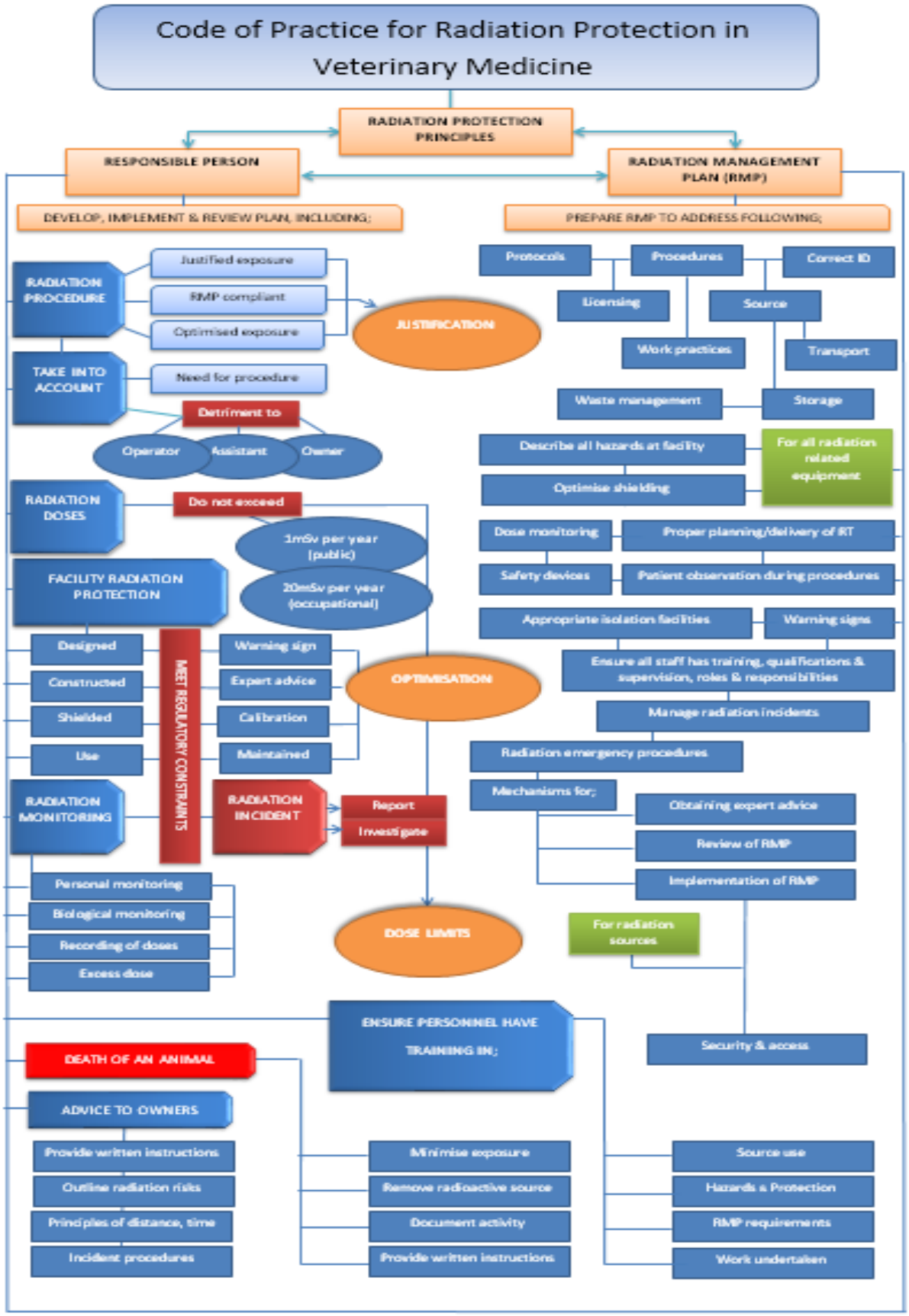

Figure 6.2: Flow-chart summarising the range of possibilities pertaining to the Responsible Person inclusive of the Radiation Management Plan (RMP)

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CHAPTER 7: DISCUSSION & CLINICAL SIGNIFICANCE

7.1 OVERVIEW

This chapter examines the key findings of the research in this thesis. It includes a summary of the research findings for each investigation and analysis undertaken, final discussion, strengths and limitations, and the implications for future research and veterinary clinical practice. The chapter closes with the final conclusions of the thesis.

7.2 INITIATION OF PHD

It was in 2009, following a discussion with a colleague around the use of radiation therapy in veterinary medicine that the concept for this PhD was born. Anecdotal evidence suggested RT in the form of brachytherapy was or had been used in an equine clinic in NSW, Australia. Investigations followed and led to a series of meetings with the clinic to establish current practice and investigate the potential for significant collaborative research.

Follow up discussion revealed that RT had indeed been used on horses for OSCC/POSCC among other sites however, the principles, approach and prescribing and recording of these treatments came into question.

7.3 AIMS & OBJECTIVES OF RESEARCH

The researchers aimed to investigate treatment practice in horses in Australia for OSCC/POSCC. Practice was defined as methods applied currently and in the past by veterinarians. A secondary aim was directed at the potential for contributing to the current evidence base by providing veterinary medicine with a brachytherapy alternative to treatment of OSCC/POSCC in view of its known treatment benefits in human SCC.

The research process included a series of objectives, each designed to support and inform the development of each study through their many facets. The research commenced with a comprehensive literature search to ascertain previous research in the field and to conduct a necessary gap analysis. To better guide the research, there was a need to recruit a veterinary expert. A veterinarian expert in Equine Ophthalmology was located in the UK and recruited. From this international collaboration a horse cadaver CT dataset was sourced which was later used to gather multiple data to develop the Protocol. To

better gauge Australian veterinarian perceptions and current practice, two separate surveys were distributed and analysis of these aided in the development of the Radiation Protection Summary and the Protocol.

7.4 SUMMARY OF FINDINGS

Squamous Cell Carcinoma (SCC) is the most common non-melanocytic tumour of the eye and adnexa in horses representing up to 75% of tumours. [1-3] The management of ocular squamous cell carcinoma (OSCC) and/or periocular squamous cell carcinoma (POSCC) in horses endures as an ongoing challenge regardless of its high prevalence among horses. Literature indicates a number of treatment modalities currently exist; surgery, photodynamic therapy, cryotherapy, carbon dioxide (CO_2) laser ablation, radiofrequency hyperthermia, topical or intratumoral chemotherapy, and radiation therapy (RT), predominantly in the form of brachytherapy (implantation of sealed radioactive sources). [4] Whilst no technique can irrefutably be identified as the best approach to the treatment of OSCC/POSCC, successful treatment commonly includes one of the above therapies combined with cytoreductive surgery. Furthermore, the value of combining radiation therapy with surgery or using radiation therapy alone has been identified in relation to benefits in decreasing cosmetic and functional defects.

The research in this thesis investigated the literature surrounding OSCC and/or POSCC treatment within Australia and internationally to ascertain current practice and to seek out protocols related to any standardised treatment approach that may exist. The investigations revealed that whilst there is a large number of research published in the field, treatment approaches are diverse and reporting on outcomes lack consistency making it impossible to make comparative conclusions on treatment outcomes. This was the basis for further research to establish a best-practice protocol. The research in this thesis was conducted in five investigation phases. A summary of the findings from each research investigation follows.

7.4.1 INVESTIGATION ONE - LITERATURE REVIEW

The literature review (Chapter 2) consisted of five components;

1. Review of squamous cell carcinoma, OSCC/POSCC in horses, and horse eye anatomy
2. Narrative review of current treatment options in OSCC/POSCC in horses
3. Review of the role of radiation therapists within veterinary oncology
4. Review of brachytherapy principles, physical characteristics of radionuclides, the biological effects of ionising radiation and radiation protection principles

The review on squamous cell carcinoma and in particular OSCC/POSCC reported a very high prevalence of the cancer within horses, principally in those exposed to on-going UV exposure, those with a genetic disposition to carcinogenesis or the degree of pigmentation with incites such conditions. The condition (SCC) in the ocular and/or periocular region is generally locally invasive and usually detected within early stages of progression due to their visible locations. [1, 5, 6]

A narrative review of current treatment options in OSCC/POSCC in horses was conducted to determine if a 'best practice treatment' could be identified. The review revealed that whilst the published evidence is large, the quality of reporting is poor and lacks conformity, making cross-study comparisons problematic. The overall tendency toward global reporting without details on tumour location, size or previous treatment increased the complexity in identifying a best practice treatment. A broad range of treatment options were identified for OSCC/POSCC in horses including ; photodynamic therapy (PDT), carbon dioxide (CO_2) laser ablation, radiofrequency hyperthermia, cryotherapy, topical or intratumoral chemotherapy and radiation therapy (these were discussed in Chapter 2). However, a definitive best practice treatment approach was not found. The investigations did however reveal that whilst no technique can conclusively be identified as the best approach to the treatment of OSCC/POSCC, successful treatment commonly involves one of the above therapies combined with cytoreductive surgery. Furthermore, the value of combining radiation therapy with surgery or using radiation therapy alone has been identified in relation to benefits in decreasing cosmetic and functional defects. [7, 8] This review identified a significant gap within the current

approach in the treatment of OSCC/POSCC which the research in this thesis has attempted to remedy.

A review into the role of radiation therapists in the field of veterinary oncology was investigated and reported that successful radiation therapy techniques are based on not only veterinary knowledge and skills but radiation therapy expertise in the form of planning and treatment and radiation oncology proficiency combined with physics knowledge in the area of radiation protection.

The review of brachytherapy principles outlined the longstanding benefits of the technique in view of its ability to deliver of a high radiation dose to a localised affected area (cancer) whilst sparing surrounding normal tissue due to the effects of the fast fall-off of radiation. [9] Brachytherapy is a standard technique in human cancer treatment, and is increasingly aligned with organ preservation and the satisfactory cosmetic results the technique offers. [10] The review described the type of brachytherapy implantations available (surface, intracavitary and interstitial) before describing radionuclide properties in detail. The review reported on the importance of radiation protection standards in veterinary medicine as governed by ARPANSA and included the principles of justification, optimisation and limitation as related to the veterinary specialty in view of brachytherapy being one of the most hazardous (radiation) procedures in health care. [11]

Three publications were produced as part of the literature review. A narrative review on the role of radiation therapists in veterinary oncology was accepted for publication in *Radiography* in January 2011. A narrative review on current treatment options for ocular and/or periocular SCC in horses was accepted for publication in the *Journal of Equine Veterinary Science* in April, 2014. A short communication review article was accepted for publication in the *Australian Equine Veterinarian* in the Autumn of 2015.

7.4.2 INVESTIGATION TWO - TREATMENT MODELLING

In 2010, 160 medical records (1999-2007) directly related to previous brachytherapy in horses conducted within one clinic in Australia, were collected, categorised and analysed for inclusion into the research. A total of 75 cases were deemed to meet all prescribed criteria; identifiable lesion location; wire location; number of wires; radioactivity; SCC diagnosis and site of diagnosis and included in the research. The intention of the retrospective analysis was to replicate the treatments using RT specific computerised planning and validate outcomes against ICRU-58 [12] recommendations for human RT treatments for the same cancer type (in lieu of equivalent standards within veterinary oncology). The efficacy and toxicity of brachytherapy treatment of OSCC/POSCC was assessed by applying contemporary radiation therapy treatment methods to the clinical series of cases.

Each case was replicated with the use of Radiation Therapy Treatment Planning Software Varian BrachyVision™ (Varian, Palo Alto, United States of America) and a prescription of 50 Gy applied (Minimum Target Dose). Exploratory statistical analysis was performed on radiation dose distribution parameters, including; treated volume coverage (Target Volume – TV), dose to organs at risk and Maximum, Minimum and Mean doses, with the intention of determining treatment efficacy in terms of meeting conventional human treatment constraints recommended by the International Commission on Radiation Units and Measurements (ICRU-58). [12]

It must be noted that the outcomes of this retrospective analysis need to be considered with some scrutiny in view of the multiple assumptions made in its development. The quality of the information in the medical records is such that there are limitations in the ability to make absolute and accurate comparisons regarding compliance with each dose-specification recording systems (ICRU-58) currently used in brachytherapy. Should the records have contained accurate, 3-dimensional representations of volumes (as opposed to 2-dimensional schematic diagrams), 'estimates' would be unnecessary and results would have been reported with more confidence and accuracy.

In summary, the findings of the retrospective analysis suggest that;

1. The 50 Gy Structure Volume coverage (V_{50Gy}) showed great variability across all 75 cases.
2. Without a pre-determined prescription and lesion volume, it is difficult to establish how many cases may have been under-dosed or overdosed.
3. Without a biologically significant volume to compare the Maximum Volumes (75 Gy and 100 Gy as well as overall Maximums), it is impossible to establish the potential for side-effects.
4. Treated volumes are unusually small (due to site and nature of cancer) hence overall and OAR maximums are relatively small (volume).

Using brachytherapy allows a high radiation dose to be delivered locally to the tumour with good sparing to surrounding normal tissues.[11] The outcome of this practice is not without risk to the treating veterinarian and assistants, and potentially, to the horse and owners due to the radiation exposure. The long-term outcome of the cases treated is largely unknown hence recommendations or assumptions of the benefits of its application cannot be made. In sum, several limitations and weaknesses reduced the ability of the study to conclusively report on the outcomes of the treatment modelling however, it can be stated that great variability in general isodose distribution is evident.

7.4.3 INVESTIGATION THREE - SURVEYS

The first online survey was sent to equine veterinarians working in Australia in 2011. The survey was delivered both online and in hardcopy format for the purposes of generating maximum response rates; it comprised 49 open and closed format questions. The participants were asked about their current or past use of brachytherapy and about their knowledge of its applications, benefits and perceived associated risks. Participants were asked to comment on their level of interest in the treatment regime if it was made clinically available. Information was collected regarding their level of knowledge and application of radiation safety standards with regard to the radiation-producing equipment they currently possess and in view of potentially introducing brachytherapy treatment into their clinics.

A total of 86 participants responded to the first survey. The use of radiation-producing equipment was evident in 94% of responding clinics (a combination of X-ray, CT and/or Nuclear Medicine Cameras). Of those with radiation producing equipment, 94% indicated that they hold a radiation license, 78% had never completed a certified radiation safety course and 19% of participants did not use a personal radiation monitor. In 14% of cases, radiation safety manuals or protocols were not available within clinics.

The first survey results has shown that knowledge and application of guidelines as provided by the Code of Practice for Radiation Protection in Veterinary Medicine (2009) is poorly adhered to. Whilst the nature of the profession and the need for handling animals often makes the application of such regulations difficult, it does not minimise the importance of compliance with regulatory requirements. Occupational exposure to radiation in veterinary medicine is common, and thus there is a need for increased education and training in the area. Two abstracts of the results from this study were accepted for poster presentation at the Proceedings of the UK Radiological Congress, Manchester, United Kingdom, 6-8th June, 2011 and the Proceedings of the 9th Annual Scientific Meeting of Medical Imaging and Radiation Therapy (ASMMIRT) in Sydney Australia, 20-22nd April 2012. A third abstract of the results from the radiation safety component of this study was accepted for poster presentation at the ESTRO 31 (European Society for Radiotherapy and Oncology) Proceedings in Barcelona, Spain in May 2012 and subsequently published in the *Radiography* Journal (UK). The three abstracts and the poster presentations are available in Appendix B.

Following the low response rate from the first survey and in response to concern regarding the strength of some of the questioning around ophthalmic anatomical sites and their delineation, it was decided to develop a second survey for distribution. The second survey was validated by a panel of veterinary experts in the field of ophthalmology, led by the veterinarian collaborator on the research.

The survey was delivered online and contained 52 open and closed format questions. Equine veterinarians were asked about their treatment methods for squamous cell carcinoma in horses with distinct emphasis on OSCC and/or POSCC and the use of brachytherapy as a treatment preference. Results from the survey were complemented

by previously collected survey data (2011) in the area of brachytherapy for the same veterinarian cohort.

A total 24 surveys were returned from the second survey (2015), results from the 2011 (n=86) were included wherever questions were written in an exact format. Fourty-four percent of respondents (from a possible 110) suggested they would be willing to learn more about brachytherapy and pursue it as a treatment option. Previous brachytherapy use was reported by 9% of respondents. The surveys did not discover any current users of brachytherapy within Australia. Results from the 2015 survey also reported that the most commonly preferred treatment approach for OSCC/POSCC sites and for sites outside of this classification (ear pinnae, muzzle, lips, nostrils, vulva, penis or prepuce, perianal/perineum and extremities), was surgery followed by cryotherapy.

The results from the 2015 survey (with some additional data contributing to analyses form 2011 survey), was submitted to the *Australian Equine Veterinarian Journal* in October 2015 and is currently under review.

7.4.4 INVESTIGATION FOUR - TREATMENT PROTOCOL

Following the comprehensive analysis of the retrospective study in 75 horses treated with brachytherapy, it was evident that the treatments were performed without the use of a treatment planning system (computerised). Wires were implanted manually and source placement and dose calculations were also conducted manually. Recording of OAR doses was not apparent in any of the cases. The process followed by the clinic in the application of brachytherapy for OSCC/POSCC in 75 horses was recorded as a Flow-Chart, referred to as the **Retrospective Process-Flow**. The process was examined and compared to currently accepted human brachytherapy planning/treatment processes as recommended by ICRU-58 and reinforced by the GEC Handbook of Brachytherapy (based on ICRU recommendations for all brachytherapy procedures). [12, 13] As a result, a second Flow-Chart was developed established on current accepted practice and referred to as the **Protocol**.

The **Retrospective Treatment Process** and **Protocol** were formatted side-by-side to aid in identifying any areas where the **Retrospective Treatment Process** did not meet the **Protocol** conditions. Further to the Flow-Charts, it was considered essential to test the **Protocol** against a number of treatment cases. A total of nine cases were chosen for testing, each case representative of the nine different sets of conditions identified in the treatment applications.

The opportunity to plan treatment volumes using optimisation tools such as Brachyvision offered the potential to enhance planning outcomes. The results from the replan of the nine cases improved plan Minimums and in some cases, the $V_{(50Gy)}$ coverage. However it was not these improvements that illustrated the benefits of using radiation therapy expertise and computerised planning systems, these are highlighted by the ability to *record* doses to not only the tumour volume but also the OARs and hence procuring accurate records to compare clinical outcomes. Furthermore, it was the ability provided by the optimisation capabilities of the software (combined with RT expertise) that allowed for a 'trial and error' approach to planning prior to the implantation of radioactive sources within a horse.

Computerised replans resulted in the increase of Minimum doses in nine from nine cases however this must be considered with some caution since the size of the minimum volumes (isodose overlapping the 50 Gy Structure Volume) were too small and calculation too complex to identify conclusively.

Increased coverage of the 50 Gy Structure Volume was successful in the replans in eight from nine cases however in four of these, the increase was minor and would ultimately not contribute significantly to the treatment outcome.

In evaluating the coverage increase of the 50 Gy Structure Volume in the replans, it must be considered that;

a. The original intended treatment volumes were largely unknown and,
b. The treatment volumes resulting from the replans were significantly small, varying from 0.1 cm^3 at its smallest and 5.8 cm^3 at its largest.

An increase to the OAR doses from the replans occurred in both the cornea and the lens. The original over tolerance for the lens in the retrospective plans occurred in eight plans, whereas the replans resulted in over tolerance in all nine cases. The cases where an over tolerance was identified increased from five cases in the retrospective series, to seven cases in the replans for the cornea. These increases highlighted the compromise/s made in the pursuit of increasing the Structure Volume (50 Gy) coverage and Minimums. Whilst this may appear to be an undesirable outcome in terms of the increased Maximum doses to both the lens and the cornea, it is prudent to acknowledge the significantly small volumes on which this analysis is based.

It must also be noted that the tolerance doses for both the cornea and lens were specified for the 'whole organ', that is, the whole cornea or whole lens. Following analysis it is discernible that the Maximums to these highly sensitive organs are evident in very small volumes. It is impossible to ascertain the potential biological significance (damage), short term or long term, with the Maximum volumes ranging from <0.0001 cm^3 to 0.02 cm^3 at their largest dimension.

The retina, as a result of its posterior anatomic position remained largely intact with Maximum doses remaining below tolerance levels for all nine cases, in both, the initial retrospective plans and replans.

7.4.5 INVESTIGATION FIVE - RADIATION SAFETY CODE OF PRACTICE SUMMARY

The final stage of the research involved the development of a summary of ***The Code of Practice for Radiation Protection in Veterinary Medicine (2009)*** and the ***Safety Guide for Radiation Protection in Veterinary Medicine*** – Radiation Protection Series No.17 (RPS17), in the form of a flowchart.

The summary was developed in response to the known harmful nature of radiation and the identification through the literature review and national survey that suggested the knowledge and compliance of radiation protection principles are not always of a satisfactory standard in veterinary medicine. The document/flow-chart was not intended to be a comprehensive manual on all aspects of radiation protection but a summary of the key aspects. The document included the following:

1. A summary of key features extracted from the Code of Practice for Radiation Protection in Veterinary Medicine as it pertains to the 'Responsible Person' and the 'Radiation Management Plan', presented in tabulated form
2. A flow-chart summarising the Code of Practice for Radiation Protection in Veterinary Medicine (radiation protection principles, regulatory requirements, roles and responsibilities).

