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SCIENTIFIC PAPER

Implications for dosimetric changes when introducing MR-guided brachytherapy for small volume cervix cancer: a comparison of CT and MR-based treatments in a single centre

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Abstract To evaluate cervix brachytherapy dosimetry with the introduction of magnetic resonance (MR) based treatment planning and volumetric prescriptions and propose a method for plan evaluation in the transition period. The treatment records of 69 patients were reviewed retrospectively. Forty one patients were treated using computed tomography (CT)-based, Point A-based prescriptions and 28 patients were treated using magnetic resonance (MR)-based, volumetric prescriptions. Plans were assessed for dose to Point A and organs at risk (OAR) with additional high-risk clinical target volume (HR-CTV) dose assessment for MR-based brachytherapy plans. ICRU-38 point doses and GEC-ESTRO recommended volumetric doses ($D2_{cc}$ for OAR and D_{100}, D_{98} and D_{90} for HR-CTV) were also considered. For patients with small HR-CTV sizes, introduction of MR-based volumetric brachytherapy produced a change in dose delivered to Point A and OAR. Point A doses fell by 4.8 Gy ($p = 0.0002$) and ICRU and D2cc doses for OAR also reduced ($p < 0.01$). Mean Point A doses for MR-based brachytherapy treatment plans were closer to those of HR-CTV D_{100} for volumes less than 20 cm^3 and HR-CTV D_{98} for volumes between 20 and 35 cm^3, with a significant difference ($p < 0.0001$) between Point A and HR-CTV D_{90} doses in these ranges. In order to maintain brachytherapy dose consistency across varying HR-CTV sizes there must be a relationship between the volume of the HR-CTV and the prescription dose. Rather than adopting a 'one size fits all' approach during the transition to volume-based prescriptions, this audit has shown that separating prescription volumes into HR-CTV size categories of less than 20 cm^3, between 20 and 35 cm^3, and more than 35 cm^3 the HR-CTV can provide dose uniformity across all volumes and can be directly linked to traditional Point A prescriptions.

Keywords Cervix · HR-CTV · Prescription · Audit

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Introduction

In 2000, the American Brachytherapy Society (ABS) published recommendations for high dose rate (HDR) brachytherapy dose reporting and prescribing for intracavitary brachytherapy for cervical cancer [1] based on updates of the Manchester dosing system [2] and International Commission on Radiological Units (ICRU) report 38 [3]. Since that time, many centres have been basing prescriptions on doses normalized to geometric points (Point A), with varied levels of optimisation of individual patient dose distributions. The introduction of 3-dimensional (3D) image-based brachytherapy planning with systems such as magnetic resonance (MR) imaging and sophisticated brachytherapy treatment planning systems, have created the ability to easily manipulate dose distributions and also visualize the target volume for the first time [4, 5]. Implementation of this was initially slow with 43 % of clinical centres still using plain X-ray film and only 2 % of

clinical centres using MR-based imaging according to the ABS international survey in 2007 [6], however with increasing access to MR units, there is expected to be a rapid rise in the number of departments transitioning to MR-based treatment planning and ultimately volumetric dose prescriptions.

The shift from point dose to 3D volumetric treatment planning for brachytherapy treatment of cervical cancer can be confusing. Uniformity of how much dose to give and where to prescribe dose to is the subject of many studies and new ICRU consensus guidelines for this are imminent. At present the Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology (GEC-ESTRO) and the ABS recommend using the whole cervix and remaining residual tumour tissue at the primary site at time of brachytherapy (defined as the high risk-clinical target volume, HR-CTV), as a prescribing volume [7–11].

These recommendations are based upon studies and clinical results of several international centres and as early as 2005 results have indicated a direct link between HR-CTV D_{90} doses (the minimum dose received by 90 % of the HR-CTV) and Point A doses [7, 12–14]. Interestingly, all of these studies have results based on mean HR-CTV sizes in the order of 30 cm^3 up to 50 cm^3.

