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Title: A survey of Australian and New Zealand clinical practice with neoadjuvant systemic therapy for breast cancer

Running head: Neoadjuvant clinician survey

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Abstract

Aim

Neoadjuvant systemic therapy (NAST) has become an established treatment option for women with operable breast cancer. We aimed to better understand NAST treatment patterns, barriers and facilitators in Australia and New Zealand.

Methods

We undertook a cross-sectional survey of the current clinical practice of Australian and New Zealand breast cancer specialists. Questions included referral patterns for NAST; patient selection; logistics; decision-making and barriers.

Results

Of 207 respondents, 162 (78%) reported routinely offering NAST to selected patients with operable breast cancer (median 9% of patients offered NAST). Specialty, location, practice type, gender or years of experience did not predict for offering NAST. 45% and 58% wanted to increase the number of patients who receive NAST in routine care and in clinical trials, respectively. Facilitators included the multidisciplinary team meeting and access to NAST clinical trials. Specialist-reported patient barriers included: patient desire for immediate surgery (63% rated as important/very important); lack of awareness of NAST (50%); concern about progression (43%); and disinterest in downstaging (32%). Forty-three percent of participants experienced system-related barriers to the use of NAST, including: other clinicians' lack of interest (27%); lack of clinical trials (24%); and unacceptable wait for a medical oncology appointment (37%).

Conclusion

This group of Australian and New Zealand clinicians are interested in NAST for operable breast cancer in routine care and clinical trials. Patient- and system-related barriers that prevent the optimal uptake of this treatment approach will need to be systematically addressed if NAST is to become a more common approach.

Introduction

Neoadjuvant systemic therapy (NAST) has become a treatment option for selected women with larger (>2cm) early stage breast cancer. Patients who receive NAST followed by optimal locoregional therapy have equivalent disease-free and overall survival outcomes to those who receive systemic therapy after surgery¹. NAST has some advantages over a surgery-first approach including: downstaging to breast conserving surgery for some women who would otherwise have required a mastectomy; reducing the volume of surgically resected breast and axillary tissue; and providing prognostic information depending on the degree of tumour response²⁻⁴. Maximal response, referred to as pathological complete response (pCR), refers to a lack of identifiable invasive tumour on histopathologic examination of the breast and lymph nodes⁵. A pCR is achieved in 50% of hormone receptor negative, HER2 positive breast cancer (15% of the breast cancer population), and in 33% of hormone receptor negative, HER2 negative breast cancer (triple negative, 15% the breast cancer population)⁴. Lesser responses can be quantified using a score such as the residual cancer burden (RCB), which has prognostic value in hormone receptor positive disease, where approximately 15% patients achieve a pCR³. Novel treatment strategies for early breast cancer may receive fast-track provisional regulatory approval based on pCR as an early endpoint, particularly in triple-negative and HER2 positive disease where pCR is more likely to act as a surrogate of survival outcomes. However meta-analyses have not yet shown a correlation between pCR and disease-free or overall survival endpoints^{2,4} and confirmatory results from trials powered for these survival outcomes are required for full approval⁶.

Given equivalent survival outcomes, NAST is an option that may be preferred by some patients with operable breast cancer, however the rate of use in Australia and New Zealand appears low, at fewer than 3% of all operable breast cancer patients⁷. According to one report, approximately 3.8% of women with operable breast cancer in the United States receive NAST, however

benchmarking is difficult as the optimal rate is not known⁸. International guidelines support the use of NAST as an option for operable breast cancer⁹⁻¹¹, patient advocates support the use of neoadjuvant clinical trials¹², and patients with a past diagnosis of breast cancer also endorse the option of NAST being discussed with patients as part of routine clinical care¹³. As such, NAST is expected to remain an important treatment option for women with early breast cancer and their treating clinicians.

Data are limited on routine clinical practice, facilitators and barriers to the use of NAST both internationally and in Australia/New Zealand. We sought to understand how NAST is currently used in Australia and New Zealand, in order to inform strategies to optimise its appropriate use in routine practice and in clinical trials.

Material and methods

Population and design

A cross-sectional cohort study of Australian and New Zealand breast cancer specialists was undertaken. Eligible participants were clinicians who treat patients with breast cancer, including medical oncologists, surgeons, radiation oncologists and breast physicians. An email invitation was sent to clinician members of the Australia and New Zealand Breast Cancer Trials Group (ANZBCTG), the Medical Oncology Group of Australia, Breast Surgeons of Australia and New Zealand (BreastSurgANZ) and the New Zealand Breast Special Interest Group, the major professional bodies representing breast cancer specialists in the region. Some clinicians are members of multiple organisations, however to maintain members' confidentiality, only duplicates between the ANZBCTG distribution list and the BreastSurgANZ members on their publically available website could be removed. A total of 930 invitation emails were sent, excluding known duplicates. The invitation email contained brief description of the study and a

hyperlink to participate in an online survey, hosted by the ANZBCTG. Two reminder emails were sent.