It is envisaged that the summary be used as a ***general guide*** for staff involved either directly or indirectly, with the use of ionising radiation including radioactive sources for the diagnosis and/or treatment of disease in animals. The manual provides a summary of guidance on good radiation practice and regulatory requirements as they apply and are appropriate for each practice. It is ***not*** intended to be a ***comprehensive*** manual on all aspects of radiation protection. The reader is led to the full radiation protection principles and Australian regulatory requirements at;

http://www.arpansa.gov.au/publications/codes/rps17.cfm

7.5 STRENGTHS & LIMITATIONS

In addition to the strengths and limitations of each research investigation described within the published or submitted papers, a detailed description is described below.

7.5.1 RESEARCH STRENGTHS

The research was initiated as a result of a series of informal conversations and the collection of anecdotal information which led to the development of the enquiry into current treatment practices for the treatment of OSCC/POSCC. A comprehensive literature review confirmed the anecdotal findings that a standardised approach to the treatment of OSCC/POSCC is currently non-existent. The research provides knowledge and advice in the form of a Protocol for veterinarians on a treatment alternative (brachytherapy) to OSCC/POSCC which is supported by literature in relation to improved outcomes and effectiveness. The research considered a number of issues as related to the implementation of the treatment technique including radiation protection guidelines and compliance. As a result, and as an accompaniment to the Protocol, a summary of the ***Code of Practice for Radiation Protection in Veterinary Medicine (2009)***

and the ***Safety Guide for Radiation Protection in Veterinary Medicine*** has been developed and presented in table format as well as a flow-chart for ease of understanding.

This research provides a significant contribution to the limited evidence base available in this area. Whilst it is acknowledged the response rates were statistically low, the surveys were able to provide information to further develop the research. They also served the purpose of promulgating the research and its aims to the wider veterinary community. As a result, an invitation to speak on the research at the **Upper Hunter Branch of the Australian Veterinary Association Annual Meeting and Continuing Professional Development Seminar**, ensued in August 12th, 2015. Furthermore, following dissemination of the research among equine veterinarians, the research team has been approached and invited to test the Protocol at Australia's largest Equine Clinic.

The findings of the research provide a practical and valuable contribution to current treatment approaches in OSCC/POSCC.

7.5.2 RESEARCH LIMITATIONS

As with any research, a number of limitations must be observed. The surveys were conducted solely within Australia which may limit the transferability of findings to other countries. However, the literature review was globally encompassing hence adding to the validity of findings. Additionally, the low number of participants in the surveys may affect the validity of results.

The retrospective study posed the greatest range of limitations based on the number of assumptions which were necessary for modelling to proceed. The nature of the information in the medical records was such that there was a need for assumptions to be made on a number of clinical themes including;

1. Records failed to have accurate, 3-dimensional representations of volumes (as opposed to 2-dimensional schematic diagrams), hence requiring 'estimates' on volumes to be made
2. Prescriptions were not provided hence an assumption was made to apply (based on evidence based practice) 50 Gy as the Minimum Target Dose, and 150% (75 Gy) and 200% (100 Gy) as the reportable Maximums for the 50 Gy (100%) prescription
3. The nature of the hand-drawn schematic representations of treatments led to the potential for incorrect interpretation of treatment intent.
4. Diagrams did not have a scale by which to guide researchers in identifying exact dimensions resulting in assumptions and estimates.
5. The same data set (CT) was used for all planning (n=75), therefore not being representative of all anatomical possibilities
6. Researcher 'bias' must be considered when transferring data (from medical records) regardless of quality assurance checks on all plans
7. Limited ability to make complete and accurate comparisons regarding compliance with each dose-specification recording systems (ICRU-58) currently used in brachytherapy.

7.6 IMPLICATIONS FOR CLINICAL PRACTICE

This research may have major implications in veterinary medicine practice. The research has highlighted variations in current practice in Australia and worldwide as related to the treatment of OSCC/POSC in horses. A lack of a consistent approach to the treatment technique and recording of such practices reduces the potential for comparisons in outcomes and hence the foundation of a standardised treatment approach based on evidence based practice becomes unattainable.

This research provides important information on current treatment practice and presents a developed, workable approach to brachytherapy as a treatment option based on successful human application and evidence based practice. The research provides veterinarians with the information required to commence the practice safely and effectively. The research has been published widely and disseminated among

veterinarians in Australia, prompting interest and invitations for presentations among horse experts.

At the commencement of the research, it was speculated whether the re-introduction of brachytherapy in veterinary medicine within Australia could be a feasible and positive outcome. The research has provided supporting evidence to suggest not only that the re-introduction, supported by an evidence based Protocol and RT /RO expertise would be beneficial for horses but also that the interest in the technique is existent among Australian veterinarians. To that end, the clinical implications are not solely reported in by the research papers that have resulted from this thesis, but it is clear that the re-introduction of the technique has the potential to improve outcomes in OSCC/POSCC in horses.

7.7 FUTURE RESEARCH

This thesis has developed a treatment Protocol and a radiation protection flowchart and summary for horses with OSCC/POSCC. Future research includes the testing of the Protocol in a clinical situation. As a result of the dissemination of the research among Australian veterinarians, the largest equine practice in Australia (Scone Equine Clinic) with a case load of approximately 1000 horses per annum, has approached the research team and offered to test the Protocol in their clinic in the Upper Hunter. Upon further development and validation as a result of the testing, the Protocol could provide a consistent approach to OSCC/POSCC treatment and enable the practice of brachytherapy to be reported on over long periods of time.

This research, whilst inclusive of international practice findings through the literature review, was limited to Australia in the collection of survey data. It is proposed that the surveys are extended internationally with a view of comparing outcomes to the results and to seek international collaborations in the research.

Whilst the research has concentrated on OSCC/POSCC, it would be possible to translate it to sarcoids, a commonly occurring lesion in horses as well as other cancer types.

7.8 THE WAY FORWARD

The results of the multiple investigations within this research have identified a clear gap in current veterinary practice for the treatment of OSCC/POSCC. The closing of this gap is not without some challenges but already, as a result of publications in the area, a veterinarian group located in Scone (Horse Country Australia) and owners of the largest equine clinic in Australia, have expressed interest in involvement in advancing the research by offering to test the Protocol.

Preliminary plans to commence testing of the Protocol include the following actions;

- Evaluate veterinary facilities to establish they are adequate for the purposes of conducting radiation procedures, provide advice for alterations where required
- Evaluate current veterinary staff knowledge and understanding of radiation protection and safety recommendations, provide education where required based on Code of Practice for Radiation Protection in Veterinary Medicine (Key Summary and Flowchart Chapter 6)
- Establish working relationship (team) to include veterinarian, radiation oncologist and radiation therapist, provide training on radiation therapy application where necessary (for veterinarian)
- Identify horse cases, lesion types and establish treatment planning approach (clinical lesion identification, orthogonal films or CT)
- Develop standard form for consistency in treatment and outcome reporting
- RT to plan individual treatments using treatment protocol and record approach for future reference and lodge in 'treatment library'
- Radioactive sources to be attained via RT/RO as permitted through radiation license authorisation
- Application of treatment at equine clinic
- Recording of all processes, including follow-up practice

It is envisaged the commencement of testing will occur within 6-12 months of PhD submission.

The varied research approaches within this thesis have supported the development of a Protocol to circumnavigate the paucity in a standardised treatment approach within Australia. It is envisaged the research will continue within Australia with the testing of the Protocol but also it is proposed that the research continue internationally with the initial dissemination of the surveys in the UK followed by Europe.

It has been a research journey not without its tribulations at times, with particular emphasis on overcoming the barrier initially encountered among the veterinary group. However the raising of awareness of the research has overcome the initial hesitance and the research team are pleased that the research has the potential to make a vast impact on how OSCC/POSCC could be treated in the future. It is not unwarranted to suggest this treatment approach could be applied to other lesion types and sites also. Consultations are currently underway within the research team with proposals to test the Protocol and commence recording outcomes (dose distributions, implant variations) in the aim of creating an online consultation service in the long term.

To conclude, it is accepted that without a standardised approach, variations in practice may lead to inconsistent outcomes and reduce the possibility for ongoing reporting and cross-comparisons in treatment outcomes thus reducing the likelihood for a 'best-practice' approach to the treatment of the most common skin cancer among horses. The tangible outcomes of this research seek to overcome the currently inadequate treatment options available and provide a platform for future advancement in the area of radiation therapy in veterinary medicine.

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APPENDICES

APPENDIX A: SURVEYS

APPENDIX B: CONFERENCE PRESENTATIONS, INVITED PRESENTATION

APPENDIX A: SURVEYS

THE UNIVERSITY OF NEWCASTLE AUSTRALIA

RESEARCH

INFORMATION STATEMENT FOR PARTICIPANTS OF THE NATIONAL SURVEY FOR:

The Research Project on Interstitial Brachytherapy Treatment of Ocular Squamous Cell Carcinoma in Equine

You are invited to participate in the research project identified above which is being conducted by Yolanda Surjan, Associate Professor Helen Warren-Forward (principal supervisor), from the Faculty of Health at the University of Newcastle and Associate Professor Christopher Milross, Royal Prince Alfred Hospital, Sydney, Australia.

This research is part of Yolanda Surjan's Research Higher Degree studies at the University of Newcastle.
This research aims to;

1. Assess current veterinary practice across Australia in relation to ocular treatment of equine squamous cell carcinoma
2. Design a treatment protocol for Au198 use in equine (ocular SCC) via brachytherapy inclusive of radiation safety guidelines

It is envisaged that a combination of veterinary skills and knowledge, radiation therapy expertise (in the form of application of planning and treatment) and radiation oncology expertise will form the basis of this research project.

The significance there lies in the realisation of a standardised treatment protocol to be implemented and used throughout Veterinary Oncology and with the prospect of acquiring new projected data to measure the efficacy of such treatment as it may be applicable to other cancer types and other animal types.

What do you need to do to participate?
Please read the full version of the Information Statement **(included within this pack)** and be sure you understand its contents. If there is anything you do not understand, or you have questions, please contact the researcher.

If you would like to participate, please complete the questionnaire enclosed and return it in the reply-paid envelope provided. The survey will take approximately 10-12 minutes to complete.

Thank you for considering this invitation

Kind Regards

STUDY

www.newcastle.edu.au

Helen Warren-Forward
Associate Professor
The University of Newcastle
Ph: 02 49 21 7142

Yolanda Surjan
Radiation Therapy Lecturer
The University of Newcastle
Ph: 02 49 21 7850

Complaints about this research
This project has been approved by the University's Human Research Ethics Committee, Approval No. H – 2009 – 0136.Should you have concerns about your rights as a participant in this research, or you have a complaint about the manner in which the research is conducted, it may be given to the researcher, or, if an independent person is preferred, to the Human Research Ethics Officer, Research Office, The Chancellery, The University of Newcastle, Australia, Ph: (02) 49216333, email Human-Ethics@newcastle.edu.au.

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THE UNIVERSITY OF NEWCASTLE AUSTRALIA

INFORMATION STATEMENT FOR QUESTIONNAIRE PARTICIPANTS

Information Statement for the Research Project:
Interstitial Brachytherapy Treatment of Ocular Squamous Cell Carcinoma in Equine.

You are invited to participate in the research project identified above which is being conducted by Yolanda Surjan, Associate Professor Helen Warren-Forward (principal supervisor), from the Faculty of Health, at the University of Newcastle and Associate Professor Christopher Milross, Royal Prince Alfred Hospital, Sydney, Australia.

The research is part of Yolanda Surjan's Doctor of Philosophy Research studies at the University of Newcastle.

Why is the research being done?
Squamous Cell Carcinoma (SCC) is the most commonly found tumour of the eye and adnexa in horses representing up to 75% of tumours. It is a locally invasive tumour with a potential to metastasise (distant spread) in 10-15% of cases. SCC threatens visual outcome and long term survival in equine. Current known treatment options within Australia include surgical removal; a treatment with a known recurrence-rate (postoperative regrowth) of 62% as a result of incomplete surgical margin resection. Alternatively a thorough excision may significantly impair eyelid function sometimes resulting in removal of an otherwise normal globe.

The use of radiation therapy in the form of ***Interstitial Brachytherapy*** is the implantation of radioactive needles or seeds throughout radiosensitive neoplasms. The delivery of high doses to the neoplasmic tissues contributes to improved local control, limited scarring and distortion of surrounding skin and inconsequential skin loss. Whilst the long term local control and recurrence for ocular SCC in equine is clearly favourable as a result of brachytherapy treatments, the process by which these treatments are routinely performed within Australia are generally undocumented.

This research aims to;

1. Assess current veterinary practice across Australia in relation to ocular treatment of equine and radiation safety guidelines **via questionnaire**.
2. Design a treatment protocol for Au198 use in equine (ocular SCC) via brachytherapy inclusive of radiation safety guidelines.

It is envisaged that a combination of veterinary skills and knowledge, radiation therapy expertise (in the form of application of planning and treatment) and radiation oncology expertise will form the basis of this research project.

The significance there lies in the realisation of a standardised treatment protocol to be implemented and used throughout Veterinary Oncology and with the prospect of acquiring new projected data to measure the efficacy of such treatment as it may be applicable to other cancer types.

Who can participate in the research?
You have received this information as you are a current practicing Equine Veterinary Clinic.

What choice do you have?
Participation in this research is entirely your choice. Whether or not you decide to participate, your decision will not disadvantage you.

What would you be asked to do?
If you agree to participate, you will be asked to complete a questionnaire and return it via the reply-paid envelope provided.

How much time will it take?
The questionnaire should take approximately 10-12 minutes to complete.

What are the risks and benefits of participating?
No risks have been identified. There are no direct benefits for the participant.

How will your privacy be protected?
Data will be retained for at least 5 years in a secure cabinet within the School of Health Sciences at the University of Newcastle. All findings from the analysis of the data will be stored as electronic data and will be password protected. This information will be accessible only by the student and the supervisors of the project.

How will the information collected be used?
The data collected may be presented at relevant conferences, published in scientific journals and will be submitted for Yolanda Surjan's Research Higher Degree studies (Doctor of Philosophy).

Individual participants will not be identified in any reports arising from the project.

It is expected that any qualitative data (comments) of relevance may be used in published articles and/or the final thesis.

Participants who wish to be informed of the results of the research may contact the researcher (Yolanda Surjan) directly to receive the written results after December 2011. Alternatively a summary of the results will be made available through the Australian Veterinary Association (Equine Veterinarians Australia) monthly newsletter.

What do you need to do to participate?
Please read this Information Statement and be sure you understand its contents. If there is anything you do not understand, or you have questions, please contact the researcher.

If you would like to participate, please complete the questionnaire included within this pack and return it in the reply-paid envelope.

Further information
If you would like further information please contact Associate Professor Helen Warren-Forward or Yolanda Surjan.

Thank you for considering this invitation.

Kind Regards

Helen Warren-Forward
Associate Professor
Medical Radiation Science
Ph: 02 49 21 7142

Yolanda Surjan
Radiation Therapy Lecturer
Medical Radiation Science
Ph: 02 49 21 7850

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SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

SECTION A: DEMOGRAPHICS

RESEARCH PROJECT ON INTERSTITIAL BRACHYTHERAPY TREATMENT FOR OCULAR SQUAMOUS CELL CARCINOMA IN EQUINE

*** 1. In what State are you presently practising?**

- ☐ NSW
- ☐ QLD
- ☐ SA
- ☐ WA
- ☐ VIC
- ☐ ACT
- ☐ NT

*** 2. What is the highest qualification gained by you? (Please specify in box provided)**

Veterinary degree	
Masters	
PhD	
Australian College of Veterinary Scientists Fellowship (Please state area of veterinary science specialisation)	
Other	

*** 3. At what institution did you gain your qualification?**

- ☐ The University of Sydney
- ☐ Murdoch University
- ☐ Charles Sturt University
- ☐ The University of Melbourne
- ☐ The University of Queensland
- ☐ James Cook University
- ☐ Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

4. How long have you been practicing Veterinary Science?

- [ ] < 12 months
- [ ] 1-2 years
- [ ] 3-5 years
- [ ] 6-10 years
- [ ] 11-15 years
- [ ] 16-25 years
- [ ] 26-30 years
- [ ] >30 years
- [ ] Other

If other, please specify

* 5. What animal types do you service at your clinic?

- [ ] Cats
- [ ] Dogs
- [ ] Birds
- [ ] Horses
- [ ] Guinea Pigs
- [ ] Rabbits
- [ ] Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

SECTION B: SQUAMOUS CELL CARCINOMA (SCC) CASE PRESENTATION & DIAGNOSIS

*** 6. How many cases of skin squamous cell carcinoma would you see in a month?**

- [ ] 0
- [ ] 1-2
- [ ] 3-6
- [ ] 7-15
- [ ] 15-30
- [ ] >30
- [ ] Other

If other, please specify

*** 7. In your experience, what type/s of animals most commonly present with skin squamous cell carcinoma?**

- [ ] Cats
- [ ] Dogs
- [ ] Birds
- [ ] Horses
- [ ] Guinea Pigs
- [ ] Rabbits
- [ ] Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 8. In your experience, the most common area/s for the presentation of skin squamous cell carcinoma is:**

- [ ] Nose
- [ ] Eyelid
- [ ] Around eye (adnexa)
- [ ] Lip
- [ ] Ear
- [ ] Legs
- [ ] Back
- [ ] Other

If other, please specify

*** 9. Of the cases that you see, how do you diagnose and confirm the presence of skin squamous cell carcinoma?**

- [ ] Diagnosis based on clinical EXPERIENCE
- [ ] Diagnosis based on clinical APPEARANCE
- [ ] Diagnosis based on texture of lesion
- [ ] Punch biopsy followed by histopathology
- [ ] Scrape biopsy followed by histopathology
- [ ] Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 10. The histopathology services you commonly use are located;**

- ◯ Within your veterinary clinic
- ◯ Provided by an external VETERINARY pathology laboratory
- ◯ Provided by an external HUMAN pathology laboratory
- ◯ Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

11. The cost of the INTERNAL histopathology service within your own practice/clinic (to the pet owner/client) is generally;

- ◯ 0-$49
- ◯ $50-$99
- ◯ $100-$149
- ◯ $150-$199
- ◯ $200-$249
- ◯ Other

If other, please specify

12. The cost of the EXTERNAL (outside of your practice/clinic) histopathology service (to the pet owner/client) is generally;

- ◯ 0-$49
- ◯ $50-$99
- ◯ $100-$149
- ◯ $150-$199
- ◯ $200-$249
- ◯ Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

13. Does the cost of pathology testing and the need to impart this cost on to the animal owner influence your decision to self-diagnose (clinically as opposed to histopathologically)?