There is a large body of evidence-based outcomes on traditional Point A dose prescription [15–17], and 3D volumetric prescriptions have shown early indications of improving local control compared to traditional methods, particularly for advanced disease and large residual tumours which previously lay beyond Point A [18–20]. There are international studies being undertaken, such as the European study on MR-guided brachytherapy in locally advanced cervical cancer (EMBRACE, www.embracestudy.dk and RetroEMBRACE, www.retroembrace.com) to better understand the impact these changes will have on dose-volume-outcome relationships. Until long-term results of these studies are known, centres must use caution when changing their prescribing and optimisation methods as they incorporate HR-CTV volumetric prescriptions into departmental protocols.

This study was designed to audit, compare and evaluate dosimetry of HDR cervix brachytherapy treatment plans in a single centre with smaller average HR-CTV sizes than other publications. Plans that were generated using a simplified 3D approach; CT-based planning images with Point A normalisation and optimisation to reduce bladder and rectal organs at risk (OAR) volumes were compared to those patients treated after introduction of MR-based imaging and volume-based prescriptions. The purpose of this was to quantify any dosimetric differences between planning techniques and determine a methodology to maintain consistency of treatment in the transition between point dose and volumetric treatment planning particularly for smaller HR-CTV sizes.

Table 1 Patient characteristics

	CT-based treatment plan	MR-based treatment plan
Number of patients	41	28
Age: median (range), years	57 (21–83)	56 (28–82)
Staging (FIGO 2009)		
IB/IIA	8	4
IIB	24	14
IIIB	8	5
IVA	1	5
EBRT		
45 Gy in 25 #	20	19
50 Gy in 25 #	4	1
50.4 Gy in 28 #	17	7
52.2 Gy in 29 #	0	1
Brachytherapy		
Prescribed dose (to 100 % isodose)	24 Gy in 3 fractions	24 Gy in 3 fractions
Applicator		
Tandem + Ovoids	32	6
Tandem + Ring	8	18
Tandem + Ring + Interstitial needles	0	2
Tandem + vaginal cylinder		
Single channel	1	0
Multi-channel	0	2

CT computed tomography, *MR* magnetic resonance, *FIGO* international federation of gynecology and obstetrics, *EBRT* external beam radiation therapy

Methods

Study population

The HDR brachytherapy clinical treatment plans of 69 patients treated with curative intent for cervical cancer were retrospectively reviewed. Of these patients, 83 % had squamous cell carcinoma, 13 % had adenocarcinoma and 4 % had adenosquamous carcinoma. Some patients (n = 41) were treated using a CT-imaged, Point A-based treatment planning approach (July 2006–July 2011) and others (n = 28) were planned using MR-imaged, volumetric-prescription techniques (July 2011–December 2013). Each patient underwent three brachytherapy insertions with a total of 207 treatment fractions studied. The summary of patient information is shown in Table 1.

Radiation therapy

All patients underwent external beam radiation therapy (EBRT) to between 45 and 52.2 Gy in 1.8 or 2 Gy fractions without midline boost. HDR brachytherapy of 24 Gy in three fractions was commenced either in the final week, or within a week of finishing EBRT. Each insertion was given 1 week apart, with the applicator removed after each insertion. All brachytherapy plans were prescribed to either Point A (in CT-based plans) or the 100 % isodose line (in MR-based plans).

Brachytherapy treatment planning

All patients had treatment applicators inserted under general anaesthetic and, after leaving recovery, had 3D imaging of the treatment volume with the applicator in situ for every fraction. CT scans (GE Lightspeed RT, GE Healthcare, USA and Toshiba Aquilion, Toshiba Medical Systems, Japan) were conducted in the Radiation Oncology department while MR scanning (Skyra 3T MRI, Siemens Healthcare AG, Germany) was undertaken in the Radiology department within the same hospital. CT scans were axially taken with the patient supine using 1.5–2.5 mm slice thicknesses while MR scans were taken para-axially using a 1.5 mm slice thickness [21].

Treatment planning was performed on the Nucleton PLATO^{TM} planning system (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden) for patients prior to December 2009 and on the Oncentra Brachy treatment planning system (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden) beyond this.

For all cases, ICRU 38 [3] and ABS [1] guidelines were followed for placement of Point A, bladder and rectal dose points. The rectum and bladder were contoured by Radiation Oncologists according to GEC-ESTRO guidelines and used to determine D_{2cc} (the minimum dose to the highest irradiated 2 cm^3 volume) of the bladder and rectum.

In MR-based patient cases, Radiation Oncologists contoured the HR-CTV in agreement with GEC-ESTRO and ABS recommendations [7, 8, 10, 11]. These were used to determine the HR-CTV D_{90} (the minimum dose received by 90 % of the HR-CTV), HR-CTV D_{98} (the minimum dose received by 98 % of the HR-CTV) and HR-CTV D_{100} (the minimum dose received by the entire HR-CTV).

For CT-based treatment plans, the prescription dose was first normalized to Point A using a standard departmental loading. This plan was then manually optimized by altering dwell weights and positions in order to keep maximum biologically equivalent 2 Gy doses (EQD_2) to a 2 cm^3 volume (D_{2cc}) of the bladder and rectum to $D_{2cc} < 90$ Gy for bladder and $D_{2cc} < 75$ Gy for rectum without compromising coverage of Point A.

For MR-based volumetric planning, initial planning stages were the same as CT-based planning, however optimisation of dose distributions were completed based on visualisation of the volumetric coverage of the HR-CTV whilst monitoring bladder and rectum D_{2cc}. Dose was prescribed to the 100 % isodose line, which surrounded the HR-CTV, during the transition from CT to MR-based planning as directed by the Radiation Oncologists. Optimisation in these cases occurred using a combination of manual optimisation, graphical optimisation or inverse planning based on the treatment applicator used and the size of the HR-CTV.

Post radiotherapy follow-up (average of 36 months) of CT-based cervix brachytherapy patients in this centre indicated an EQD_2 dose of 83 Gy to Point A resulted in local control rates of 88 and 95 % without and with combined chemotherapy respectively. There was a complication rate of 15 % including grade 3 or 4 complications to the bladder, rectum and sigmoid colon for these patients. From these in-house figures, it was decided to try and maintain similar doses to Point A as previous CT-based plans when introducing MR-based volumetric prescriptions but with the aim of improving HR CTV coverage where necessary and decreasing the bladder, rectum and sigmoid doses to reduce complications.

Dose analysis

Statistical analysis of dosimetric data was performed using paired samples (two-sided *t* test) to determine significance and the Pearson correlation coefficient to determine any relationships between values. Doses for both EBRT and HDR brachytherapy were first converted to biological equivalent doses for 2 Gy fractions (EQD_2) using the linear quadratic model with $\alpha/\beta = 3$ Gy for OAR and $\alpha/\beta = 10$ Gy for the target in order to allow addition of EBRT radiation dose for each patient treatment.

Comparisons between cases planned using CT-imaged, Point A prescriptions and those using MR-imaged, volumetric prescriptions were performed for both ICRU and D_{2cc} doses for bladder and rectum as well as Point A. In addition, the HR-CTV D_{90}, D_{98} and D_{100} were compared to Point A doses and the relationship between HR-CTV dose and the volume encompassed by the HR-CTV for each volumetrically planned patient was determined.

Results

The patient population between the CT and MR-based arms contained similar ratios of tumour staging, suggesting that a comparison of the two patient groups could be achieved with minimal influence overall on differences in

Table 2 Comparison of total EQD_2 doses between CT- and MR-based planning. Doses given as mean ± SD

	Point A dose	Bladder ICRU dose	Bladder D_{2cc} dose	Rectum ICRU dose	Rectum D_{2cc} dose
All patients (n = 69)	81.0 ± 6.2	96.3 ± 31.7	99.7 ± 20.5	72.4 ± 12.4	71.8 ± 11.9
CT-based plans (n = 41)	82.7 ± 5.8	98.0 ± 30.0	105.9 ± 18.0	75.2 ± 12.4	74.5 ± 13.0
MRI-based plans (n = 28)	77.9 ± 5.7	92.6 ± 34.7	89.8 ± 20.8	67.7 ± 11.0	67.7 ± 9.1
Difference CT-MRI (Gy)	−4.8	−5.4	−16.1	−7.5	−6.8
Significance	p = 0.0002	p = 0.26	p = 0.001	p = 0.008	p = 0.009