- ◯ Never
- ◯ Sometimes
- ◯ Often
- ◯ Always
- ◯ Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

SECTION C: CURRENT TREATMENT OF SQUAMOUS CELL CARCINOMA

*** 14. Brachytherapy (the implantation of radioactive seeds or needles in tumour sites; a recognised treatment regime in squamous cell carcinoma) is a common treatment approach in human cancer. In your experience, would you consider brachytherapy to be a well known treatment method in veterinary science?**

- ◯ Yes
- ◯ No

Comments

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 15. What is your current choice of treatment for skin squamous cell carcinoma?**

- [ ] Surgery
- [ ] External radiation therapy (Linear Accelerator)
- [ ] Brachytherapy implantation
- [ ] Plaque therapy
- [ ] Cryotherapy
- [ ] Photodynamic therapy
- [ ] Immunotherapy
- [ ] Carbon dioxide laser ablation
- [ ] Topical cream (Fluorouracil 5-FU)
- [ ] Other topical creams
- [ ] Chemotherapy drug (ADRIAMYCIN: DOXOrubicin HCl)
- [ ] Chemotherapy drug (ASPARAGINASE ELSPAR)
- [ ] Other chemotherapy drugs

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 16. How often have you found surgery in and around the ocular region which requires an extensive margin resection, result in the removal of the globe?**

- ◯ Never
- ◯ Sometimes
- ◯ Often
- ◯ Always
- ◯ Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

SECTION D: BRACHYTHERAPY (Gold Au198 or other)

*** 17. Have you/do you use/d brachytherapy?**

- ◯ No - PLEASE PROCEED TO SECTION E, PAGE 17, QUESTION 29
- ◯ Yes - PLEASE PROCEED TO QUESTION 18
- ◯ Yes, I have in the past but do not use it any longer PLEASE PROCEED TO QUESTION 18

Please specify why you no longer use brachytherapy

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 18. How long have you been using/did you use brachytherapy?**

Year commenced using brachytherapy

Year ended using brachytherapy

Comments

*** 19. How often do you/did you use brachytherapy?**

- [ ] Daily
- [ ] Once Weekly
- [ ] Once Monthly
- [ ] Once 6-monthly
- [ ] Once Yearly
- [ ] Other

If other, please specify

*** 20. What type/s of animals do you/did you use brachytherapy on?**

- [ ] Cats
- [ ] Dogs
- [ ] Birds
- [ ] Horses
- [ ] Guinea pigs
- [ ] Rabbits
- [ ] Other

If other, please specify

*** 21. What anatomical area/s do you/did you treat with brachytherapy?**

- [ ] Nose
- [ ] Eyelid
- [ ] Around eye (adnexa)
- [ ] Third eyelid
- [ ] Lip
- [ ] Ear
- [ ] Legs
- [ ] Back
- [ ] Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 22. What types of radioactive sources have you used?**

- [ ] Gold 198
- [ ] Iodine 125
- [ ] Iridium 192
- [ ] Cesium 137
- [ ] Strontium 90
- [ ] Other

If other, please specify

*** 23. What form did the radioactive sources come in?**

- [ ] Wires
- [ ] Seeds
- [ ] Plaque
- [ ] Other

If other, please specify

*** 24. Where did you obtain the radioactive sources from?**

- [ ] ANSTO - Australian Nuclear Science and Technology Organisation
- [ ] GMS - Global Medical Solutions
- [ ] Other

If other, please specify

*** 25. The application of brachytherapy requires;**

- Individual dose delivery parameters (dose and time)
- Preparation of sources to deliver the parameters

In your experience, the calculation of the amount of DOSE and TIME to be applied to lesions is;

- [ ] Predetermined by a 'treatment plan' design using radiation therapy software and principles
- [ ] Decided at the time of implantation based on clinical observation of the lesion
- [ ] The same for each treatment based on previous observed rates of local control
- [ ] The same for each treatment based on a standardised protocol applied to all lesions
- [ ] Varies each time depending on the amount of source remaining
- [ ] Varies each time depending on the size of the lesion
- [ ] Other

If other, please specify

*** 26. Once you have established the amount of dose to be delivered, how do you PREPARE the SOURCES for implantation?**

- [ ] Use a dose calibrator to prepare sources
- [ ] Cut wires to same lengths every time based on what has worked in the past WITHOUT the use of a dose calibrator
- [ ] Cut wires to same lengths every time based on what has in the past WITH the use of a dose calibrator
- [ ] Cut wires to same lengths every time regardless of lesion size
- [ ] Cut wires to size depending on the source certificate values (as per manufacturer)
- [ ] Use pre-prepared seeds, the number used is dependent on the radioactivity (half-life, dose) at time of implantation
- [ ] Other

If other, please specify

* 27. How do you calculate the POSITION of the sources for treatment?

- [ ] As per predetermined 'treatment plan' designed using radiation therapy software and principles
- [ ] Approximately 1cm apart
- [ ] Depends on the SHAPE of the lesion
- [ ] Decided at time of implantation based on SIZE of lesion (clinical examination)
- [ ] Other

If other, please specify

* 28. What equipment have you owned/used in relation to brachytherapy?

- [ ] After-loading machine
- [ ] Dose calibrator
- [ ] Geiger counter
- [ ] Seed gun
- [ ] Lead shield
- [ ] Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

SECTION E: RADIATION SAFETY

*** 29. The type of radiation producing or imaging equipment you have in your clinic includes;**

Nil:

X-ray machine (Type):

Nuclear Medicine Camera (Type):

Portable Ultrasound Machine (Type):

Stationary Ultrasound (Type):

OPG (orthopantomogram) (Type):

Magnetic Resonance Imaging– large animal (Type):

Magnetic Resonance Imaging – small animal (Type):

Magnetic Resonance Imaging – large & small animal (Type):

Magnetic Resonance Imaging – equine limb (Type):

Computed Tomography (Type/s):

Other:

*** 30. Do you have a radiation safety manual for the equipment within your clinic?**

- ◯ Yes
- ◯ No
- ◯ Other

If other, please specify

*** 31. Do you hold a radiation license for the equipment noted in the question above?**

- ◯ Yes
- ◯ No
- ◯ Currently lapsed
- ◯ Other

If other, please specify

*** 32. Please select the staff within your clinic who are monitored for potential radiation exposure? (Monitoring in the form of personal monitoring devices such as film badges etc).**

- ☐ Veterinary Surgeons; only when performing procedures
- ☐ Veterinary Nurses; only when performing procedures
- ☐ Veterinary Surgeons wear them at all times
- ☐ Veterinary Nurses wear them at all times
- ☐ Administration staff
- ☐ No monitoring used
- ☐ Other

If other, please specify

*** 33. What type/s of monitoring devices do you use?**

- [ ] Photographic film badge
- [ ] Direct reading pocket dosimeter
- [ ] Optically stimulated device (OSD)
- [ ] Thermoluminescent Dosimeters (TLD's) Badge
- [ ] Finger sachet monitoring (TLD)
- [ ] Other

If other, please specify

*** 34. If you wear a monitoring device, where do you usually wear the monitors?**

- [ ] Waist level
- [ ] Thyroid level
- [ ] Fingers
- [ ] Under lead protective gowns
- [ ] On top of lead protective gowns
- [ ] Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 35. Please note the type/s of radiation protection DEVICES and/or PRINCIPLES you use when conducting imaging or treatment techniques involving radiation.**

- [ ] Radiation protection aprons
- [ ] Thyroid protection
- [ ] Eye protection
- [ ] Exit room when exposing animals to x-rays
- [ ] Stand behind radiation shield when exposing animal to x-rays
- [ ] Use radiation safety signs
- [ ] Keep a distance from the source
- [ ] Decrease the amount of time you spend nearby radiation exposure
- [ ] Other

If other, please specify

*** 36. Do you have a radiation protection PROTOCOL within your clinic?**

- ◯ Yes
- ◯ No
- ◯ Do not need
- ◯ Not sure
- ◯ Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 37. When using brachytherapy sources, your general storage system involves;**

- [ ] Not applicable, we do not use radioactive sources - please go to Q40
- [ ] A room specifically designed for the storing of radioactive sources
- [ ] The general store room
- [ ] Lead storage container
- [ ] Shipping lead container
- [ ] Other

If other, please specify

*** 38. When using radioactive sources, your PREPARATION system involves;**

- [ ] Any space available
- [ ] A specifically designed space with a leaded glass window used to prepare sources
- [ ] Prepare in operating theatre at time of implantation
- [ ] Other

If other, please specify

39. When using radioactive sources, the IMPLANTATION system you use involves;

- [ ] Manual implantation (sutures and placement of sources by hand)
- [ ] Seed Gun
- [ ] Afterloading device
- [ ] Applicator
- [ ] Other

If other, please specify

*** 40. Have you ever completed a certified radiation safety course?**

- ◯ Yes
- ◯ No

Comments

41. If you have completed a radiation safety course, who was the provider?

- ◯ University
- ◯ In-service
- ◯ Conference
- ◯ Other

If other, please specify

*** 42. Do you believe your radiation safety knowledge is well developed?**

- ◯ Yes
- ◯ No
- ◯ Somewhat
- ◯ Other

If other, please specify

43. Are you familiar with the radiation safety principles of TIME, DISTANCE & SHIELDING?

- ◯ Yes
- ◯ No
- ◯ Somewhat
- ◯ Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

SECTION F: TREATMENT FOLLOW-UP

*** 44. After treating an animal for squamous cell carcinoma (using any of the treatment options available), what are your follow-up practices?**

- [ ] Monthly review
- [ ] 3-monthly review
- [ ] 6-monthly review
- [ ] 12-monthly review
- [ ] 18-monthly review
- [ ] 2-year review
- [ ] Review by telephoning owners for evaluation
- [ ] Only review if owners contact clinic with concerns
- [ ] Do not review
- [ ] Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 45. In relation to HORSES: If you have used brachytherapy to treat animals in the past, your quarantine procedure includes;**

- [ ] Not applicable, we do not use radioactive sources - please go to Q48
- [ ] Quarantine in a paddock
- [ ] Allowed return to their owner's property
- [ ] Remain in the clinic until risk of exposure is minimal

Please describe area used for quarantine

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 46. In relation to DOMESTIC ANIMALS: If you have used brachytherapy to treat animals in the past, your quarantine procedure includes;**

- [ ] Quarantine in a paddock/outdoors
- [ ] Allowed return to their owner's property
- [ ] Remain in the clinic until risk of exposure is minimal

Please describe area used for quarantine

*** 47. If you have used brachytherapy to treat animals in the past, your quarantine period of time is;**

- [ ] Dependent on the half-life of the source (and dose level at time of implantation)
- [ ] Other

If other, please specify

*** 48. Given the benefits of brachytherapy treatment in squamous cell carcinoma (as discussed within the information statement) would you be interested in introducing/recommencing this type of treatment in your practice?**

- ◯ Yes
- ◯ No
- ◯ I need more information

Any comments related to your response above would be most welcome

49. Please feel free to make any further comments here.

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

Your Rights

Further information
If you would like further information please contact Associate Professor Helen Warren-Forward or Yolanda Surjan.
Thank you for considering this invitation.
Kind Regards
Helen Warren-Forward
Associate Professor
The University of Newcastle
Ph: 02 49 21 7142

Yolanda Surjan
Radiation Therapy Lecturer
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Complaints about this research
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SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

SECTION A: DEMOGRAPHICS

RESEARCH PROJECT ON INTERSTITIAL BRACHYTHERAPY TREATMENT FOR OCULAR SQUAMOUS CELL CARCINOMA IN EQUINE

*** 1. In what State are you presently practising?**

- ☐ NSW
- ☐ QLD
- ☐ SA
- ☐ WA
- ☐ VIC
- ☐ ACT
- ☐ NT

*** 2. What is the highest qualification gained by you? (Please specify in box provided)**

Veterinary degree	
Masters	
PhD	
Australian College of Veterinary Scientists Fellowship (Please state area of veterinary science specialisation)	
Other	

*** 3. At what institution did you gain your qualification?**

- ☐ The University of Sydney
- ☐ Murdoch University
- ☐ Charles Sturt University
- ☐ The University of Melbourne
- ☐ The University of Queensland
- ☐ James Cook University
- ☐ Other

If other, please specify

4. How long have you been practicing Veterinary Science?

- [ ] < 12 months
- [ ] 1-2 years
- [ ] 3-5 years
- [ ] 6-10 years
- [ ] 11-15 years
- [ ] 16-25 years
- [ ] 26-30 years
- [ ] >30 years
- [ ] Other

If other, please specify

* 5. What animal types do you service at your clinic?

- [ ] Cats
- [ ] Dogs
- [ ] Birds
- [ ] Horses
- [ ] Guinea Pigs
- [ ] Rabbits
- [ ] Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

SECTION B: SQUAMOUS CELL CARCINOMA (SCC) CASE PRESENTATION & DIAGNOSIS

*** 6. How many cases of skin squamous cell carcinoma would you see in a month?**

- [ ] 0
- [ ] 1-2
- [ ] 3-6
- [ ] 7-15
- [ ] 15-30
- [ ] >30
- [ ] Other

If other, please specify

*** 7. In your experience, what type/s of animals most commonly present with skin squamous cell carcinoma?**

- [ ] Cats
- [ ] Dogs
- [ ] Birds
- [ ] Horses
- [ ] Guinea Pigs
- [ ] Rabbits
- [ ] Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 8. In your experience, the most common area/s for the presentation of skin squamous cell carcinoma is:**

- [ ] Nose
- [ ] Eyelid
- [ ] Around eye (adnexa)
- [ ] Lip
- [ ] Ear
- [ ] Legs
- [ ] Back
- [ ] Other

If other, please specify

*** 9. Of the cases that you see, how do you diagnose and confirm the presence of skin squamous cell carcinoma?**

- [ ] Diagnosis based on clinical EXPERIENCE
- [ ] Diagnosis based on clinical APPEARANCE
- [ ] Diagnosis based on texture of lesion
- [ ] Punch biopsy followed by histopathology
- [ ] Scrape biopsy followed by histopathology
- [ ] Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 10. The histopathology services you commonly use are located;**

- ◯ Within your veterinary clinic
- ◯ Provided by an external VETERINARY pathology laboratory
- ◯ Provided by an external HUMAN pathology laboratory
- ◯ Other

If other, please specify

11. The cost of the INTERNAL histopathology service within your own practice/clinic (to the pet owner/client) is generally;

- ◯ 0-$49
- ◯ $50-$99
- ◯ $100-$149
- ◯ $150-$199
- ◯ $200-$249
- ◯ Other

If other, please specify

12. The cost of the EXTERNAL (outside of your practice/clinic) histopathology service (to the pet owner/client) is generally;

- ◯ 0-$49
- ◯ $50-$99
- ◯ $100-$149
- ◯ $150-$199
- ◯ $200-$249
- ◯ Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

13. Does the cost of pathology testing and the need to impart this cost on to the animal owner influence your decision to self-diagnose (clinically as opposed to histopathologically)?

- ◯ Never
- ◯ Sometimes
- ◯ Often
- ◯ Always
- ◯ Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

SECTION C: CURRENT TREATMENT OF SQUAMOUS CELL CARCINOMA

*** 14. Brachytherapy (the implantation of radioactive seeds or needles in tumour sites; a recognised treatment regime in squamous cell carcinoma) is a common treatment approach in human cancer. In your experience, would you consider brachytherapy to be a well known treatment method in veterinary science?**

- ◯ Yes
- ◯ No

Comments

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 15. What is your current choice of treatment for skin squamous cell carcinoma?**

- [ ] Surgery
- [ ] External radiation therapy (Linear Accelerator)
- [ ] Brachytherapy implantation
- [ ] Plaque therapy
- [ ] Cryotherapy
- [ ] Photodynamic therapy
- [ ] Immunotherapy
- [ ] Carbon dioxide laser ablation
- [ ] Topical cream (Fluorouracil 5-FU)
- [ ] Other topical creams
- [ ] Chemotherapy drug (ADRIAMYCIN: DOXOrubicin HCl)
- [ ] Chemotherapy drug (ASPARAGINASE ELSPAR)
- [ ] Other chemotherapy drugs

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 16. How often have you found surgery in and around the ocular region which requires an extensive margin resection, result in the removal of the globe?**

- ◯ Never
- ◯ Sometimes
- ◯ Often
- ◯ Always
- ◯ Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

SECTION D: BRACHYTHERAPY (Gold Au198 or other)

*** 17. Have you/do you use/d brachytherapy?**

- ◯ No - PLEASE PROCEED TO SECTION E, PAGE 17, QUESTION 29
- ◯ Yes - PLEASE PROCEED TO QUESTION 18
- ◯ Yes, I have in the past but do not use it any longer PLEASE PROCEED TO QUESTION 18

Please specify why you no longer use brachytherapy

*** 18. How long have you been using/did you use brachytherapy?**

Year commenced using brachytherapy

Year ended using brachytherapy

Comments

*** 19. How often do you/did you use brachytherapy?**

- [ ] Daily
- [ ] Once Weekly
- [ ] Once Monthly
- [ ] Once 6-monthly
- [ ] Once Yearly
- [ ] Other

If other, please specify

*** 20. What type/s of animals do you/did you use brachytherapy on?**

- [ ] Cats
- [ ] Dogs
- [ ] Birds
- [ ] Horses
- [ ] Guinea pigs
- [ ] Rabbits
- [ ] Other

If other, please specify

*** 21. What anatomical area/s do you/did you treat with brachytherapy?**

- [ ] Nose
- [ ] Eyelid
- [ ] Around eye (adnexa)
- [ ] Third eyelid
- [ ] Lip
- [ ] Ear
- [ ] Legs
- [ ] Back
- [ ] Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 22. What types of radioactive sources have you used?**

- [ ] Gold 198
- [ ] Iodine 125
- [ ] Iridium 192
- [ ] Cesium 137
- [ ] Strontium 90
- [ ] Other

If other, please specify

*** 23. What form did the radioactive sources come in?**

- [ ] Wires
- [ ] Seeds
- [ ] Plaque
- [ ] Other

If other, please specify

*** 24. Where did you obtain the radioactive sources from?**

- [ ] ANSTO - Australian Nuclear Science and Technology Organisation
- [ ] GMS - Global Medical Solutions
- [ ] Other

If other, please specify

*** 25. The application of brachytherapy requires;**

- Individual dose delivery parameters (dose and time)
- Preparation of sources to deliver the parameters

In your experience, the calculation of the amount of DOSE and TIME to be applied to lesions is;

- [ ] Predetermined by a 'treatment plan' design using radiation therapy software and principles
- [ ] Decided at the time of implantation based on clinical observation of the lesion
- [ ] The same for each treatment based on previous observed rates of local control
- [ ] The same for each treatment based on a standardised protocol applied to all lesions
- [ ] Varies each time depending on the amount of source remaining
- [ ] Varies each time depending on the size of the lesion
- [ ] Other

If other, please specify

*** 26. Once you have established the amount of dose to be delivered, how do you PREPARE the SOURCES for implantation?**

- [ ] Use a dose calibrator to prepare sources
- [ ] Cut wires to same lengths every time based on what has worked in the past WITHOUT the use of a dose calibrator
- [ ] Cut wires to same lengths every time based on what has in the past WITH the use of a dose calibrator
- [ ] Cut wires to same lengths every time regardless of lesion size
- [ ] Cut wires to size depending on the source certificate values (as per manufacturer)
- [ ] Use pre-prepared seeds, the number used is dependent on the radioactivity (half-life, dose) at time of implantation
- [ ] Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

* 27. How do you calculate the POSITION of the sources for treatment?

- [ ] As per predetermined 'treatment plan' designed using radiation therapy software and principles
- [ ] Approximately 1cm apart
- [ ] Depends on the SHAPE of the lesion
- [ ] Decided at time of implantation based on SIZE of lesion (clinical examination)
- [ ] Other

If other, please specify

* 28. What equipment have you owned/used in relation to brachytherapy?

- [ ] After-loading machine
- [ ] Dose calibrator
- [ ] Geiger counter
- [ ] Seed gun
- [ ] Lead shield
- [ ] Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

SECTION E: RADIATION SAFETY

*** 29. The type of radiation producing or imaging equipment you have in your clinic includes;**

Nil:

X-ray machine (Type):

Nuclear Medicine Camera (Type):

Portable Ultrasound Machine (Type):

Stationary Ultrasound (Type):

OPG (orthopantomogram) (Type):

Magnetic Resonance Imaging– large animal (Type):

Magnetic Resonance Imaging – small animal (Type):

Magnetic Resonance Imaging – large & small animal (Type):

Magnetic Resonance Imaging – equine limb (Type):

Computed Tomography (Type/s):

Other:

*** 30. Do you have a radiation safety manual for the equipment within your clinic?**

- ◯ Yes
- ◯ No
- ◯ Other

If other, please specify

*** 31. Do you hold a radiation license for the equipment noted in the question above?**

- ◯ Yes
- ◯ No
- ◯ Currently lapsed
- ◯ Other

If other, please specify

*** 32. Please select the staff within your clinic who are monitored for potential radiation exposure? (Monitoring in the form of personal monitoring devices such as film badges etc).**

- ☐ Veterinary Surgeons; only when performing procedures
- ☐ Veterinary Nurses; only when performing procedures
- ☐ Veterinary Surgeons wear them at all times
- ☐ Veterinary Nurses wear them at all times
- ☐ Administration staff
- ☐ No monitoring used
- ☐ Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 33. What type/s of monitoring devices do you use?**

- [ ] Photographic film badge
- [ ] Direct reading pocket dosimeter
- [ ] Optically stimulated device (OSD)
- [ ] Thermoluminescent Dosimeters (TLD's) Badge
- [ ] Finger sachet monitoring (TLD)
- [ ] Other

If other, please specify

*** 34. If you wear a monitoring device, where do you usually wear the monitors?**

- [ ] Waist level
- [ ] Thyroid level
- [ ] Fingers
- [ ] Under lead protective gowns
- [ ] On top of lead protective gowns
- [ ] Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 35. Please note the type/s of radiation protection DEVICES and/or PRINCIPLES you use when conducting imaging or treatment techniques involving radiation.**

- [ ] Radiation protection aprons
- [ ] Thyroid protection
- [ ] Eye protection
- [ ] Exit room when exposing animals to x-rays
- [ ] Stand behind radiation shield when exposing animal to x-rays
- [ ] Use radiation safety signs
- [ ] Keep a distance from the source
- [ ] Decrease the amount of time you spend nearby radiation exposure
- [ ] Other

If other, please specify

*** 36. Do you have a radiation protection PROTOCOL within your clinic?**

- ◯ Yes
- ◯ No
- ◯ Do not need
- ◯ Not sure
- ◯ Other

If other, please specify

*** 37. When using brachytherapy sources, your general storage system involves;**

- [ ] Not applicable, we do not use radioactive sources - please go to Q40
- [ ] A room specifically designed for the storing of radioactive sources
- [ ] The general store room
- [ ] Lead storage container
- [ ] Shipping lead container
- [ ] Other

If other, please specify

*** 38. When using radioactive sources, your PREPARATION system involves;**

- [ ] Any space available
- [ ] A specifically designed space with a leaded glass window used to prepare sources
- [ ] Prepare in operating theatre at time of implantation
- [ ] Other

If other, please specify

39. When using radioactive sources, the IMPLANTATION system you use involves;

- [ ] Manual implantation (sutures and placement of sources by hand)
- [ ] Seed Gun
- [ ] Afterloading device
- [ ] Applicator
- [ ] Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 40. Have you ever completed a certified radiation safety course?**

- ◯ Yes
- ◯ No

Comments

41. If you have completed a radiation safety course, who was the provider?

- ◯ University
- ◯ In-service
- ◯ Conference
- ◯ Other

If other, please specify

*** 42. Do you believe your radiation safety knowledge is well developed?**

- ◯ Yes
- ◯ No
- ◯ Somewhat
- ◯ Other

If other, please specify

43. Are you familiar with the radiation safety principles of TIME, DISTANCE & SHIELDING?

- ◯ Yes
- ◯ No
- ◯ Somewhat
- ◯ Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

SECTION F: TREATMENT FOLLOW-UP

*** 44. After treating an animal for squamous cell carcinoma (using any of the treatment options available), what are your follow-up practices?**

- [ ] Monthly review
- [ ] 3-monthly review
- [ ] 6-monthly review
- [ ] 12-monthly review
- [ ] 18-monthly review
- [ ] 2-year review
- [ ] Review by telephoning owners for evaluation
- [ ] Only review if owners contact clinic with concerns
- [ ] Do not review
- [ ] Other

If other, please specify

*** 45. In relation to HORSES: If you have used brachytherapy to treat animals in the past, your quarantine procedure includes;**

- [ ] Not applicable, we do not use radioactive sources - please go to Q48
- [ ] Quarantine in a paddock
- [ ] Allowed return to their owner's property
- [ ] Remain in the clinic until risk of exposure is minimal

Please describe area used for quarantine

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 46. In relation to DOMESTIC ANIMALS: If you have used brachytherapy to treat animals in the past, your quarantine procedure includes;**

- [ ] Quarantine in a paddock/outdoors
- [ ] Allowed return to their owner's property
- [ ] Remain in the clinic until risk of exposure is minimal

Please describe area used for quarantine

*** 47. If you have used brachytherapy to treat animals in the past, your quarantine period of time is;**

- [ ] Dependent on the half-life of the source (and dose level at time of implantation)
- [ ] Other

If other, please specify

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

*** 48. Given the benefits of brachytherapy treatment in squamous cell carcinoma (as discussed within the information statement) would you be interested in introducing/recommencing this type of treatment in your practice?**

- ◯ Yes
- ◯ No
- ◯ I need more information

Any comments related to your response above would be most welcome

49. Please feel free to make any further comments here.

SQUAMOUS CELL CARCINOMA IN ANIMALS- AUSTRALIAN SURVEY

Your Rights

Further information
If you would like further information please contact Associate Professor Helen Warren-Forward or Yolanda Surjan.
Thank you for considering this invitation.
Kind Regards
Helen Warren-Forward
Associate Professor
The University of Newcastle
Ph: 02 49 21 7142

Yolanda Surjan
Radiation Therapy Lecturer
The University of Newcastle
Ph: 49 21 7850

Complaints about this research
This project has been approved by the University's Human Research Ethics Committee, Approval No. H – 2009 – 0136. Should you have concerns about your rights as a participant in this research, or you have a complaint about the manner in which the research is conducted, it may be given to the researcher, or, if an independent person is preferred, to the Human Research Ethics Officer, Research Office, The Chancellery, The University of Newcastle, Australia, Ph: (02) 49216333, email Human-Ethics@newcastle.edu.au.

Please note that you may have completed a similar survey a year or two ago. If this is the case, we would appreciate it if you could also complete the current survey.

Information Statement for the Research Project:

Treatment of Ocular/Periocular Squamous Cell Carcinoma in Horses

You are invited to participate in the research project identified above which is being conducted by Yolanda Surjan, Ass Prof Helen Warren-Forward, Faculty of Health and Medicine, University of Newcastle and Ass Prof Chris Milross, Royal Prince Alfred Hospital, Sydney, Australia, and Dr David Donaldson (BVSc (Hons) DipECVO, Specialist in Veterinary Ophthalmology). The research is part of Yolanda Surjan's PhD studies at the University of Newcastle.

Why is the research being done?

Squamous Cell Carcinoma (SCC) is the most commonly found tumour of the eye and adnexa in horses representing up to 75% of tumours. It is a locally invasive tumour with a potential to metastasise in 10-15% of cases. SCC threatens visual outcome and long term survival in horses. The management of equine ocular squamous cell carcinoma (OSCC - cornea, limbus and bulbar conjunctiva) and/or periocular squamous cell carcinoma (POSCC - eyelids and third eyelid) remains a challenge despite its high prevalence among horses. Literature suggests a number of treatment modalities currently exist; surgery, photodynamic therapy, cryotherapy, carbon dioxide (CO_2) laser ablation, radiofrequency hyperthermia, topical or intratumoral chemotherapy, and radiation therapy (RT), predominantly in the form of brachytherapy (implantation of sealed radioactive sources). Whilst no technique can conclusively be identified as the best approach to the treatment of OSCC/POSCC, literature suggests successful treatment of OSCC/POSCC commonly involves one of the above therapies combined with cytoreductive surgery. Furthermore, the value of combining radiation therapy with surgery or using radiation therapy alone has been identified in relation to benefits in decreasing cosmetic and functional defects.

For comparison, there is significant evidence based practice for the use of radiation therapy (RT), by various methods, in treating SCC in humans. The choice to use RT for

SCC is less dependent on the probability of tumour control, which is typically high, than on the predicted cosmetic and functional results, which can be better with RT than some forms of surgery. For this reason, RT is often favoured for lesions located on or near the nose, ears, lips and eyelids.

The use of RT in humans in the form of Interstitial Brachytherapy is the implantation of radioactive needles or seeds throughout radiosensitive neoplasms. The delivery of high doses of radiation to the neoplastic tissues contributes to improved local control, limited scarring and distortion of surrounding skin and inconsequential skin loss. The same can be said for this treatment type in horses however, whilst the long term local control and recurrence for ocular SCC in horses is clearly favourable as a result of brachytherapy, the process by which these treatments have routinely been performed within Australia are generally undocumented.

This research aims to assess current veterinary practice across Australia in relation to ocular/periocular SCC treatment of horses.

Who can participate in the research?
You have received this information as you are an Australian Veterinarian who consults equine cases.

What would you be asked to do?
If you agree to participate, you will be asked to complete an online survey.

What choice do you have?
Participation in this research is entirely your choice. Whether or not you decide to participate, your decision will not disadvantage you.

How much time will it take?
The survey should take approximately 10-15 minutes.

What are the risks and benefits of participating?
No risks have been identified. Entry into the prize draw is optional. If you would like to enter the prize draw, you will have the opportunity upon completion of the survey. Your

personal details will be maintained anonymously. The awarding of the prize draw will be conducted by a third person, not involved with the research.

How will your privacy be protected?

The survey is anonymous and it will not be possible to identify you from your answers. Data will be retained for at least 5 years in a secure cabinet within the School of Health Sciences at the University of Newcastle. All findings from the analysis of the data will be stored as electronic data and will be password protected. This information will be accessible only by the student and the supervisors of the project.

How will the information collected be used?

The data collected may be presented at relevant conferences/published in scientific journals and will be submitted for Yolanda Surjan's PhD studies.

It is expected that any qualitative data (comments) of relevance may be used in published articles and/or the final thesis. As the survey is anonymous, it will not be possible to identify individual participants from this reporting.

Thank you for considering this invitation.

Kind Regards

Helen Warren-Forward
Associate Professor
Medical Radiation Science
Ph: 02 49 21 7142

Yolanda Surjan
Radiation Therapy Lecturer
Medical Radiation Science
Ph: 02 49 21 7850

Complaints about this research

This project has been approved by the University's Human Research Ethics Committee, Approval No. H – 2009 – 0136.

Should you have concerns about your rights as a participant in this research, or you have a complaint about the manner in which the research is conducted, it may be given to the researcher, or, if an independent person is preferred, to the Human Research Ethics Officer, Research Office, The Chancellery, The University of Newcastle, University Drive, Callaghan NSW 2308, Australia, telephone (02) 49216333, email human-ethics@newcastle.edu.au

INVITATION TO PARTICIPATE IN AN ONLINE SURVEY ON THE

Treatment of Ocular/Periocular Squamous Cell Carcinoma in Equine

RESEARCH STUDY

www.newcastle.edu.au

You are invited to participate in the research project identified above which is being conducted by Yolanda Surjan, Associate Professor Helen Warren-Forward (principal supervisor), from the Faculty of Health and Medicine, at the University of Newcastle, Australia and Associate Professor Christopher Milross, Royal Prince Alfred Hospital, Sydney, Australia. The research is supported by Dr David Donaldson (BVSc (Hons)DipECVO Specialist in Veterinary Ophthalmology).

The research is part of Yolanda Surjan's PhD studies at the University of Newcastle and aims to assess current veterinary practice and radiation safety practice across Australia in relation to ocular/periocular SCC treatment of horses.

What do you need to do to participate?
Please read the Information Statement (found once you enter the online survey) and be sure you understand its contents. If there is anything you do not understand, or you have questions, please contact the researcher.

If you would like to participate, please complete the online survey.

Please click here to access the link: https://www.surveymonkey.com/s/Equine_OPSCC

By participating in this survey, you have the chance to enter the draw to win the latest 'Equine Ophthalmology' Textbook by Dr. Brian C. Gilger.

Thank you for considering this invitation.

Kind Regards

Helen Warren-Forward
Associate Professor
Medical Radiation Science
Ph: 02 49 21 7142

Yolanda Surjan
Radiation Therapy Lecturer
Medical Radiation Science
Ph: 02 49 21 7850

SQUAMOUS CELL CARCINOMA IN EQUINE: AUSTRALIAN NATIONAL

INFORMATION STATEMENT FOR SURVEY PARTICIPANTS

Please note, you may have completed a similar survey a year or two ago. If this is the case, we would appreciate it if you could also complete the current survey.

Treatment of Ocular/Periocular Squamous Cell Carcinoma in Horses

You are invited to participate in the research project identified above which is being conducted by Yolanda Surjan, Ass Prof Helen Warren-Forward, Faculty of Health and Medicine, University of Newcastle and Ass Prof Chris Milross, Royal Prince Alfred Hospital, Sydney, Australia, and Dr David Donaldson, Specialist in Veterinary Ophthalmology.

Why is the research being done?
Squamous Cell Carcinoma (SCC) is the most common tumour of the eye and adnexa in horses representing up to 75% of tumours. It is a locally invasive tumour with a potential to metastasise in 10-15% of cases. SCC threatens visual outcome and long term survival in horses. The management of equine ocular SCC and/or periocular SCC remains a challenge despite its high prevalence among horses. Literature suggests a number of treatment modalities currently exist; surgery, photodynamic therapy, cryotherapy, carbon dioxide (CO_2) laser ablation, radiofrequency hyperthermia, topical or intratumoral chemotherapy, and radiation therapy (RT), predominantly in the form of brachytherapy (implantation of sealed radioactive sources). Whilst no technique can conclusively be identified as the best approach to the treatment of equine SCC, literature suggests successful treatment commonly involves one of the above therapies combined with cytoreductive surgery. Furthermore, the value of combining RT with surgery or using RT alone has been identified in relation to benefits in decreasing cosmetic and functional defects.

This research aims to assess current veterinary practice across Australia in relation to equine ocular/periocular SCC.

Who can participate in the research?
You have received this information as you are an Australian Veterinarian who consults equine cases.

What would you be asked to do?
If you agree to participate, you will be asked to complete an online survey.

What choice do you have?
Participation in this research is entirely your choice. Whether or not you decide to participate, your decision will not disadvantage you.

How much time will it take?
Approximately 7-15 minutes.

What are the risks and benefits of participating?
No risks have been identified. Entry into the prize draw is optional. If you would like to enter the prize draw, you will have the opportunity upon completion of the survey. Your personal details will be maintained anonymously. The awarding of the prize draw will be conducted by a third person, not involved with the research.

How will your privacy be protected?
The survey is anonymous and it will not be possible to identify you from your answers. Data will be retained for at least 5 years in a secure cabinet at the University of Newcastle. All findings from data analysis will be stored electronically and will be password protected. This information will be accessible only by the researchers.

How will the information collected be used?
The data collected may be presented at relevant conferences/published in scientific journals and will be submitted for Yolanda Surjan's PhD.

Thank you for considering this invitation.

Helen Warren-Forward
Ph: 02 49 217142
Yolanda Surjan
Ph: 02 49 217850

Complaints about this research
This project has been approved by the University's Human Research Ethics Committee, Approval No. H – 2009 – 0136.

Should you have concerns about your rights as a participant in this research, or you have a complaint about the manner in which the research is conducted, it may be given to the researcher, or, if an independent person is preferred, to the Human Research Ethics Officer, Research Office, The Chancellery, The University of Newcastle, Australia, telephone (02) 49216333, email Human-Ethics@newcastle.edu.au.

What do you need to do to participate?
Please read this 'Information Statement for Survey Participants' (previous text) and be sure you understand its contents. If there is anything you do not understand, or you have questions, please contact the researcher/s.

If you would like to participate, please complete the online survey that follows this information.

SQUAMOUS CELL CARCINOMA IN EQUINE: AUSTRALIAN NATIONAL

SECTION A: DEMOGRAPHICS

The following survey aims to collect data from individual practices. Only one nominated individual should complete the survey per practice.

Given the technical nature of the survey it is best completed by a Veterinarian .

*1. What is your role in the practice?

- ◯ Veterinary Surgeon
- ◯ Other

If Other (please specify)

*2. In what state/territory are you presently practicing? (Tick all that apply).

- ☐ NSW
- ☐ QLD
- ☐ VIC
- ☐ SA
- ☐ WA
- ☐ TAS
- ☐ NT
- ☐ ACT

*3. What is the highest qualification/s gained by an individual in your practice? (Please specify in the box provided, tick all that apply)

- ☐ Veterinary degree
- ☐ Masters
- ☐ PhD
- ☐ (Fellow) Australian and New Zealand College of Veterinary Surgeons (FANZCVS) (Please state area of veterinary specialisation)
- ☐ (Member) Australian and New Zealand College of Veterinary Surgeons (MANZCVS) (Please state area of veterinary specialisation)
- ☐ Other

Please specify area/s of veterinary specialisation or details for 'other'

SQUAMOUS CELL CARCINOMA IN EQUINE: AUSTRALIAN NATIONAL

***4. What percentage of your practice constitutes an EQUINE service? (if your practice is NOT 100% equine, what percentage is attributed to equine clients only)**

- ◯ <10%
- ◯ 10-25%
- ◯ 26-50%
- ◯ 51-75%
- ◯ 76-100%

***5. What would best describe your practice setting?**

- ◯ Private clinic/first opinion
- ◯ Referral clinic
- ◯ University
- ◯ Other

Other (please specify)

SQUAMOUS CELL CARCINOMA IN EQUINE: AUSTRALIAN NATIONAL

SECTION B: EQUINE SQUAMOUS CELL CARCINOMA CASE PRESENTATION & DIAGNOSIS

***6. How many cases of EQUINE squamous cell carcinoma (all locations) would you see in a month?**

- ◯ 0
- ◯ 1-2
- ◯ 3-6
- ◯ 7-15
- ◯ 16-30
- ◯ >30

If other, please specify:

***7. In particular relation to OSCC/POSCC; (cornea, limbus, bulbar conjunctiva, eyelid, third eyelid, medial canthus)**

Please rank the anatomical locations (from most common to least common) where you have previously identified equine OSCC/POSCC. (Please note: list will automatically reorder as you rank the areas).

- ☐ Cornea
- ☐ Limbus (cornea-scleral junction)
- ☐ Bulbar conjunctiva
- ☐ Eyelid (eyelid skin and margin)
- ☐ Third eyelid
- ☐ Medial canthus

SQUAMOUS CELL CARCINOMA IN EQUINE: AUSTRALIAN NATIONAL

***8. In particular relation to equine SCC at sites OTHER THAN OSCC/POSCC;**

Please rank the anatomical locations (from most common to least common) where you have previously identified equine (non OSCC/POSCC). (Please note: list will automatically reorder as you rank the areas).

- [ ] Ear Pinnae
- [ ] Muzzle
- [ ] Lips
- [ ] Nostrils
- [ ] Vulva
- [ ] Penis or Prepuce
- [ ] Perianal/perineum
- [ ] Extremities
- [ ] Other

***9. Of the cases that you see (any location), how do you diagnose and confirm the presence of squamous cell carcinoma? (Tick all that apply).**

- [ ] Diagnosis based on clinical presentation alone (appearance, texture of lesion)
- [ ] Diagnosis based on incisional biopsy
- [ ] Diagnosis based on excisional biopsy
- [ ] Diagnosis based on cytology
- [ ] Other

Other (please specify)

***10. Does the cost of pathology testing and the need to convey this cost to the animal owner influence your decision as to whether or not the diagnosis is based on clinical presentation rather than cytological/histopathological examination?**

- ◯ Never
- ◯ Sometimes
- ◯ Often
- ◯ Always
- ◯ Other

Other (please specify)

SECTION C: CURRENT TREATMENT OF EQUINE SQUAMOUS CELL CARCINOMA

11. IN THE CASE OF OCULAR SQUAMOUS CELL CARCINOMA (cornea, limbus, bulbar conjunctiva);

KEY: (RT: Radiation Therapy, Brachy: Brachytherapy, Sr-90: Strontium, Cryo: Cryotherapy, PDT: Photodynamic Therapy, Immuno: Immunotherapy, CO2: Carbon Dioxide Laser Ablation)

Please choose your preferred treatment option/s for each of the following sites. Tick all that apply.

	Surgery	RT	Brachy	Sr-90	Plaque RT	Cryo	CO2	PDT	Immuno (topical)	Immuno (intralesional)	Chemo (topical)	Chemo (intralesional)
Cornea	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Limbus (corneo-scleral junction)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Bulbar conjunctiva	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

12. IN THE CASE OF PERIOCULAR SQUAMOUS CELL CARCINOMA (eyelid, third eyelid, medial canthus);

KEY: (RT: Radiation Therapy, Brachy: Brachytherapy, Sr-90: Strontium, Cryo: Cryotherapy, PDT: Photodynamic Therapy, Immuno: Immunotherapy, CO2: Carbon Dioxide Laser Ablation)

Please choose your preferred treatment option/s for each of the following sites. Tick all that apply.

	Surgery	RT	Brachy	Sr-90	Plaque RT	Cryo	CO2	PDT	Immuno (topical)	Immuno (intralesional)	Chemo (topical)	Chemo (intralesional)
Eyelid	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Third eyelid	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Medial canthus	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

13. IN THE CASE OF SQUAMOUS CELL CARCINOMA at OTHER SITES (Ear Pinnae, Muzzle, Lips, Nostrils, Vulva, Penis or Prepuce, Perianal/perineum, Extremities, other);

KEY: (RT: Radiation Therapy, Brachy: Brachytherapy, Sr-90: Strontium, Cryo: Cryotherapy, PDT: Photodynamic Therapy, Immuno: Immunotherapy, CO2: Carbon Dioxide Laser Ablation)

Please choose your preferred treatment option/s for each of the following sites. Tick all that apply.

	Surgery	RT	Brachy	Sr-90	Plaque RT	Cryo	CO2	PDT	Immuno (topical)	Immuno (intralesional)	Chemo (topical)	Chemo (intralesional)
Ear Pinnae	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Muzzle	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lips	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Nostrils	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Vulva	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Penis or Prepuce	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Perianal/perineum	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Extremities	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

***14. In particular reference to equine OSCC/POSCC, how often have you found that surgical intervention with the aim to provide clear surgical margins has resulted in the removal of the globe?**

- ◯ Never
- ◯ Sometimes
- ◯ Often
- ◯ Always
- ◯ Other

If other please specify:

SQUAMOUS CELL CARCINOMA IN EQUINE: AUSTRALIAN NATIONAL

SECTION D: BRACHYTHERAPY

***15. Brachytherapy (a form of radiation therapy in which the radiation source is placed in direct contact with the patient through the implantation of radioactive seeds/wires or needles in tumour sites; a recognised treatment in squamous cell carcinoma) is a common treatment approach in human cancer. In your experience, would you consider brachytherapy to be a well-known method in Veterinary Medicine?**

- ◯ Yes
- ◯ No
- ◯ Not sure

Comments:

***16. Radiation therapy is a highly specialised field of cancer treatment. Does your practice (individual/s) have any formal training in the area of RADIATION THERAPY?**

	Yes	No
Radiation Therapy (Treatment Therapist/Dosimetrist)	◯	◯

If yes, please specify training/qualification type (radiation therapy)

***17. Radiation oncology is a highly specialised field of cancer treatment. Does your practice (individual/s) have any formal training in the area of RADIATION ONCOLOGY?**

	Yes	No
Radiation Oncology (Specialist)	◯	◯

If yes, please specify training/qualification type (radiation oncology)

***18. With regard to your practice, do you CURRENTLY use brachytherapy?**

- ◯ Yes
- ◯ No

***19. With regard to your practice, have you used brachytherapy in the PAST?**

- ◯ Yes
- ◯ No

SQUAMOUS CELL CARCINOMA IN EQUINE: AUSTRALIAN NATIONAL

Previous Use of Brachytherapy

*20. How long did you use brachytherapy?