EDQ_2 biologically equivalent dose in 2 Gy fractions, *CT* computed tomography, *MR* magnetic resonance, *ICRU* international commission on radiological units (ICRU), *D_{2cc}* minimum dose to the hottest 2 cm^3 of the volume

tumour sizes. The average EBRT EQD_2 doses were 1.2 Gy higher in the CT-based arm, also indicating that total EQD_2 doses would not be greatly affected by EBRT differences.

There was a significant decrease in brachytherapy EQD_2 when shifting from CT-based prescription planning to MR-based prescription planning. The EQD_2 Point A dose for brachytherapy fell from 36 to 30 Gy and the overall total EQD_2 to Point A dropped by a mean of 4.8 Gy ($p < 0.0003$) due to the lower brachytherapy doses. All OAR doses were also reduced using MR-based planning compared to CT-based planning. These decreases were determined to be significant ($p < 0.03$) for all OAR doses except for the bladder ICRU point. Results of these are shown in Table 2.

Looking more closely at MR-based data, the correlation between the HR-CTV D_{90}, HR-CTV D_{98}, HR-CTV D_{100} and Point A doses to the size of the HR-CTV itself was considered. Figure 1 shows the relationship between these values. Overall there is little dependence on the size of the HR-CTV for HR-CTV D_{90}, D_{98}, and D_{100} doses, with Pearson correlation coefficients of 0.13, 0.06 and 0.06 respectively indicating that all patients received roughly the same volumetric doses regardless of HR-CTV size. However there was a HR-CTV volume dependence on Point A dose with a Pearson correlation coefficient of 0.67.

There was no significant difference between Point A doses and HR-CTV D_{100} for volumes smaller than 20 cm^3 or between HR-CTV D_{98} and Point A doses for volumes between 20 and 35 cm^3 although there were significant differences ($p < 0.001$) between Point A and HR CTV D_{90} doses in these ranges. Results are indicated in Table 3. For volumes above 35 cm^3 the sample size was not large enough to provide statistical analysis however it appears that the relationship between Point A and HR CTV D_{90} dose is established at volumes in this range.

When considering the volume of the HR-CTV and the associated bladder and rectal doses (both ICRU and D_{2cc}), there was minimal dependence on dose with respect to the HR-CTV size with correlation coefficients of 0.17 for the bladder and 0.15 for the rectal dose (Fig. 2). ICRU and D_{2cc} doses correlated well with each other for both MR-based and CT-based treatments and had Pearson correlation coefficients of 0.66 and 0.56 for the rectum and bladder respectively.

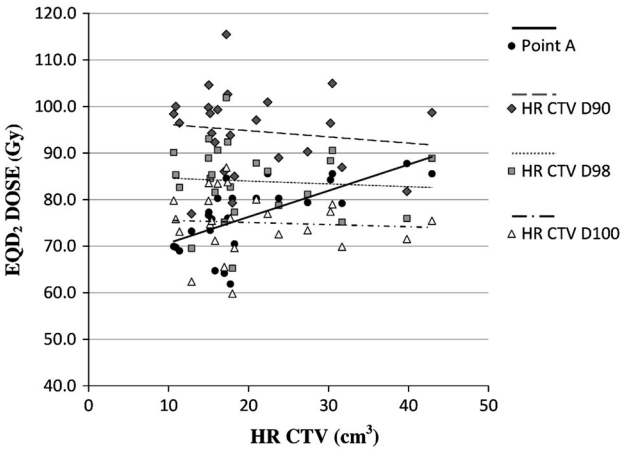

Fig. 1 Plot of EQD_2 doses for Point A, HR-CTV D_{90} and HR-CTV D_{100} against HR-CTV for MR-imaged volumetric-based treatment plans

Discussion

In 2010, Tanderup et al. completed a MR-based planning study looking into the difference between Point A prescribed treatments and HR-CTV volumetrically prescribed treatments [22]. They determined a volume dependence between Point A doses and the size of the HR-CTV for standard plans that did not incorporate any OAR constraints but did not report on relationship between Point A dose and HR-CTV size for optimised treatment plans. From their non-optimised data, they found that Point A corresponded to the HR-CTV D_{90} for a volume of 33 cc. As their data set had an average HR-CTV size of 31 cc, they concluded that Point A 'provided a reasonable estimate of the average HR-CTV D_{90}' and that 'it is possible to go from prescription at Point A to prescription to HR-CTV

Table 3 Analysis of dose for various HR-CTV volume groups

	Mean EDQ_2 Dose ± SD (Gy)			
	Point A	HR-CTV D90	HR-CTV D98	HR- CTV D100
All patients (n = 28)	77.9 ± 5.7	94.7 ± 8.8	84.0 ± 8.1	75.1 ± 6.6
HR-CTV < 20 cm^3 (n = 19)	73.0 ± 6.3	95.2 ± 9.7	84.1 ± 9.2	75.0 ± 7.9
HR-CTV 20–35 cm^3 (n = 7)	82.1 ± 2.9	95.1 ± 6.6	84.0 ± 5.7	75.6 ± 3.7
HR-CTV > 35 cm^3 (n = 2)	86.7 ± 1.6	90.2 ± 12.0	82.4 ± 9.1	73.5 ± 2.8

The values underlined are those that are not significantly different from the corresponding Point A ($p < 0.0007$). Statistical analysis of volumes of HR-CTV greater than 35 cm^3 was not performed due to the small sample size (n = 2)

HR-CTV high-risk clinical target volume, *EDQ_2* biologically equivalent dose in 2 Gy fractions, *D90* minimum dose to the hottest 90 % of the volume, *D98* minimum dose to the hottest 98 % of the volume, *D100* minimum dose to the hottest 100 % of the volume

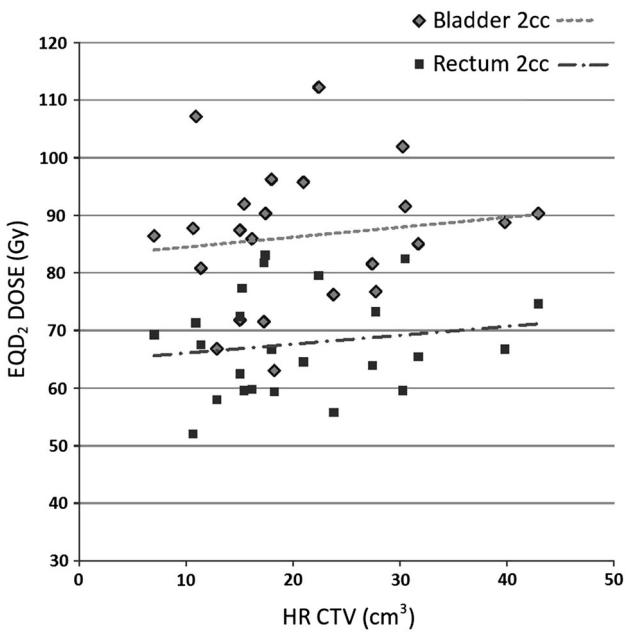

Fig. 2 Plot of EQD_2 doses for bladder and rectum D_{2cc} against HR-CTV for MR-imaged volumetric-based treatment plans

without introducing any major dose escalation or de-escalation across the patient population.'