- ◯ <6 months
- ◯ 7-12 months
- ◯ 13-18 months
- ◯ 19-24 months
- ◯ 25-35 months
- ◯ 3-4 years
- ◯ >4 years

*21. How often did you use brachytherapy?

- ◯ Daily
- ◯ Once monthly
- ◯ Once 3-monthly
- ◯ Once 6-monthly
- ◯ Once yearly
- ◯ Other

Other (please specify)

22. What types of radioactive sources did you use?

	Seeds	Wires	Mold	Plaque	Other form
Gold-198	☐	☐	☐	☐	☐
Iridium-192	☐	☐	☐	☐	☐
Iodine-125	☐	☐	☐	☐	☐
Cesium-137	☐	☐	☐	☐	☐
Strontium-90	☐	☐	☐	☐	☐
Palladium-103	☐	☐	☐	☐	☐
Ruthenium-106	☐	☐	☐	☐	☐
Other	☐	☐	☐	☐	☐

If other please specify:

***23. Where did you obtain the radioactive sources?**

- [ ] ANSTO - Australian Nuclear Science and Technology Organisation
- [ ] GMS - Global Medical Solutions
- [ ] Other

If other please specify:

***24. Did your practice have 'treatment protocols' (procedural guidelines) for the application of brachytherapy?**

- ◯ Yes
- ◯ No
- ◯ Not Sure

Other (please specify)

***25. The application of brachytherapy requires;**

- Individual dose delivery parameters (dose and time)
- Preparation of sources to deliver the parameters

In your experience, the calculation of the amount of dose/time to be applied to lesions is;

- [ ] Predetermined by a 'treatment plan' design using radiation therapy software and principles
- [ ] The same for each treatment based on previous observed rates of local control
- [ ] The same for each treatment based on a standardised protocol applied to all lesions
- [ ] Varies each time depending on the source radioactivity
- [ ] Varies each time depending on the size of the lesion
- [ ] Other

If other please specify:

***26. Once you had established the amount of dose to be delivered, and if the form of radioactive sources were wires, how did you prepare the SOURCES for implantation?**

- [ ] Use a dose calibrator to prepare sources
- [ ] Cut wires to same lengths every time based on what has worked in the past WITHOUT the use of a dose calibrator
- [ ] Cut wires to same lengths every time based on what has worked in the past WITH the use of a dose calibrator
- [ ] N/A - have never used wires
- [ ] Other

Other (please specify)

***27. When using radioactive sources, your PREPARATION system involved;**

- [ ] Any space available
- [ ] A specifically designed space with a leaded glass window used to prepare sources
- [ ] Prepare in operating theatre
- [ ] Other

***28. When using brachytherapy sources, your GENERAL STORAGE system involved;**

- [ ] A room specifically designed for the storing of radioactive sources
- [ ] The general storeroom
- [ ] Lead shipping container
- [ ] Other

***29. How did you calculate the POSITION of the sources for treatment? (Tick all that apply).**

- [ ] As per predetermined 'treatment plan' designed using radiation therapy software and principles
- [ ] Approximately 1cm apart
- [ ] Depends on the SHAPE of the lesion
- [ ] Depends on the SIZE of the lesion
- [ ] As a result of previous experience
- [ ] As a result of anecdotal (passed down) information
- [ ] Other

If other please specify

***30. What equipment/methods did you use in relation to the DELIVERY of brachytherapy? (Tick all that apply).**

- [ ] After-loading machine
- [ ] Seed gun
- [ ] Plaques
- [ ] Pre-placed catheters
- [ ] Needles
- [ ] Manual implant
- [ ] Other

Other (please specify)

***31. What equipment did you use in relation to radiation safety MONITORING and PROTECTION in brachytherapy? (Tick all that apply).**

- [ ] Dose calibrator
- [ ] Lead shield
- [ ] Geiger counter/Survey Meter
- [ ] Photographic film badges (personal monitoring device)
- [ ] Thermoluminescent dosimeter (personal monitoring device)
- [ ] Direct reading dosimeters
- [ ] Radiation protection aprons
- [ ] Lead-lined gloves
- [ ] Thyroid protectors
- [ ] Lead glasses
- [ ] Keeping a distance from the source
- [ ] Other

Other (please specify)

*32. Why did you stop using brachytherapy? (Tick all that apply).

- [ ] Too expensive
- [ ] Licensing requirements prevented the purchase of radioactive sources
- [ ] Could no longer source radioactive sources
- [ ] Demand for the treatment decreased
- [ ] No trained personnel in practice
- [ ] Don't know
- [ ] Other

Other (please specify)

*33. When did you stop using brachytherapy?

Date (approximate date)

Current Use of Brachytherapy

***34. How LONG have you been using brachytherapy?**

- ◯ <6 months
- ◯ 7-12 months
- ◯ 13-18 months
- ◯ 19-24 months
- ◯ 25-35 months
- ◯ 3-4 years
- ◯ >4 years

***35. How OFTEN do you use brachytherapy?**

- ◯ Daily
- ◯ Once monthly
- ◯ Once 3-monthly
- ◯ Once 6-monthly
- ◯ Once yearly
- ◯ Other

If other please specify:

***36. What types of radioactive sources do you use? (Tick all that apply).**

	Seeds	Wires	Mold	Plaque	Other form
Gold-198	☐	☐	☐	☐	☐
Iridium-192	☐	☐	☐	☐	☐
Iodine-125	☐	☐	☐	☐	☐
Cesium-137	☐	☐	☐	☐	☐
Strontium-90	☐	☐	☐	☐	☐
Palladium-103	☐	☐	☐	☐	☐
Ruthenium-106	☐	☐	☐	☐	☐
Other	☐	☐	☐	☐	☐

If other please specify:

***37. Where do you obtain the radioactive sources from?**

- ☐ ANSTO - Australian Nuclear Science and Technology Organisation
- ☐ GMS - Global Medical Solutions
- ☐ Other

If other please specify:

***38. Does your practice have 'treatment protocols' (procedural guidelines) for the application of brachytherapy?**

- ◯ Yes
- ◯ No
- ◯ Not Sure

Other (please specify)

***39. The application of brachytherapy requires;**

- Individual dose delivery parameters (dose and time)
- Preparation of sources to deliver the parameters

In your experience, the calculation of the amount of dose/time to be applied to lesions is;

- [ ] Predetermined by a 'treatment plan' design using radiation therapy software and principles
- [ ] The same for each treatment based on previous observed rates of local control
- [ ] The same for each treatment based on a standardised protocol applied to all lesions
- [ ] Varies each time depending on the source radioactivity
- [ ] Varies each time depending on the size of the lesion
- [ ] Other

If other please specify:

***40. Once you have established the amount of dose to be delivered, and if the form of radioactive sources are wires, how do you prepare the SOURCES for implantation?**

- [ ] Use a dose calibrator to prepare sources
- [ ] Cut wires to same lengths every time based on what has worked in the past WITHOUT the use of a dose calibrator
- [ ] Cut wires to same lengths every time based on what has worked in the past WITH the use of a dose calibrator
- [ ] N/A - have never used wires
- [ ] Other

Other (please specify)

***41. When using radioactive sources, your PREPARATION system involves;**

- [ ] Any space available
- [ ] A specifically designed space with a leaded glass window used to prepare sources
- [ ] Prepare in operating theatre
- [ ] Other

***42. When using brachytherapy sources, your GENERAL STORAGE system involves;**

- [ ] A room specifically designed for the storing of radioactive sources
- [ ] The general storeroom
- [ ] Lead shipping container
- [ ] Other

***43. How do you calculate the POSITION of the sources for treatment? (Tick all that apply).**

- [ ] As per predetermined 'treatment plan' designed using radiation therapy software and principles
- [ ] Approximately 1cm apart
- [ ] Depends on the SHAPE of the lesion
- [ ] Depends on the SIZE of the lesion
- [ ] As a result of previous experience
- [ ] As a result of anecdotal (passed down) information
- [ ] Other

If other please specify

***44. What equipment/methods do you use in relation to the DELIVERY of brachytherapy? (Tick all that apply).**

- [ ] After-loading machine
- [ ] Seed gun
- [ ] Plaques
- [ ] Pre-placed catheters
- [ ] Needles
- [ ] Manual implant
- [ ] Other

Other (please specify)

***45. What equipment do you use in relation to radiation safety MONITORING and PROTECTION in brachytherapy? (Tick all that apply).**

- [ ] Dose calibrator
- [ ] Lead shield
- [ ] Geiger counter/Survey Meter
- [ ] Photographic film badges (personal monitoring device)
- [ ] Thermoluminescent dosimeter (personal monitoring device)
- [ ] Direct reading dosimeters
- [ ] Radiation protection aprons
- [ ] Lead-lined gloves
- [ ] Thyroid protectors
- [ ] Lead glasses
- [ ] Keeping a distance from the source
- [ ] Other

Other (please specify)

SQUAMOUS CELL CARCINOMA IN EQUINE: AUSTRALIAN NATIONAL

SECTION E: TREATMENT FOLLOW-UP

***46. After treating a horse for SCC (using any of the treatment options available/any location), what are your follow-up practices? How is the review carried out? (Tick all that apply).**

	Review by telephoning owners for evaluation	Review by visiting horse at owner's property	Review by examining horse at clinic	Review by speaking with referring veterinarian	Only review if owners contact practice with concerns	Other
Monthly review	☐	☐	☐	☐	☐	☐
3-monthly review	☐	☐	☐	☐	☐	☐
6-monthly review	☐	☐	☐	☐	☐	☐
12-monthly review	☐	☐	☐	☐	☐	☐
18-monthly review	☐	☐	☐	☐	☐	☐
2-year review	☐	☐	☐	☐	☐	☐
Not Applicable	☐	☐	☐	☐	☐	☐
Other	☐	☐	☐	☐	☐	☐

If other please specify

***47. In relation to horses: If you have used brachytherapy to treat SCC in the past, your quarantine procedure for PERMANENT IMPLANTS includes;**

- ☐ Not applicable
- ☐ Allowed to return to owner's property
- ☐ Remain in clinic (isolation stall) until risk of exposure is nil
- ☐ Remain in clinic (paddock) until risk of exposure is nil
- ☐ Other

Other (please specify)

***48. In relation to horses: If you have used brachytherapy to treat SCC in the past, your quarantine procedure for TEMPORARY IMPLANTS includes;**

- [ ] Not applicable
- [ ] Quarantine in clinic (paddock) until removal of implant is required
- [ ] Quarantine in clinic (isolation stall) until removal of implant is required
- [ ] Quarantine in clinic (any available stall) until removal of implant is required
- [ ] Quarantine in owners (paddock) until removal of implant is required
- [ ] Other

Other (please specify)

***49. The type of radiation producing or imaging equipment you have in your clinic includes;**

- [ ] X-ray Machine
- [ ] Nuclear Medicine Camera
- [ ] Computed Tomography
- [ ] Portable Ultrasound Machine
- [ ] Stationary Ultrasound Machine
- [ ] OPG (orthopantomogram)
- [ ] Magnetic Resonance Imaging– large animal
- [ ] Magnetic Resonance Imaging – small animal
- [ ] Magnetic Resonance Imaging – large & small animal
- [ ] Other

Other (please specify)

***50. Given the benefits of brachytherapy treatment of equine OSCC/POSCC (as discussed within the information letter) would you be interested in introducing/recommencing this type of treatment in your practice?**

- ◯ Yes
- ◯ No
- ◯ I need more information
- ◯ Not sure

Please explain

51. Any further comments? Please feel free to make comments here.

52. Would you like to go in the draw to win the latest edition of the textbook, 'Equine Ophthalmology' by Dr. C Brian Gilger?

- ◯ Yes
- ◯ No

APPENDIX B: CONFERENCE PRESENTATIONS, INVITED PRESENTATION

THE UPPER HUNTER BRANCH OF THE AUSTRALIAN VETERINARY ASSOCIATION ANNUAL MEETING and CONTINUING PROFESSIONAL DEVELOPMENT SEMINAR, 2015

Invited Presentation

Title: Brachytherapy treatment in horses for ocular/periocular squamous cell carcinoma.

Surjan Y, Warren-Forward HM, Donaldson D, Milross C, Ostwald, T.

THE UNIVERSITY OF NEWCASTLE AUSTRALIA

CELEBRATING 50 YEARS

50

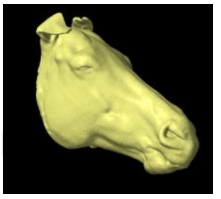
1965-2015

What is Radiation Therapy?

Who?

Yolanda Surjan

BMedRadTech(Radiation Therapy)
GCertHProm
MHealthSci(Ed)



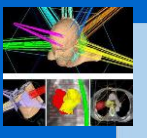
What?

Radiation Therapist
Academic - Undergraduate & Postgraduate
Researcher

Where?

Faculty of Health and Medicine
School of Health Sciences
The University of Newcastle,Australia

Radiation Therapy

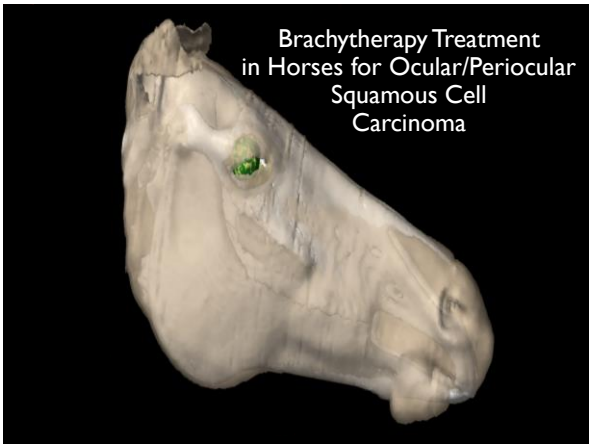


Linear Accelerator delivers External Beam Radiation Therapy (EBRT)

CELEBRATING 50 YEARS

50

1965-2015



What is Brachytherapy?

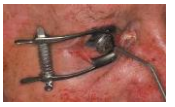
Brachytherapy

Radioactive **seeds** or **sources** are placed in or near a tumour, giving a high radiation dose to the tumour while reducing the radiation exposure in the surrounding healthy tissues.

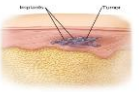
Brachytherapy

- Intracavitary

- Surface Application



- Interstitial



Brachytherapy

Intracavitary
Remote Afterloading Technique

Surface Application
Manually directly onto tumour surface

Interstitial
Manual or Remote Afterloading

Brachytherapy

Permanent
- Requires a one-time implantation procedure
- Radioactive material remains within the neoplastic tissues and is left to decay to a non-radioactive form

Temporary
- Radioactive material is implanted temporarily and removed once the required radiation dose is achieved

Radioactive Sources

- Artificially produced radioisotopes
- Permanent implants – lower energy emissions, shorter half-life (gold-198, iodine-125)
- Gold half-life = 2.7 days
- Iodine half-life = 59.4 days

Radioactive Sources

- Temporary implants – high energy emissions and longer half-life (iridium-192, cobalt-60)
- Iridium half-life = 73.8 days
- Cobalt half-life = 5.26 years
- Gamma emitters (most common) and beta emitters

The Research

THE RESEARCH TEAM

1. Yolanda Surjan (Principal)
2. Associate Professor Helen Warren-Forward (Physicist – UON)
3. Associate Professor Chris Milross (Radiation Oncologist – RPA)
4. Dr Trish Ostwald (Medical Physicist – Newcastle Mater Hospital)
5. Dr David Donaldson (Equine Ophthalmologist – Animal Health Trust Cambridge, UK)

THE RESEARCH

An investigation into current treatment practice of ocular (OSCC) and periocular squamous cell carcinoma (POSCC) in horses.

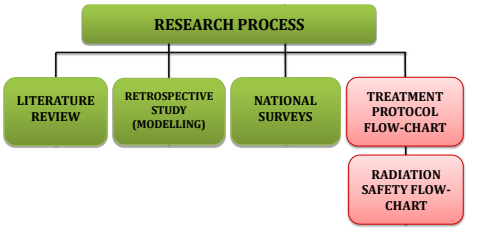
Research Question/s?

- If ocular and/or periocular SCC is the most common tumour of the eye and adnexa in horses, what is currently 'best practice' management approach?
- Can current evidence based practice (human) in the treatment of skin SCC be transferred to veterinary medicine?

THE RESEARCH

Initial anecdotal source of enquiry suggested a standardised treatment technique is non-existent

What the research seeks to identify…



PROCEEDINGS OF THE ITALIAN SOCIETY FOR EQUINE VETERINARY (SIVE), MILAN ITALY, FEBRUARY 2014.

Poster presentation

Title: Brachytherapy treatment of ocular/periocular squamous cell carcinoma in the horse: treatment results in 74 Cases (1999-2007).

Surjan Y, Milross C, Ostwald, Donaldson D, Warren-Forward HM.

Objective: The purpose of this study was to systematically analyse and evaluate the effectiveness of interstitial brachytherapy on periocular/ocular squamous cell carcinoma (POSCC/OSCC) in horses in decreasing tumour recurrence rates. Evaluation of treatment technique will define appropriateness of wire placement and dose specification in relation to dose distribution parameters.

Materials/Method: The study included records of 86 horses with histologically or clinically confirmed periocular/ocular squamous cell carcinoma (POSCC/OSCC). The patients were treated in a rural Australian clinic between 1999 and 2007 with permanent Gold (Au^{198}) wire implants manually implanted without the use of radiation therapy specific planning software, dosimetry or expertise. Recurrence was defined as the post-irradiation regrowth of SCC at the same site of treatment. Follow-up information was obtained for 44 of the 86 cases. Treatment applications for each individual case (86) were modelled and replicated and dose distributions calculated through the use of Varian BrachyVision™ Treatment Planning Software.

Results: Recurrence was noted in 30 of the 44 cases where follow-up was evident (as reported via owner or veterinarian). The treated lesions were reported to have resolved in 14 of the 44 cases, however, follow-up information was not collected for 42/86 cases. In addition, the treatment protocols used demonstrated random application of wires in relation to number and position. Dose distributions varied significantly (as a result of hap-hazard implantation of wires) between cases and irrespective of lesion similarity in size or position.

Conclusions and clinical relevance: The results of this study question the efficacy of brachytherapy treatment applications without appropriate radiation therapy planning, dosimetry and expertise. The results further support the need for protocol based treatment implementation within veterinary oncology to mirror current applications in human treatments and with a view to enhancing treatment outcomes with reference to recurrence rates.

THE UNIVERSITY OF NEWCASTLE AUSTRALIA

BRACHYTHERAPY TREATMENT OF PERIOCULAR/OCULAR SQUAMOUS CELL CARCINOMA IN THE HORSE: TREATMENT RESULTS IN 74 CASES (1999-2007)

Authors: Yolanda Surjan* BMedRadTech (RT), GCertHProm, MHealthSc(ED), PhD Candidate (yolanda.surjan@newcastle.edu.au)
Associate Prof. Helen Warren-Forward* BSc (Physics), PhD , Associate Prof. Chris Milross§ MB BS Med, FRANZCR, MD, Dr. Patricia Ostwald# BSc (Physics), MSc, PhD, Dr. David Donaldson‡ BVSc (Hons), CertVOphthal, DipECVO, MRCVS
Institutes: *The University of Newcastle, Australia, §Royal Prince Alfred Hospital, Sydney Australia, #Calvary Mater Hospital, Newcastle Australia, ‡Animal Health Trust, Lanwades Park, United Kingdom

OBJECTIVE: This study sought to systematically analyse and evaluate the effectiveness of ^{198}Au (Gold) interstitial brachytherapy on ocular/periocular squamous cell carcinoma (OSCC/POSCC) in horses as previously used within an Australian veterinary clinic (1999-2007). This poster focusses on dose distribution, evaluates dose prescription parameters and reports on dose received by organs at risk.

BACKGROUND: OSCC/POSCC is the most commonly found tumour of the eye and adnexa in horses.[1, 2] Prevalence of equine OSCC/POSCC increases with age and whilst most tumours are slow growing and invade locally, metastases may occur in 10% to 15% of cases.[2, 3] A wide range of treatment options exist for OSCC/POSCC. In view of the multiple treatments available and of their varied reported outcomes, a consistently favoured treatment for OSCC/POSCC in horses does not currently exist. It is plausible however, to rank brachytherapy as the most effectual of treatment applications; despite the high cost, training and radiation safety compliance requirements.[4] This analysis provides a basis for further research to establish a best-practice protocol for the treatment of OSCC/POSCC.