It would appear that the cohort of patients within the current study have smaller HR-CTV (average volume of 20.5 cm^3, range between 10.6 and 42.9 cm^3) than those in other published studies, making this data unique in that regard and providing evidence that a generalised 'new' HR-CTV D_{90} to 'old' Point A relationship may not be appropriate for all departments. The centre in the current study went from an 'old' (CT-based) brachytherapy EQD_2 Point A dose of 36 Gy to a 'new' EQD_2 HR-CTV D_{90} of 49 Gy with a Point A dose of 30 Gy. In order to fulfil the Tanderup et al. criteria [22] of using the 'old' Point A prescription dose to match the 'new' HR-CTV D_{90} dose, the centre in this study would have to reduce the average HR-CTV D_{90} dose by 36 %, effectively giving these patients a total EQD_2 dose of 60 Gy to Point A (for combined EBRT and brachytherapy). This is a significant dose de-escalation to Point A and well below any endorsed dose recommendation. Granted these smaller HR-CTV were mostly likely being 'over-treated' in the past, given the limited available dose-outcome data for these new prescription conventions at the present time and the history of good clinical outcome within the department, the centre in this study was willing to effectively dose-escalate these small HR-CTV patients instead of reducing doses by such a large amount.

When adopting a volume-based prescription methodology, the fundamental aim is to prescribe consistent doses to the HR-CTV. The low correlation coefficients between HR-CTV D_{90}, D_{98} or D_{100} and HR-CTV size within the current study indicate the HR-CTV D_{90} dose was consistent across the majority of treatment volumes and at a dose level similar to other published studies, which is an ideal outcome. Table 4 gives a summary of results from the current audit compared to other published studies [12, 14, 19, 22–25].

However, the Point A dose showed a dependence on the volume of the HR-CTV, particularly for volumes below 20 cm^3. The present study indicates a correlation between Point A and the HR-CTV D_{100} for volumes less than 20 cm^3, the HR-CTV D_{98} for volumes between 20 and 35 cm^3 and HR-CTV D_{90} for volumes greater than 35 cm^3.

One of the largest studies into the dose-outcome relationship for brachytherapy treatment of cervix cancer is currently being undertaken. The EMBRACE study (www.embracestudy.dk), along with the Retro-EMBRACE study (www.retroembrace.com) is focussed on generating a large database for cervix brachytherapy treatments that have been planned using MR-imaged, volumetric prescriptions. Retro-EMBRACE, being a retrospective study, did not define a dose prescription methodology however the EMBRACE study is prospective and has distinct protocols for cervix brachytherapy treatment prescription volumes although the value of the prescription dose is dependent on

Table 4 Comparison of parameters between this study and other published studies for MR-based brachytherapy treatments

	Patients/fractions	HR-CTV (cm^3)	Mean EDQ_2 dose ± SD (Gy)			
			Point A	HR-CTV D90	Bladder D_{2cc}	Rectum D_{2cc}
This study	28/84	20 ± 9	78 ± 6	95 ± 9	90 ± 21	68 ± 9
Georg (2012) [19]	141/282			84–89	95 ± 22	65 ± 12
Pötter (2011) [17]	156/312			93 ± 13	86 ± 17	64 ± 9
Beriwal (2011) [12]	44/44	29	78	82	82	57
Tanderup (2010) [20]	72/166	38 ± 20		91 ± 7	73 ± 6	66 ± 5
Lindegaard (2008) [22]	21/56	34 ± 12	82 ± 6	91 ± 8	73 ± 6	67 ± 6
Koom (2007) [21]	71/355	47 ± 19	78 ± 7	85 ± 10	84 ± 15	67 ± 9
Kirisits (2005) [10]	22/93	34 ± 17	82 ± 9	87 ± 10	83 ± 9	64 ± 6

HR-CTV high-risk clinical target volume, *EDQ_2* biologically equivalent dose in 2 Gy fractions, *MR* magnetic resonance, *D90* minimum dose to the hottest 90 % of the volume, *D_{2cc}* minimum dose to the hottest 2 cm^3 of the volume

individual departmental protocols. The EMBRACE study protocol states "for centres previously prescribing using Point-A, it is recommended to use the Point-A dose as the dose (D90) used for prescription to the HR-CTV". Here again, the risk of de-escalating doses in smaller HR-CTVs is high if using this methodology. Presently there is no clear understanding on the precise radiation therapy dose needed so there is an inherent risk in radically changing the dose given to small HR-CTV cervix brachytherapy patients from what has historically been given to Point A.