MATERIALS/METHODS: This study included the records of 74 horses (94 SCC's) with histologically or clinically confirmed OSCC/POSCC at varied ocular locations. The horses were treated in an Australian clinic between 1999 and 2007 with permanent Gold (^{198}Au) wire implants (Figure 1) manually implanted without the use of radiation therapy specific planning software or dosimetry. Gold wires manually cut to "1mm lengths" were used in all cases. Recorded data on each treatment included radioactivity used (40, 80 or 100MBq per wire), number of 1mm wires implanted and a not-to-scale schematic representation showing the position of the wires at implant (Figure 2). Each treatment was replicated and dose distributions calculated and analysed through the use of Varian BrachyVision™ Treatment Planning Software. A horse head CT data set was used as a representative phantom (Figure 3). Prescribed (delivered) doses were compared to human recommended dosing schedules for superficial skin squamous cell carcinoma[5,6] (50Gy dose dependent on size of lesion and involvement). Critical organ dose was observed and recorded in accordance with known tolerances of normal tissue to therapeutic radiation for the lens, retina and cornea.[6,7]

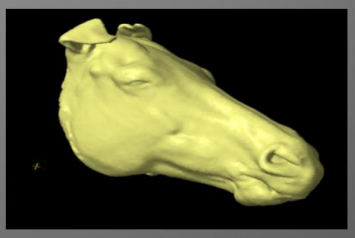
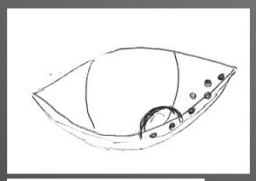


Figure 3: CT Horse Data Set



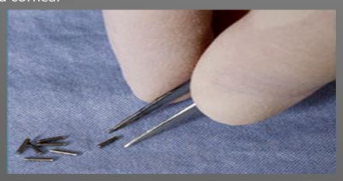


Figure 1:Radioactive Gold Wire Implants

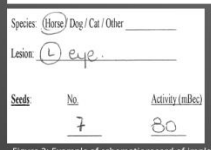


Figure 2: Example of schematic record of implant

RESULTS: 74 horse treatments were replicated. The number of wires implanted ranged from 1 to 13 wires. The wire placement arrangements varied significantly however nominal implant distances ranged from 0.25mm (clustered) to 1cm (planar). It was difficult to estimate if this was the case for each treatment as the diagrams provided were hand-drawn (Figure 2) and at best a visual representation of the day's events as opposed to a measured means of capturing the exact location of the wires.

The treatment volumes at 50Gy (Patient Tumour Volume) (Figure 4) were compared to the visually (schematic) estimated greatest diameter of the lesions. Statistical analysis demonstrates a lack of correlation between the estimated diameter (greatest length) and the calculated volume for the prescribed 50Gy (Figure 5). Analysis demonstrates the trend for underdosing in larger lesions (>2cm) and overdosing in smaller lesions (<2cm).

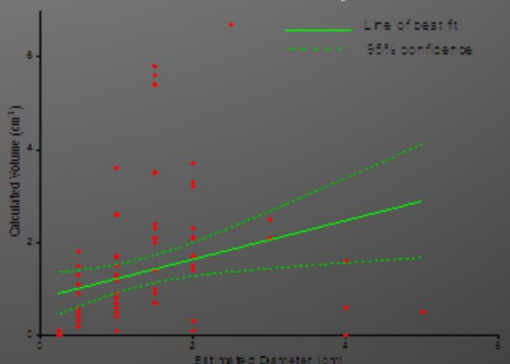


Figure 5: Calculated Volume (^{cm3}) v Estimated Volume (cm)

The dose to the critical organs was maintained within limits for the retina 55-70Gy[6], with all 74 cases reporting well under the accepted tolerance dose. The cornea received doses between 50-60Gy tolerance in 3 cases and above 60Gy in 40 cases, increasing the potential rate of injury of 5% and 50% within 5 years, respectively. [6] The lens also received doses outside of accepted tolerance parameters (5Gy-12Gy) [6]. Of the cases, 14/74 received 5/12Gy and 49/74 exceeded 12Gy to the lens, again inevitably leading to an increased 5% and 50% injury rate within 5 years respectively.[6,7]

It is established that a dose of approximately 100Gy is likely to be significant in determining late effects. It is recommended in ICRU-Report 58[8] that the size of the region receiving more than 150% of the Mean Central Dose should be reported. For the purposes of this study and in lieu of the Mean Central Dose data, the high-dose volumes are reported upon in relation to the prescribed dose; that is, a dose equating to 150% or more of the prescription reported on as a volume of high dose. This equates to 75Gy. It must be noted that the exact tolerance dose and volume for interstitial therapy are not yet known or recorded in the literature.[8] Of the cases, 68% recorded a maximum dose of 75Gy to a volume less than 0.5cm^3, 15% to a volume of between 0.5cm^3 and 1cm^3. A total of 17% of cases recorded 75Gy maximums being received by volumes in the range of 1.5-4cm^3. Anecdotally, side effects were not found to eventuate in any of the cases regardless of the implant type.

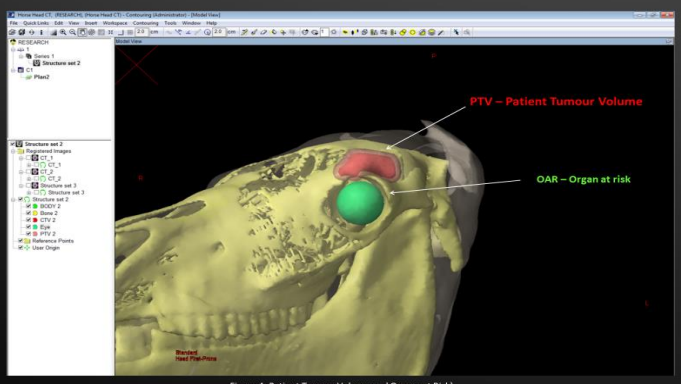


Figure 4: Patient Tumour Volume and Organs at Risk)

CONCLUSION: As a result of the dose to the lesions (as compared to 50Gy), it may be hypothesised that in most cases, the larger lesions were under-dosed significantly and the smaller lesions overdosed. Interestingly, the high doses recorded to the organs at risk (cornea and lens) have not resulted in any adverse side effects to date. The results of this study question the efficacy of brachytherapy treatment applications without appropriate radiation therapy planning, dosimetry and expertise. The results further support the need for protocol based treatment implementation within veterinary oncology to mirror current applications in human treatments and with a view to enhancing treatment outcomes with reference to recurrence rates.

FUTURE DIRECTIONS: The same treatments will be replicated for a second time however using Iridium^{192} HDR temporary implant planning principles. It is envisaged that the outcome of this will be compiled and analysed in a 'treatment library' for implementation within the veterinary sphere. Key radiation oncology and radiations safety principles will be included in the development of treatment protocols.

1. Dugan SJ, Roberts SM, Curtis CR, Severin GA. *Prognostic factors and survival of horses with ocular/adnexal squamous cell carcinoma; 147 cases (1978-1988).* J Am Vet Med Assoc 1991. 198: 298-303.
2. Giuliano EA, McDonald I, McCaw DL, et al. *Photodynamic therapy for the treatment of periocular squamous cell carcinoma in horses: a pilot study.* Vet Ophthalmol 2008. 11: p. 27-34.
3. Hendrix DVH. *Equine Ocular Squamous Cell Carcinoma.* Clin Tech Equine Prac 2005. 4: p. 87-94.
4. Giuliano EA. *Equine ocular adnexal and nasolacrimal disease*, in *Equine Ophthalmol*, Gilger BC, Editor. Elsevier, Philadelphia, 2011: p. 133-180.
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8. ESTRO guidelines, Reporting in brachytherapy: Dose and volume specification chapter 6.

PROCEEDINGS OF THE EUROPEAN SOCIETY FOR RADIOTHERAPY AND ONCOLOGY (ESTRO) GENEVA SWITZERLAND, APRIL 2013.

Poster presentation

Title: Brachytherapy treatment of periocular squamous cell carcinoma in the horse: treatment results and recurrence in 42 cases (1999-2007).

Surjan Y, Milross C, Ostwald, Donaldson D, Warren-Forward HM.

Objective: This study sought to systematically analyse and evaluate the effectiveness of Au^{198} interstitial brachytherapy on ocular squamous cell carcinoma (OSCC) in horses as previously used within an Australian veterinary clinic (1999-2007). Analyses focusses on dose distribution, accepted tolerances and prescription schedule thresholds.

Design: This study included the records of 42 horses with available follow-up information and with histologically or clinically confirmed OSCC of varied ocular locations. The horses were treated in an Australian clinic between 1999 and 2007 with permanent Gold (Au^{198}) wire implants manually implanted without the use of radiation therapy specific planning software, dosimetry or expertise. Recorded data on each treatment included dosing used (80MBq per wire), number of 1mm wires implanted and a not-to-scale schematic representation showing the position of the wires at implant. Each treatment was replicated and dose distributions calculated and analysed through the use of Varian BrachyVision™ Treatment Planning Software.

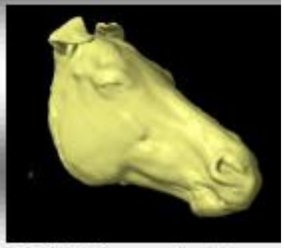
Results: Of the 42 horses treated with Au^{198} implants, 12 did not provide recorded data of the diagram and/or the dose delivered. These were therefore not planned. The remaining 30 horse treatments were replicated. Of these, 22 recurred anywhere between 5 months and 5 years following treatment. The number of wires implanted ranged from 1 to 13 wires. It was difficult to estimate if this was the case for each treatment as the diagrams provided were merely hand-drawn and at best a visual representation of the day's events as opposed to a measured means of capturing the location of the wires. The dose to the critical organs was maintained within limits for the retina and cornea, 5500-7000cGy and 5000-6000cGy respectively, for each treatment application. The lens, however, received exceedingly high doses in the realm of 1337cGy to 1438.8cGy in 2 of the cases.

Conclusion: Whilst a reasonable connection could be made between increased peripheral dose and the number of wires used, it became clear that this hypothesis did not hold true for all treatments and that the arrangement of the wires impacted far more significantly on the dosing outcomes. Furthermore, and as a result of the high recurrence rates and the low dose to the lesions, it may be hypothesised that in most cases, the lesions were under-dosed significantly hence the recurrence rate. The results of this study question the efficacy of brachytherapy treatment applications without appropriate radiation therapy planning, dosimetry and expertise.

THE UNIVERSITY OF NEWCASTLE AUSTRALIA

Brachytherapy treatment of Periocular Squamous Cell Carcinoma in the Horse: Treatment Results and Recurrence in 42 Cases (1999-2007)

Yolanda Surjan. The University of Newcastle, Australia.
Associate Professor Helen Warren-Forward. The University of Newcastle, Australia.
Associate Professor Christopher Milross. Royal Prince Alfred Hospital, Sydney Australia.
Dr. Patricia Ostwald. Calvary Mater Hospital, Newcastle Australia.
Dr. David Donaldson. Animal Health Trust, Lanwades Park United Kingdom.



OBJECTIVE: This study sought to systematically analyse and evaluate the effectiveness of Au^{198} interstitial brachytherapy on ocular squamous cell carcinoma (OSCC) in horses as previously used within an Australian veterinary clinic (1999-2007). Analyses focussed on dose distribution, accepted tolerances, and prescription schedule thresholds. Further analysis in later stages of the research will determine comparative tumour recurrence rates and wire placement requirements in relation to dose distribution parameters.

BACKGROUND: Ocular squamous cell carcinoma (OSCC) is the most commonly found tumour of the eye and adnexa in horses.[1,2] Prevalence of equine OSCC increases with age and whilst most tumours are slow growing and invade locally, metastases may occur in 10% to 15% of horses.[3,4] A wide range of treatment options exist for OSCC, however, as a definitive or adjunct therapy, interstitial brachytherapy has been identified to be the most effective with regard to recurrence rates, local control, and limiting side-effects.[4]

DESIGN: This study included the records of 42 horses with available follow-up information and with histologically or clinically confirmed OSCC of varied ocular locations. The horses were treated in an Australian clinic between 1999 and 2007 with permanent gold (Au^{198}) wire implants manually implanted without the use of specific radiation therapy specific planning software, dosimetry or expertise. Gold wires manually cut to 1mm lengths were used in 100% of cases. Recorded data on each treatment included dosing used (80MBq per wire), number of 1mm wires implanted and a not-to-scale schematic representation showing the position of the wires at implant. Each treatment was replicated and dose distributions calculated and analysed through the use of Varian BrachyVision™ Treatment Planning Software. Prescribed (delivered) doses were compared to human recommended dosing schedules for superficial skin squamous cell carcinoma[5] (50Gy mean dose dependent on size of lesion and involvement). Critical organ dose was observed and recorded in accordance with Emami et al (1991) tolerances of normal tissue to therapeutic radiation for the lens, retina and cornea.[6]

No. wires/no cases	Peripheral Dose range (Gy)	Lens Dose Range (Gy)	Retina Dose Range (Gy)	Cornea Dose Range (Gy)
13/1	19.529	9.008	4.461	33.231
10/5	44.54-49.5	3.4-8.571	0.491-2.221	5.909-42.55
9/1	19.529	8.407	2.087	11.348
8/6	18.947-27.444	0.4755-14.488	1.718-1.954	5.5-46.452
7/3	27.444-33.590	5.671-7.213	1.124-1.461	11.4-21.818
6/3	14.949-15.257	1.845-4.964	0.820-0.932	4.319-16.533
5/2	16.209-18.440	2.031-2.584	0.589-0.644	1.802-4.226
4/5	27.419-45.873	1.357-4.429	0.535-1.546	6.173-19.884
3/9	8.463-13.497	0.970-4.602	0.209-0.742	1.349-5.5
2/2	9.515-14.209	1.940-2.5	0.417-0.524	1.496-1.683

Table 1: Dose range for periphery dose, lens dose, retina and cornea dose

RESULTS: Of the 42 horses treated with Au^{198} implants, 12 did not have recorded data of the location of Au^{198} implants and/or the dose delivered. These were therefore not planned. The remaining 30 horses' treatments were replicated. Of these, 22 recurred anywhere between 5 months and 5 years following treatment. Prescribed (peripheral mean dose) for the treatments ranged from 9.463Gy to 49.5Gy (Table 1). The number of wires implanted ranged from 1 to 13 wires. The wire placement arrangements varied significantly however in most cases the wires were implanted 1cm apart. It was difficult to estimate if this was the case for each treatment as the diagrams provided were merely hand-drawn (Figure 1) and at best a visual representation of the day's events as opposed to a measured means of capturing the location of the wires. The dose to the critical organs was maintained within limits for the retina and cornea, 5500-7000cGy and 5000-6000cGy respectively, for each treatment application.[6] The lens', however, received high doses in the realm of 1337cGy to 1438.8cGy in 2 of the cases, leading to an increased 50% injury rate within 5 years (cataracts).[6] All other cases remained well within tolerance for critical organs.

CONCLUSION: Whilst it may seem reasonable to intuit that an association would exist between increased peripheral dose and the number of wires used, it became clear that such a hypothesis did not hold true for all treatments and that the arrangement of the wires impacted far more significantly on the dosing outcomes. Furthermore, and as a result of the high recurrence rates and the low dose to the lesions (as compared to 50Gy), it may be hypothesised that in most cases, the lesions were under-dosed significantly hence the recurrence rate (Figure 2). The results of this study question the efficacy of brachytherapy treatment applications without appropriate radiation therapy planning, dosimetry and expertise. The results further support the need for protocol based treatment implementation within veterinary oncology to mirror current applications in human treatments and with a view to enhancing treatment outcomes with reference to recurrence rates.

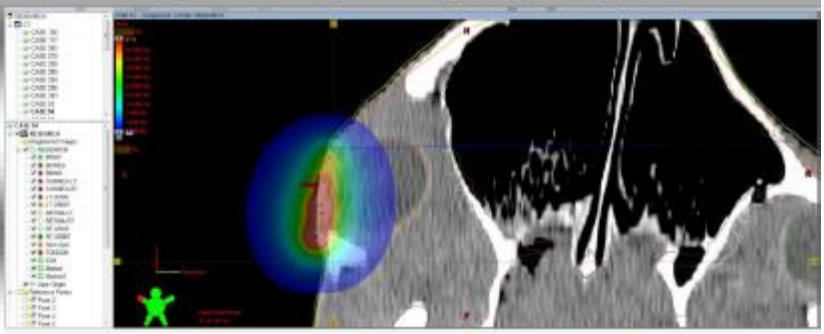
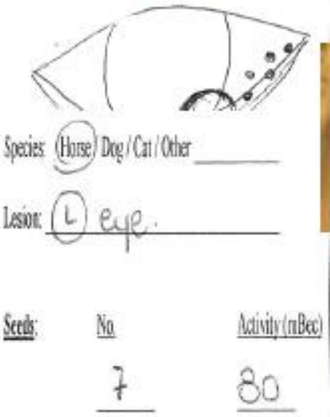
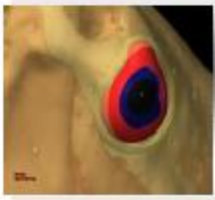


Fig 2: Nictitating membrane SCC left eye, 7 x 1mm wires @ 80MBq.

Fig 1: Example of schematic record of implant.





FUTURE DIRECTIONS: The same treatments will be replicated for a second time however using $Iridium^{192}$ HDR temporary implant planning principles. It is envisaged that the outcome of this will be compiled and analysed in a 'treatment library' for implementation within the veterinary sphere. Key radiation oncology and radiations safety principles will be included in the development of treatment protocols.

1. Dugan SJ, Roberts SM, Curtis CR, Severin GA. *Prognostic factors and survival of horses with ocular/adnexal squamous cell carcinoma; 147 cases (1978-1988)*. J Am Vet Med Assoc 1991. 198: 298-303.
2. Giuliano EA, McDonald I, McCaw DL, et al. *Photodynamic therapy for the treatment of periocular squamous cell carcinoma in horses: a pilot study*. Vet Ophthalmol 2008. 11: p. 27-34.
3. Hendrix DVH. *Equine Ocular Squamous Cell Carcinoma*. Clin Tech Equine Prac 2005. 4: p. 87-94.
4. Giuliano EA. *Equine ocular adnexal and nasolacrimal disease, in Equine Ophthalmol*, Gilger BC, Editor. Elsevier, Philadelphia, 2011: p. 133-180.
5. Leibel & Phillips. *Textbook of Radiation Oncology*. Third Edition, 2010 Elsevier Inc.
6. Emami B et al. *Tolerance of normal tissue to therapeutic radiation*. Int J Radiat Oncol Biol Phys 21:109-122, 1991.

PROCEEDINGS OF THE EUROPEAN SOCIETY FOR RADIOTHERAPY AND ONCOLOGY (ESTRO-31) 2012, BARCELONA SPAIN, MAY 9-13, 2012.

Poster presentation

Title: Radiation protection in veterinary clinics, analysis of current practice: an Australian National Survey.

Surjan Y, Milross C, Ostwald, Donaldson D, Warren-Forward HM.

Purpose: An Australian National Survey of practicing veterinary surgeons was conducted as part of current research into the treatment benefits of interstitial brachytherapy for periocular squamous cell carcinoma (POSCC) in horses. The survey was conducted to identify the perceived needs for radiation therapy input and expertise in the area of treatment and radiation safety. Radiation safety considerations related to IB differ from those related to the use of other radiation producing equipment. Seed IB requires rigorous radiation safety procedures, including consideration of the loss of seeds, storing of seeds and staff exposure during implantation. The potential for accidental irradiation of staff, patients and animal owners is significantly high if suitable radiation monitoring and safety procedures are not implemented.

Methods: The survey was structured to investigate the efficacy and successful application of IB in POSCC. It included quantitative and qualitative questions, reflecting on the benefits of IB in the treatment of POSCC. The survey was disseminated as a hardcopy and/or electronic copy and participants were given the opportunity to provide information in various areas including radiation safety knowledge, education, principles and their application.

Results: The results identify a critical gap in the application of radiation protection principles and education within the veterinary field in Australia. Of the respondents, 20% indicated radiation monitoring was not used within clinics despite 91% of respondents owning and using various types of radiation producing equipment. Radiation safety protocols were absent in 12% of clinics. Radiation safety courses had not been attended or completed in 75% of cases. Only 47% of veterinary surgeons felt they had a 'somewhat' well developed knowledge of radiation safety principles.

Conclusion: Whilst a number of responses indicated a sound knowledge and application of radiation safety principles, a significant number of responses highlighted radiation safety concerns in relation to radiation protection and monitoring as well as education and knowledge. Given that a total of 90% of respondents indicated they would be interested in recommencing, introducing or becoming involved in IB in some capacity the research seeks to develop and implement recommendations and formal training in the areas of radiation safety and protection for veterinary use and in conjunction with IB treatment for POSCC in horses.

THE UNIVERSITY OF NEWCASTLE AUSTRALIA

RADIATION SAFETY CONSIDERATIONS IN SQUAMOUS CELL CARCINOMA in HORSES:

Results of an Australian Survey

Yolanda España Baron (Surjan) The University of Newcastle, Australia
Associate Prof Helen Warren-Forward The University of Newcastle, Australia
Associate Prof Chris Milross Royal Prince Alfred Hospital, Sydney Australia
Dr. Trish Ostwald Calvary Mater Hospital, Newcastle Australia

OBJECTIVE: To examine the current application and knowledge of radiation safety principles in brachytherapy for horses in the treatment of Peri Ocular Squamous Cell Carcinoma currently within Australia.

BACKGROUND: Periocular squamous cell carcinoma (POSCC) is the most commonly found tumour of the eye and adnexa in horses; (1, 2) it is generally locally invasive and detected within their early stages due to their visible locations. The prevalence of equine POSCC increases with the age and whilst most tumours are slow growing and invade locally, metastases may occur in 10% to 15% of horses. (2, 3) The treatment of POSCC in horses remains a major challenge considering it is the most common skin tumour around the eye and adnexa in horses. A wide range of treatment options exist for POSCC however it can be stated that as a definitive or adjunct therapy, interstitial brachytherapy has been identified to be the most effective with regard to recurrence rates, local control and limiting side-effects. (4) In view of its potential use and the requirement for the application of radiation safety standards, the researchers proposed to investigate the knowledge, education and level of application of radiation safety principles within veterinary practices across Australia.

METHODS (Design): Surveys were sent to equine veterinary surgeons working in Australia. **(Materials):** The survey was delivered both online and hardcopy and comprised 49 questions including open and closed response items. Information was collected regarding their level of knowledge and application of radiation safety standards with regard to the radiation producing equipment they currently possess and in view of potentially introducing brachytherapy to their clinics. **(Participant Group):** Veterinarians were identified through records accessed through the Australian Equine Veterinary Association (AEVA) public website and through internet searches. However rigorous the process of identifying all veterinarians working with horses, it cannot be alleged that all Australian equine veterinarians were included in the study. The number of completed and analysed surveys is 86.

RESULTS: The use of radiation producing equipment was evident in 95% of responding clinics however 21% of respondents did not wear radiation monitors and in 14% of cases radiation safety manuals were not used within the clinics. Of the participants 15% do not have a radiation protection protocol within their clinic, 6% are unsure as to whether it is a necessary component of the clinic, 81% have never completed a certified radiation safety course. Of respondents, 6% did not believe their radiaiton safety knowledge was well developed and 49% described their knowledge as 'somewhat' well developed. Participlants noted being familiar with the principles of time, distance and shielding in 71% of cases whilst 25% claimed they were not familiar or where 'somewhat' familiar with the principles.

Figure 1: Staff monitored for potential exposure

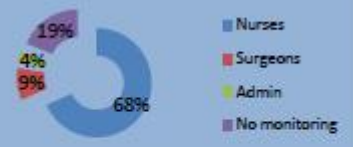


Figure 2: Do you have radiation protection protocols?

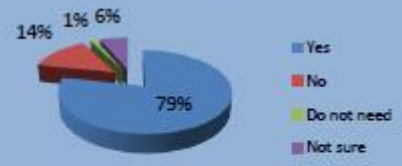
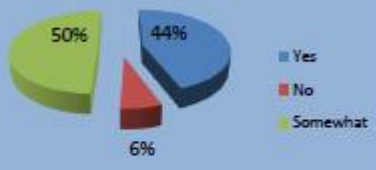


Figure 3: Do you believe your radiation safety knowledge is well developed?



CONCLUSIONS: Veterinary clinics are equipped with radiation producing equipment to aid in diagnosis of disease and other relevant pathology. Some clinics also practice interstitial brachytherapy. With the ability to use such equipment comes the responsibility of maintaining radiation safety standards and practice however there appears to be observable variations in the applications of radiation safety knowledge and practice within veterinary clinics. This may be attributable to the limited education and training some veterinary specialists have been exposed to. This research further emphasises the need for expert involvement in the area of radiation use from the Radiation Oncology fraternity and in view of the short-comings in radiation safety applications and principles within veterinary practice.

References:

1. Dugan SJ, R.S., Curtis CR et al. , *Prognostic factors and survival of horses with ocular/adnexal squamous cell carcinoma; 147 cases (1978-1988).* Journal of the American Veterinary Medical Association

2. Giuliano, E.A., et al., *Photodynamic therapy for the treatment of periocular squamous cell carcinoma in horses: a pilot study.* Veterinary Opthalmology, 2008. 11: p. 27-34.

3. Hendrix, D.V.H., *Equine Ocular Squamous Cell Carcinoma.* Clinical Techniques in Equine Practice, 2005. 4: p. 87-94.

4. Giuliano, E.A., *Equine ocular adnexal and nasolacrimal disease.* in *Equine Ophthalmology.* B.C. Gilger, Editor. 2011.

PROCEEDINGS OF THE 9TH ANNUAL SCIENTIFIC MEETING OF MEDICAL IMAGING AND RADIATION THERAPY (ASMMIRT) SYDNEY AUSTRALIA, APRIL 20-22, 2012.

Poster presentation

Title: Current use of brachytherapy treatment in periocular squamous cell carcinoma: results of an Australian survey.

Surjan Y, Milross C, Ostwald, Donaldson D, Warren-Forward HM.

Purpose: To identify the treatment variables for the implantation of interstitial gold 198 radioactive seeds for the treatment of superficial peri-orbital squamous cell carcinoma in horses.

Methods: Following a literature review into the treatment benefits of interstitial brachytherapy for periocular squamous cell carcinoma (PSCC) in horses and a National Australian Survey of practicing Veterinary Surgeons identifying the professional needs for radiation therapy input and expertise in this area, it has become evident that radiation therapy in the form of treatment protocol input and radiation safety education is necessary for the development of this treatment within Australia. A horse head was sourced and a phantom was created by filling the head with tissue equivalent material and adapting all anatomical features to accurately represent a horse. The phantom was scanned using a human planning CT system and the data forwarded on to an Eclipse 8.9 planning system for brachytherapy treatment planning. Mapping of interstitial radioactive seeds were based on a combination of currently used protocols by veterinary surgeons and known optimal seed distribution parameters. Each treatment regime (10 in total) was appraised following a pre-developed list of parameters including; globe critical dose, dose distribution, number of seeds implanted and seed implantation distance.

Results: The results of the planning and dose assessment showed that using a treatment regime based on parameters applied as a result of clinical observation of the lesion as compared to a standardised treatment regime based on evidence based parameters including isodose distribution, organs at risk and dose time are sub-optimal in the treatment of POSCC. Furthermore, without the clinical expertise provided by radiation therapists, the application of brachytherapy for the purposes of treatment of PSCC in horses could potentially result in an unnecessary loss of globes and resulting cataracts. The final outcome of the research has provided a foundation for further development and implementation of individualised treatment protocols for use within veterinary oncology.

Current Use of Brachytherapy Treatment of Peri- Ocular Squamous Cell Carcinoma in Horses: Results of an Australian Survey

Yolanda Surjan
Ass. Prof Helen Warren-Forward
Ass.Prof Chris Milross
Dr. Trish Ostwald
Faculty of Health
University of Newcastle

OBJECTIVE: To examine the current use and knowledge of brachytherapy in horses for the treatment of peri ocular squamous cell carcinoma (POSCC) within Australia.

INTRODUCTION: Radiation therapy (RT) used in the treatment of human cancer diagnosis is a highly specialised and well established treatment option within our health system. In contrast, veterinary surgeons are routinely faced with animals afflicted by cancer, yet the treatment options employed within Australia rarely involve the application of radiation therapy. Australian veterinarians employ alternate treatment therapies like surgery that have been demonstrated to be less effective with regard to recurrence and local control.(1,2)

BACKGROUND: Superficial squamous cell carcinomas (SCC) are grouped in the nonmelanocytic neoplastic lesion spectrum of conditions. [3] POSCC is the most commonly found tumour of the eye and adnexa in horses. [2, 4] SCC's in horses are generally locally invasive and detected within their early stages due to their visible locations. The prevalence of equine ocular/adnexal squamous cell carcinoma increases with the age of the horse and whilst most tumours are slow growing and invade locally, metastases may occur in 10% to 15% of horses. [3,4] The treatment of POSCC in horses remains a major challenge considering it is the most commonly found skin tumour around the eye and adnexa in horses. Given the variety of treatment therapies and the difficulties in comparing published data effectively, it is evident that a need exists for an effective therapy available data.

RATIONALE: This research reports on an Australian wide survey of veterinary surgeons investigating their perceptions into the efficacy and value of developing a brachytherapy treatment protocol inclusive of radiation safety parameters for the treatment of horses with peri ocular SCC.

METHODS

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Ass. Prof Helen Warren-Forward
Ass.Prof Chris Milross
Dr. Trish Ostwald
Faculty of Health
University of Newcastle

DESIGN: Questionnaires were sent to equine veterinary surgeons working in Australia. The survey was delivered both online and hardcopy for the purposes of gathering maximum response rates and comprised 49 questions including open and closed response items. The participants were asked about their current or past use in brachytherapy and about their knowledge of its applications, benefits and perceived risks. Participants were asked to comment on their level of interest in the treatment regime if it was made clinically available. Information was collected regarding their level of knowledge and application of radiation safety standards with regard to the radiation producing equipment they currently possess and in view of potentially introducing brachytherapy to their clinics. The results of the radiation safety component of this survey is published separately.

MATERIALS AND METHOD: Ethical approval for this survey was granted by the University of Newcastle Ethics Committee, (H-2009-0136).

PARTICIPANT GROUP: Veterinarians who work with horses were identified through records accessed through the Australian Equine Veterinary Association (AEVA) public website, through internet searches and the yellow pages. However rigorous the process of identifying all veterinarians working with horses, it cannot be alleged that all Australian equine veterinarians were included in the study. The response rate cannot be provided as it is not possible to determine how many veterinary surgeons received the survey however the number of completed and analysed surveys is 86.

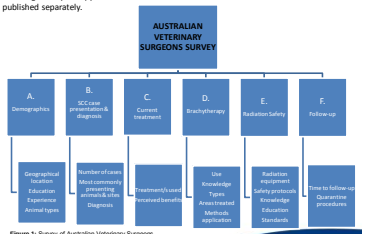

Figure 1: Survey of Australian Veterinary Surgeons.

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RESULTS

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In relation to the number of cases of SCC presenting to a veterinarian on a monthly basis, 64% noted 1-2 cases, 15% reported 3-6 cases, 1% reported 7-15 cases and 2% reported 15-30 cases per month. The respondents noted seeing more cases of SCC's during "the warmer months"; "mostly seen in cattle, horses and cats" with one response noting cases are generally 'undocumented' (Table 1).

Animal types most commonly presenting with skin SCC included horses (66%), cats (48%), dogs (27%) and rabbits (1%). Other animals reported on included cattle in (23%) of cases (Table 1). The most commonly reported areas of presentation for skin SCC included the nose (54%), eyelid (51%), around the eye (adnexa) (51%), ear (27%) and legs and back (1%). Other areas included third eyelid, cornea, penis and vulva (Table 2).

Table 1: Number of cases of SCC per month & animal types most commonly presenting with SCC.

No. Cases	No. of respondents	%	Type of animal	No. of respondents	%
0	8	9	Cats	42	48
1-2	55	64	Dogs	24	27
3-6	13	15	Birds	0	0
7-15	1	1	Horses	57	66
15-30	2	2	Guinea pigs	0	0
>30	0	0	Rabbits	1	1
Other	9	10	Other	20	23

Table 2: Most common areas for presentation of skin SCC.

Area	No. of respondents	%
Nose	47	54
Eyelid	44	51
Around eye	44	51
Lip	6	7
Ear	24	27
Legs	1	1
Back	1	1
Other	24	27

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RESULTS

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COST OF DIAGNOSIS AND ITS IMPLICATIONS: When asked if the cost of histopathology services and the need to impart this cost onto the owners contributed to the decision to self-diagnose, responses varied from 'never' in 6% of cases to 'often' in 33% of cases and 'always' in 3% of cases (Figure 2). Other responses included 'use pathology to determine clear margins', 'leave the choice up to the owners', 'the major cost is not histopathology but the collection first (removal) of the lesion'.

MOST COMMON TREATMENT: The most common treatment choices include surgery (92%), cryotherapy (63%) and a variation of chemotherapeutic drugs, topical and other (45%) (Figure 3). Participants were given the opportunity to choose one or more treatment types, as a result various treatment modality combinations were selected. Of the 83 responses, 32% used a combination of surgery and cryotherapy; other combinations included brachytherapy and cryotherapy and brachytherapy with surgery.

NEGATIVE OUTCOMES: In reference to the potential outcomes of surgery in and around the eye, respondents were asked how often this treatment has resulted in the removal of the globe. The majority of respondents (64%) suggested removal of the globe occurred 'sometimes' whilst 25% claimed it occurred 'often'.

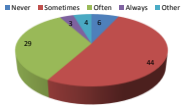

Figure 2: Decision to self-diagnose as a result of cost of pathology.

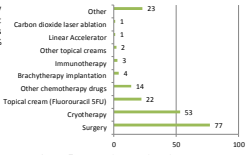

Figure 3: Treatment options currently used

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Results

BRACHYTHERAPY USE: The use of brachytherapy whether presently or in the past was evident in only 3% of respondents. Whilst brachytherapy is not currently a staple treatment modality in veterinary science within Australia, its use, by a small cohort of veterinary surgeons, has spanned over three decades. The earliest recorded use commenced in 1977, with the last of the treatments applied in 2007. Discontinuation of treatment was a result of 'poor availability', 'very expensive'. 'problems with radiation licensing', 'cannot get it anymore otherwise would still use it' and 'radiation risk'.

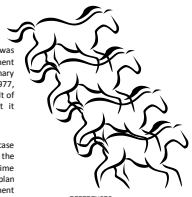
BRACHYTHERAPY APPLICATION: The calculation of dose and time in each individual case was reported to be 'decided at the time of implantation based on clinical observation of the lesion' in 40% of cases. Two respondents claimed their calculations varied each time depending on the size of the lesion. One respondent claimed the use of a 'treatment plan using radiation therapy software and principles', another used 'the same for each treatment based on previous observed rates of local control'.

Conclusion

This study explored current use, knowledge and perceptions of Australian veterinarians on the varied aspects of brachytherapy treatment for POSCC. The paper reports on data derived from veterinary surgeon responses and forms part of a larger research project aiming to identify the tools needed to introduce brachytherapy within Australia with a view to including radiation therapy principles and radiation safety standards and training.

It is evident that of those who have used brachytherapy in the past, the methods of application, protocols, equipment and treatment follow-up procedures lack a systematic or common approach. The need for a common approach has been highlighted through these results.

The overall indication from those who responded to the survey was that there is an interest in brachytherapy and its applications in veterinary oncology. It was also highlighted that the need for education and training is pivotal to the uptake of brachytherapy as a mainstream treatment modality.



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4. Giuliano, E.A., et al., *Photodynamic therapy for the treatment of periocular squamous cell carcinoma in horses: a pilot study.* Veterinary Ophthalmology, 2008. **11**: p. 27-34.

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PROCEEDINGS OF THE UK RADIOLOGICAL CONGRESS, MANCHESTER UNITED KINGDOM, JUNE 6-8, 2011.

Oral presentation

Title: Brachytherapy treatment of periocular squamous cell carcinoma in horses: the potential for the application of radiation therapy in the veterinary sphere - results of an Australian national survey.

Surjan Y, Milross C, Ostwald, Warren-Forward HM.

Purpose: Following a literature review into the treatment benefits of interstitial brachytherapy (IB) for periocular squamous cell carcinoma (PSCC) in horses, a National Australian Survey of practicing Veterinary Surgeons was conducted to identify the perceived needs for radiation therapy input and expertise in this area.

Methods: The Australian Survey was structured on literature on the efficacy and successful use of IB in PSCC. It included quantitative and qualitative questions, reflecting on the benefits of IB in the treatment of PSCC and gave participants the opportunity to provide information in areas including; current treatment options, radiation safety knowledge, radiation therapy technique knowledge and preferences for treating PSCC.

Results: Of the respondents, 33% considered IB to be well known. The current treatment options for PSCC include a combination of surgery (100%) and cryotherapy (50%), immunotherapy (8.3%) and chemotherapy (41.7%). Results indicated 33% had used brachytherapy in the past but no longer used it due to the lack of availability of the radioactive sources.

Radiation safety issues were highlighted as 36% of responses indicated radiation monitoring was not used within clinics despite 100% of participants owning and using radiation producing equipment.

Conclusion: The knowledge of and expertise in applying IB is under-developed within Australian veterinary practices. The radiation therapy fraternity could be providers of expertise in the areas of brachytherapy treatment, radiation safety, design and implementation of treatment protocols and sourcing of radioactive materials for brachytherapy.

Brachytherapy Treatment of Squamous Cell Carcinoma in Horses: The Potential for the Application of Radiation Therapy in the Veterinary Sphere – Results of an Australian National Survey

Yolanda Surjan[1], Ass. Prof. Helen Warren-Forward[1], Dr. Patricia Ostwald[1&2], Ass Prof. Christopher Milross[3]

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Squamous Cell Carcinoma in Horses

- PSCC in equine is:
  - Generally locally invasive and detected within early stages due to visible locations [1&2]
  - Not always treated immediately following detection
- Metastases occur in 10-15% of horses [1&2]

BACKGROUND & INTRODUCTION

Advanced Practice & Role Expansion in Radiation Therapy

- Enlargement of existing scope within radiation therapy and for radiation therapists
- Increased involvement in specialised areas of practice
- Responsibility to share specialist abilities, advanced knowledge and proven treatment regimes/protocols

Squamous Cell Carcinoma in Horses

- Periocular SCC (PSCC) is the most commonly found tumour in horses [1]
- Occurs as a result of [1] :-
  - Extended exposure to the ultraviolet component of solar radiation
  - Degree of horse pigmentation
  - Genetic predisposition to carcinogenesis

Current Treatment Options for Equine Periocular Sqaumous Cell Carcinoma

- Most commonly used treatment option (although benefits are not supported by literature) within veterinary oncology is surgical excision [2]
- Other treatment options include [2]:-
  - Photodynamic therapy
  - Cryotherapy
  - CO^2 ablation
  - Brachytherapy

Surgical Excision

- Surgery is considered adequate as long as the margins are consistently clear and tumours small or in situ
- Reports show recurrence as result of inadequate surgical excision are common and reported to be between 50% and 67% within 1 year of surgery [1]
- In cases where tumour margins are extensive, enucleation (removal of organ) in this case the globe (eyeball) is often required [3]
- It is therefore recommended that SCC in and around the eye and adnexa is treated with methods other than surgery[3]

A Non-Evidence Based Approach: The Implications

- **There are TWO distinct and significant implications resulting from the current practice of veterinary brachytherapy treatment within Australia:**
  - **Incorrect dosimetric parameters, resulting in;**
    - **Sub-optimal treatment result**
    - **Potential patient side-effects**
  - **Compromised radiation safety**

Equine Brachytherapy: An International Success

- Interstitial brachytherapy is the manual implantation of radioactive seeds or wires throughout tumours
- Interstitial brachytherapy using radioactive gold (Au^{198} seeds) and external radiation therapy in equine PSCC is well established in United States of America [4 & 5]
  - One year local control rate – 74%
  - Two year non-recurrence – 70%

RESEARCH AIM

The AIM of the research was to survey Australian veterinary practices to assess current veterinary oncology methods and treatment protocols with regards to periocular squamous cell carcinoma in equine

Equine Brachytherapy in Australia

- Australian veterinary oncology field is considered to be:
  - Under-developed
  - Currently at a standstill
  - Based on 'personal communication'
- Current evidence suggests that:
  - Treatment planning is non-existent
  - Treatments are applied haphazardly
  - There is no provision of dosimetry or radiation safety expertise within veterinary practice

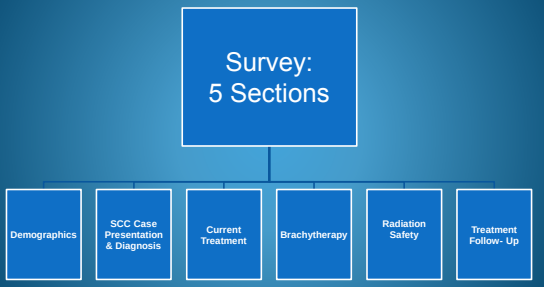
METHODOLOGY

METHODOLOGY

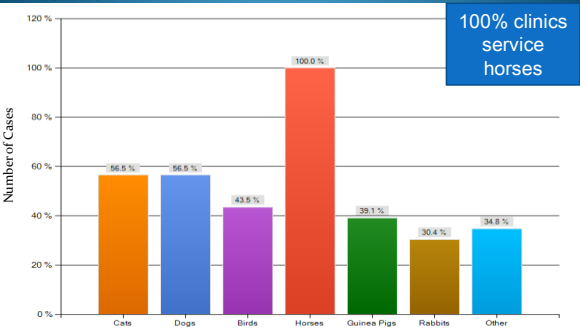
- Ethics Approval
  - Human Research Ethics Committee, University of Newcastle
- Participants
  - Members of Australian Veterinary Association & Equine Association
- Recruitment
  - Online Survey

RESULTS

- Return Rate:
  - 24 respondents to date (31% response rate)
  - 61% of these in New South Wales, Australia



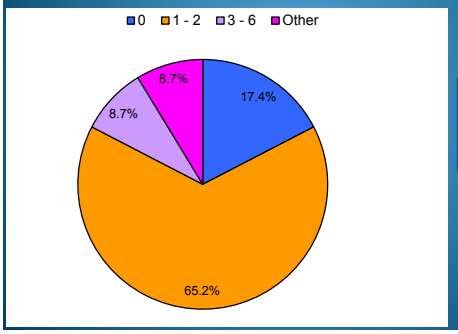
What animal types do you service at your clinic?