Several single-centre studies have shown that higher doses to the HR-CTV achieve better rates of local control [12, 14, 16–20, 22–24] and MR-based brachytherapy treatment planning can incorporate dose escalation through improvements in dose optimisation as shown in the current study. Pötter et al. presented data on 156 patients treated using MR-based volumetric planning over a 7 year period which indicated a HR-CTV D_{90} EQD_2 dose of 93 Gy provided overall local control rates at 3 years of 95 %, with higher local control rates (98 %) for smaller tumour volumes [19].

The small HR-CTVs found in this study could possibly be due to the timing of HDR brachytherapy or the staging at which patients' present. In the centre in this study HDR brachytherapy is given after the completion of EBRT, allowing the maximum tumour shrinkage. The study by Tanderup et al., Beriwal et al. and Lindegaard et al., indicated that those patients were treated with brachytherapy during the last 2 weeks of EBRT [14, 22, 25]. Brachytherapy treatments at the Medical University of Vienna are given in the final 2 weeks of EBRT for large tumours or started simultaneously with EBRT for smaller tumours [12, 19, 23]. The earlier schedule of brachytherapy treatments could provide a possible reason for the larger tumour volumes. Further analysis in the histology and pathology of the treated patients may also provide information into the small HR-CTVs generated and a national study into HR-CTV sizes is currently under development to determine if this is possibly a regional effect. Each Radiation Oncologist in the current study has been trained in contouring through GEC-ESTRO courses and a previous study into the inter-observer differences for HR-CTV contouring revealed only a 10 % volume difference between Radiation Oncologists [21].

This information is useful in those centres that are contemplating transitioning from Point A-based to volume-based prescriptions. By adhering to these relationships the risk of reducing the EQD_2 total dose to Point A to below 70 Gy is minimized, particularly for those centres that have a patient cohort with small HR-CTVs.

The major limitation to this study was the lack of larger HR-CTVs incorporated in the study analysis and the small sample size overall. Data from EMBRACE, RetroEMBRACE and a proposed national survey should provide a greater and wider sample size to test this hypothesis.

Conclusion

When moving from Point A-based prescription to volume-based prescription there is an increased need to analyse the dose-volume relationship. In order to keep brachytherapy doses consistent across a range of HR-CTV sizes there must be a relationship between the volume of the HR-CTV and the prescription dose. Current published recommendations suggest prescribing the 'old' Point A dose to the 'new' HR-CTV D_{90}. This is highly useful volumetric prescription methodology however there is still uncertainty as to the value of the prescription dose and thus there is a risk for centres implementing this methodology to radically change from their previous dose distributions if their HR-CTV volumes are less than 35 cm^3.

This study has shown that by separating the prescription volume into HR-CTV size categories of less than 20 cm^3, between 20 and 35 cm^3, and more than 35 cm^3 the HR-CTV D_{90} doses can be made uniform across all volumes without risk of dose de-escalation and can also be directly linked to the traditional Point A prescription. The benefit of a direct link to the Point A dose is to maintain an awareness of the traditional prescription paradigms used in brachytherapy, which is often still a starting point even in volume-optimised treatment plans, and to better understand how volume-based prescriptions affect conventional dose points.

The suggested protocol for centres previously using Point-A as a prescription point and considering progressing to HR-CTV based prescriptions, is to match previously used Point-A doses to:

- (D100) used for prescription to the HR-CTV if the HR-CTV is less than 20 $cm^{3.}$
- (D98) used for the prescription to the HR-CTV if the HR-CTV is between 20 and 35 $cm^{3.}$
- (D90) used for the prescription to the HR-CTV if the HR-CTV is greater than 35 $cm^{3.}$

Additional clinical dose-outcome data is required in order to have a better understanding of what value the prescription dose should be and it is hoped the results of the RetroEMBRACE and EMBRACE studies will provide this.

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