100% clinics service horses

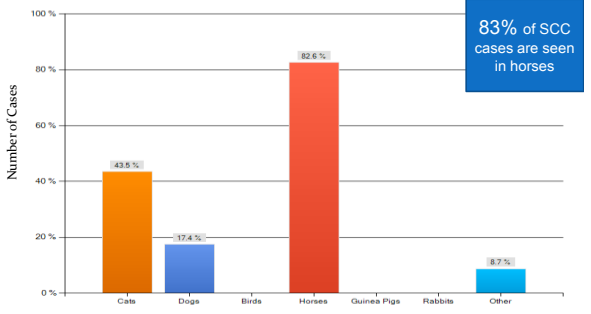
RESULTS

How many cases of skin squamous cell carcinoma would you see in a month?



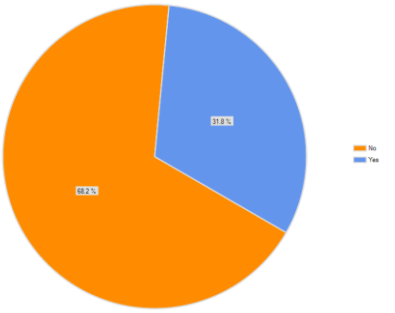
65% respondents see 1-2 cases of SCC per month

In your experience, what type/s of animals most commonly present with skin squamous cell carcinoma?



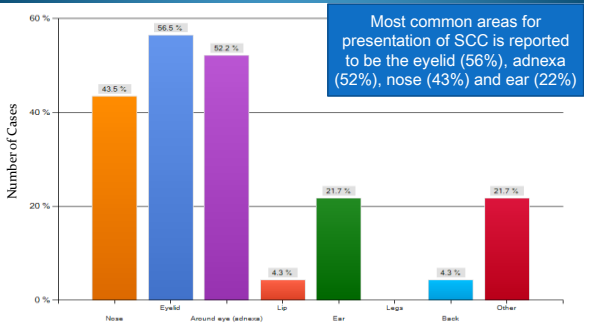
83% of SCC cases are seen in horses

In your experience, would you consider brachytherapy to be a well known treatment method in veterinary science?



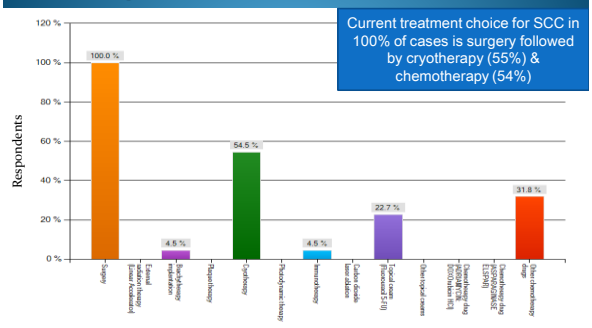
68% believe brachytherapy is not a well known method in Australia

In your experience, the most common area/s for the presentation of skin squamous cell carcinoma is;



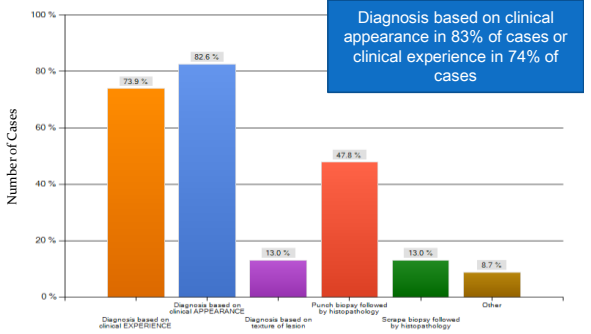
Most common areas for presentation of SCC is reported to be the eyelid (56%), adnexa (52%), nose (43%) and ear (22%)

What is your current choice of treatment for skin squamous cell carcinoma?



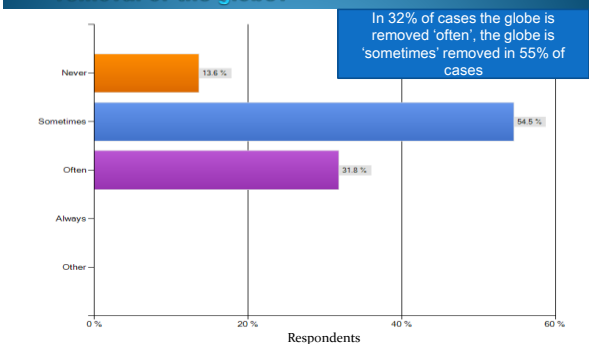
Current treatment choice for SCC in 100% of cases is surgery followed by cryotherapy (55%) & chemotherapy (54%)

Of the cases that you see, how do you diagnose and confirm the presence of SCC?



Diagnosis based on clinical appearance in 83% of cases or clinical experience in 74% of cases

How often have you found surgery in and around the ocular region which requires an extensive margin resection, result in the removal of the globe?

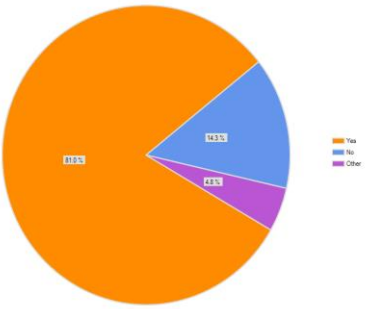


In 32% of cases the globe is removed 'often', the globe is 'sometimes' removed in 55% of cases

USE OF BRACHYTHERAPY

- Last recorded use of brachytherapy in Australia 2005
- 23% of respondents have used brachytherapy in the past
  - Of these, 100% used brachytherapy in horses
  - All would continue use if the isotopes were readily available
- Radioactive sources used:-
  - Gold 198 – 100%
  - Strontium – 25%

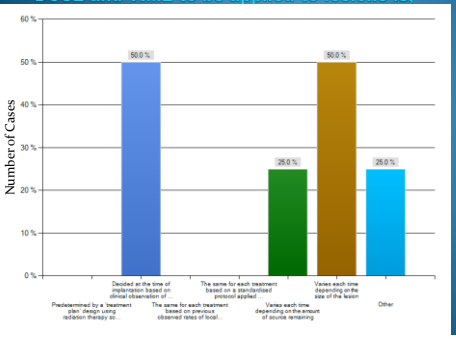
Do you have a radiation safety manual for the equipment within your clinic?



95% of respondents have radiation producing equipment in their clinic

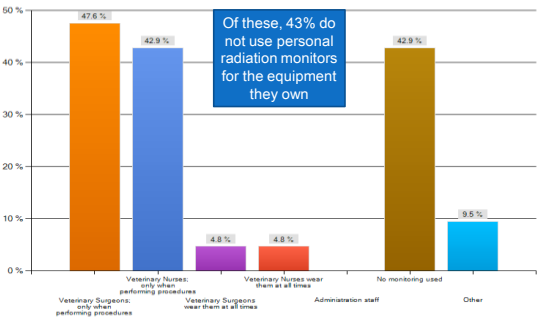
Of these, 15% do NOT have a radiation safety manual for the equipment they use

In your experience, the calculation of the amount of DOSE and TIME to be applied to lesions is:



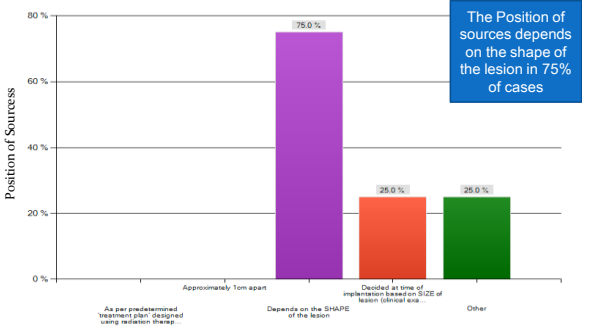
Preparation of sources in 50% of cases decided at time of implantation

Select the staff within your clinic who are monitored for potential radiation exposure.



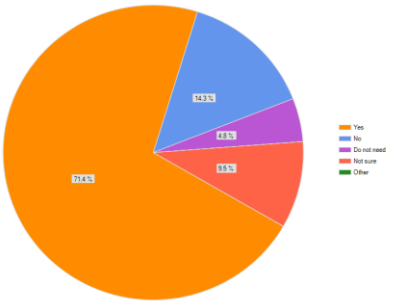
Of these, 43% do not use personal radiation monitors for the equipment they own

How do you calculate the POSITION of the sources for treatment?



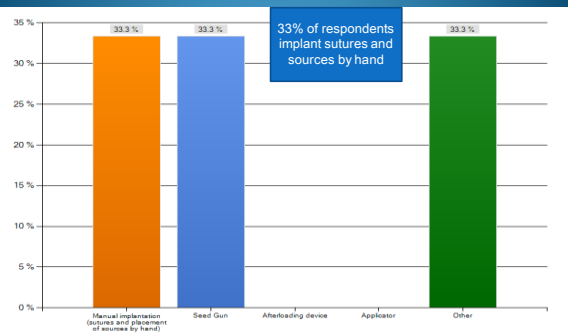
The Position of sources depends on the shape of the lesion in 75% of cases

Do you have a radiation protection protocol within your clinic?



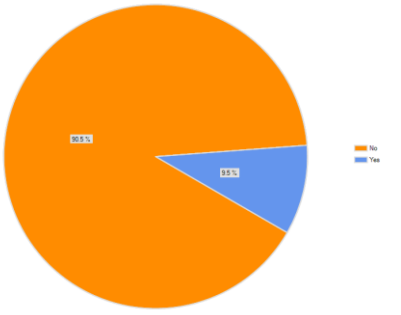
Of these, 29% either do not have a radiation protection protocol, believe they do not need one OR are unsure as to whether they need one

When using radioactive sources, the implantation system you use involves;



33% of respondents implant sutures and sources by hand

Have you ever completed a certified radiation safety course?



91% of respondents have never completed a certified radiation safety course

IMPACT OF RESULTS

These results show .....

- Current PSCC preferred treatment is limited to surgery and chemotherapy
- Loss of globe as a result of the current treatments used is not uncommon
- Radiation safety knowledge, education and application of safety standards is sub-optimal within the veterinary sphere

IMPACT OF RESULTS

- These results show that.....
  - 87% of respondents are interested in:
    - Pursuing brachytherapy as a treatment option
    - Learning more about it's applications

ON-GOING RESEARCH...

- Response rate to date = 31%
- Online survey followed by paper-based survey to increase response rates (currently on-going)
- Based on results to date there appears to be a need for information and support for the development of brachytherapy use in PSCC in Australia

ON-GOING RESEARCH...

The research is on-going and will maintain a focus on the provision of not only optimal treatment applications of brachytherapy based on radiation therapy principles but also on the provision and development and application of radiation safety guidelines and protocols for application within veterinary oncology

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THANK YOU

www.newcastle.edu.au

QUESTIONS

PROCEEDINGS OF THE 16TH ISRRT WORLD CONGRESS SCIENTIFIC PROGRAM, GOLD COAST AUSTRALIA, 2010.

Oral presentation

Title: Is there a role for radiation therapists within veterinary oncology?

Surjan Y, Milross C, Ostwald, Warren-Forward HM.

Abstract: Role expansion recognises enlargement of existing scope of practice within radiation therapy (RT). Over the past decade, there has been increasing involvement in specialised areas of practice including brachytherapy, image fusion and quality assurance. It is also recognised that radiation therapy expert practitioners exist in the areas of imaging immobilisation, treatment, education and research. The acquisition of additional skills has hastened the need for autonomy within the RT profession and with this comes the responsibility to share our knowledge and specialist abilities with the wider community. Radiation therapy is a highly specialised profession working to treat a commonly encountered ailment like cancer and we should ask ourselves what other community members could benefit from our knowledge and skills.

Cancer is not limited to the human population but affects animals as readily and severely. Particular types of cancers have been identified as being synonymous with that of human afflictions; one such tumour is the squamous cell carcinoma (SCC). Squamous cell carcinoma is the most commonly found tumour of the eye and adnexa in horses. Comparatively, SCC in humans is the most common cancer in Australia. Whilst its treatment is well established for humans with surgery and radiation therapy offering comparable control rates, the treatment within Australia's Veterinary Oncology field is currently at a standstill. It is reported, however, that the use of interstitial brachytherapy has been shown to be highly effective and thoroughly practiced and established within the United States of America (USA).

Is There a Role for Radiation Therapists Within Veterinary Oncology?

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OVERVIEW

- HOWEVER, Australia is currently at a standstill with regard to the use of radiation therapy within veterinary oncology

OVERVIEW

- Particular animal cancer types have been identified as being synonymous with human afflictions
- Of particular significance is squamous cell carcinoma (SCC): most common non-melanoma skin cancer in humans [1] AND outdoor domestic animals alike (with an emphasis on horses)
- Radiation therapy treatment for SCC in humans is shown to be highly effective with regard to control rates [1]

OVERVIEW

- This presentation will focus on the research conducted by the authors into the adaptability and potential cross-over of radiation therapy in the form of interstitial brachytherapy for the treatment of SCC in equine (horses)
- The authors seek to explore the world of veterinary oncology and assist the fraternity within Australia by providing our expertise, knowledge and skill in the provision of what is proven to be an effective means of therapy for a tumour of universal prevalence (squamous cell carcinoma)

OVERVIEW

- Equally, interstitial brachytherapy (delivery of continuous radiation exposure limited locally and delivered through implantation of radioactive seeds) within equine veterinary oncology has been shown to be highly effective in America

Role Expansion Within Radiation Therapy

- Enlargement of existing scope within radiation therapy and for radiation therapists
- Increased involvement in specialised areas of practice
- Responsibility to share our specialist abilities, advanced knowledge and proven treatment regimes/protocols

Cancer: A Shared Ailment in Human and Animal Species

- Squamous cell carcinoma (non-melanoma skin cancer) is the most commonly diagnosed cancer within Australia according to general practice and hospitals data [1]

- Comparatively, SCC is;
  - the most commonly found tumour of the eye and adnexa in horses [2] (referred to as periocular squamous cell carcinoma, PSCC)

Current Treatment Options for Equine Periocular Squamous Cell Carcinoma

- Most commonly used treatment option (although benefits are not supported by literature) within veterinary oncology is surgical excision [4]

Other treatment options include [4];
- Photodynamic therapy
- Cryotherapy
- CO^2 ablation
- Brachytherapy

Squamous Cell Carcinoma in Equine (Horses)

- Periocular SCC (PSCC) is the most commonly found tumour in horses as a result of [2];
  - Extended exposure to the ultraviolet component of solar radiation
  - Degree of horse pigmentation
  - Genetic predisposition to carcinogenesis

Benefits and Outcomes of Current Treatment Options: What the literature reports

- Literature is limited within the field of veterinary oncology

- Limited evidence suggests treatment strategies are moderately adequate on an individual basis and rarely applicable globally (general protocols non-existent)

Squamous Cell Carcinoma in Equine (Horses)

- PSCC in equine is generally locally invasive and detected within early stages due to visible locations [3&4]

- However, it is not always treated immediately following detection

- Metastases occur in 10-15% of horses [2&4]

SURGICAL EXCISION

- Surgery is considered adequate as long as the margins are consistently clear and tumours small or in situ

- Reports show recurrence as result of inadequate surgical excision are common and reported to be between 50% and 67% within 1 year of surgery [2]

SURGICAL EXCISION

•In cases where tumour margins are extensive, enucleation (removal of organ) in this case the globe (eyeball) is often required [4]

•It is therefore recommended that SCC in and around the eye and adnexa is treated with methods other than surgery[3]

NON-SURGICAL TREATMENTS

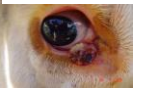
Interstitial Brachytherapy:

•Internationally brachytherapy treatment in equine is reported to be highly effective with regard to;

–Local control (one year local control , 74%) [3&7]

–Recurrence rates (two year non-recurrence 70%) [3&7]

– Organ sparing



NON-SURGICAL TREATMENTS

• Photodynamic Therapy: the use of light-sensitive compounds in an oxygen rich environment. Effects are purely hypothetical due to the unknown side-effects high volume of required drugs in horses [5]

•Cryotherapy: Use of liquid nitrogen or nitrous oxide to destroy malignant cells has the potential of causing collateral tissue damage [4]

Equine Brachytherapy: An International Success

• Interstitial brachytherapy using radioactive gold (Au^{198} seeds) and external radiation therapy in equine PSCC is well established in United States of America

•Survey conducted under sponsorship of Veterinary Radiation Therapy Oncology Group (USA), reported a total of 42 facilities across USA providing radiation therapy for veterinary [3&4]

NON-SURGICAL TREATMENTS

• CO^2 Ablation: The use of a CO^2 laser to vaporise tumours in situ. A non-invasive treatment however the cost of the instrumentation is remarkably high [6]

• Additionally, may result in corneal ulcers

Equine Brachytherapy in Australia

• Australian veterinary oncology field is under-developed and currently at a standstill

•Agnes Banks Equine Clinic (Richmond NSW) used brachytherapy in equine until 2007

•Current use of brachytherapy based on 'personal communication' from one veterinary surgeon to another

Equine Brachytherapy in Australia

•Currently no provision of dosimetry expertise or radiation safety expertise within veterinary oncology

•Treatments are applied hap-hazardly

•Treatment planning is non-existent

Incorrect Dosimetry Resulting in Patient Side-Effects

• Veterinary surgeons may legally purchase brachytherapy equipment including radioactive sources

•Veterinary surgeons do not have the background required in radiation oncology that confirms treatment delivery is optimum and dosimetry is biologically appropriate is non-existent

Equine Brachytherapy in Australia

•Experiential learning as opposed to EVIDENCE BASED LEARNING (EBP)

Incorrect Dosimetry Resulting in Patient Side-Effects

• Side-effects include;

–Soft tissue necrosis
–Potential cataracts
–Loss of globe

A Non-Evidence Based Approach: The Implications

•There are 2 distinct and significant implications resulting from the current practice of veterinary brachytherapy treatment within Australia

•1. Incorrect dosimetric parameters, resulting in;
–Sub-optimal treatment result
–Potential patient side-effects

•2. Compromised radiation safety

Incorrect Dosimetry Resulting in Loss of Revenue for Horse Owners

• The financial implications resulting from inadequately treated horses impact on the thoroughbred industry

• High levels of economy invested in these animals is potentially affected as a result of repeated procedures (where recurrence occurs) or loss of globe

Radiation Safety: Veterinary Clinics

- Safety requirements as related to radioactive sources are considerable [8]
- Current veterinary radiation safety practice is inadequate resulting from lack of education

Radiation Safety: Domestic Horses

- Management of horses post-operatively is poorly regulated: horses generally live in paddocks!
- Horses left in paddocks at risk of losing seeds

Radiation Safety: Veterinary Clinics

- Recent site visits and discussions with veterinary surgeons have made the lack of radiation safety evident
- Veterinary clinics are clearly inadequately equipped for the application of brachytherapy

Radiation Safety: Thoroughbreds

- Thoroughbreds are often reared in enclosed stables due to the nature of their athletic ability and temperament
- These horses are therefore unable to be placed in external paddocks and are held in post-operative stables for reasons of safety to them and the general public
- This results in potential radiation exposure danger to personnel within the stables' proximity

Radiation Safety: Veterinary Clinics

- Multiple personnel attend to animal patients with varied understanding of the considerable dangers associated with radiation exposure

Radiation Safety: The Owners

- A further implication is in relation to the owner's perceived safety in handling their animals post-operatively
- Veterinary surgeons disclose dangers and management strategies for owners however the likelihood of owners following instructions is unknown

CURRENT RESEARCH

The AIM of the research is to develop and implement an interstitial brachytherapy treatment protocol in equine for periocular squamous cell carcinoma with a view to incorporating radiation safety standards

CURRENT RESEARCH

Methodology:

4. Design animal models (horse head phantoms) for dosimetric assessment of varying treatment options using Au198

CURRENT RESEARCH

The main OBJECTIVE of the research is to increase the treatment options and quality of life of equine with periocular SCC

CURRENT RESEARCH

Methodology:

5. Establish radiation safety guidelines for veterinary practitioners

6. Develop & implement protocol for Au198 seed use in equine ocular SCC

7. Compare treatment outcomes between current non-systematic brachytherapy applications and newly developed treatment regime

CURRENT RESEARCH

Methodology:

1.Conduct a literature review (complete)

2. Develop and circulate a survey to Australian veterinary practices to assess current veterinary oncology methods (current)

3.Collate and analyse existing treatment data (retrospectively:1997-2006) as provided by Agnes Banks Equine Clinic

CURRENT RESEARCH: The Hypothesis

- It is envisaged that the results of the survey will inform us of the following;

- 1. There are currently limited or no systems in place with respect to interstitial brachytherapy treatment protocols or dosimetry within Australia
- 2. Current radiation safety practice within veterinary oncology is limited or inadequate in relation to brachytherapy treatment

THE FUTURE FOR RADIATION THERAPISTS?

- The provision of radiation therapy specialist functions within veterinary oncology in;
  - Treatment planning
  - Expertise support in seed implantation
  - Radiation safety principles
  - Post implant support
  - Long term collection and analyses of treatment benefits

THE FUTURE FOR RADIATION THERAPISTS?

QUESTIONS?

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