Questionnaire

The questionnaire was developed by a multidisciplinary group including medical oncologists, a surgeon, a psychologist and a consumer, then pre-tested and modified based on feedback from a small group of clinicians who had not previously seen it. Three levels of participation were possible. Surgeons and medical oncologists, as the target audience, were offered (1) a core questionnaire and (2) an optional supplementary questionnaire (Appendix). Other specialists were offered (3) an abbreviated questionnaire about demographics and barriers only. This design aimed to optimise the completion rate by allowing clinicians to minimise their time commitment by completing the core questionnaire only, and to add value if they were willing to spend additional time on the supplementary questionnaire. The core questionnaire included: demographics; neoadjuvant referral patterns; patient and tumour characteristics for which NAST was considered appropriate; barriers to the use of NAST; and interest in offering NAST as a treatment option for routine care and clinical trials. The supplementary questionnaire included questions on clinical workup and management of NAST patients; decision making; perceived patient experiences; and patient selection for clinical trials compared with routine care. Data from this survey about clinical decision-making control preferences about neoadjuvant therapy have been published previously, and will not be reported here¹⁴.

Analysis

Descriptive statistics were used to describe responses. Demographics were reported as frequencies, medians and proportions. Pearson chi-squared tests were used for categorical data,

and t-tests for continuous data. Statistical significance was set at a p-value of 0.05 for all tests. A logistic regression model was fitted including potential predictors for offering NAST.

This study was designed and conducted according to principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines. All participants provided informed, voluntary consent prior to participation. The study was prospectively approved by the Hunter New England Human Research Ethics Committee and was prospectively registered on the Australia and New Zealand Clinical Trials Registry (www.anzctr.org.au, ACTRN12613000658718).

Results

Core questionnaire

Between April and July 2014, 225 responses were received. After excluding 13 who reported not treating breast cancer patients and 5 who did treat breast cancer but indicated that they did not want to complete the survey, 207 responses were analysed, representing a conservative response rate of 23% (207/917). Eighty clinicians answered the supplementary questionnaire. Responses were received from Australia (n=155) and New Zealand (n=52): 112 surgeons (54%), 87 medical oncologists (42%), 6 radiation oncologists (3%) and 2 breast physicians (1%). This included 120 metropolitan, 81 regional and 6 rural practitioners. Fifty-two were primarily academic, 111 public hospital and 44 private practitioners. There were equal numbers of males and females. Forty-five respondents (22%) reported not offering NAST, and 162 (78%) reported routinely offering NAST to selected women with operable breast cancer.

Respondents saw a median of 80 newly diagnosed breast cancer patients per year, of whom a median of 80% (interquartile range [IQR] 70-80%) were considered to have operable disease at the time of diagnosis. Clinicians reported offering NAST to a median of 9% (IQR5-15%) of their

patients with operable disease, of whom a median of 90% (IQR 70-90%) agreed to see a medical oncologist; a median of 85% (IQR 70-90%) of those who saw a medical oncologist started NAST. Reasons for recommending or offering NAST, by the 162 respondents who use this treatment strategy, are shown in Figure 1. NAST was offered as a treatment option for selected patients with for all breast cancer subtypes, shown in Table 1, but more frequently to women with HER2 positive and triple negative cancers. Comparison of subtypes, by hormone receptor and HER2 status, did not reach statistical significance. The HER2 positive and triple negative subtypes were also numerically more likely to be offered NAST for a smaller primary tumour size. In univariate analysis, >10 years of experience as a specialist predicted for offering NAST ($p=0.048$), but specialty, location, practice type and gender were not significant predictors. In a multivariate model including specialty, location, practice type, gender or years of experience there were no significant predictors for offering NAST (data not shown).

Barriers

Table 2 lists patient, system, clinician and clinical trial-related barriers to the use of NAST. Of the 165 responses to this part of the questionnaire, more non-surgeons than surgeons reported clinician or system-related barriers (37% vs 73%, $p<0.001$). The most commonly reported barriers overall were patient-related: desire for immediate surgery, lack of awareness of NAST, fear of progression on NAST, and lack of interest in downstaging. Compared with surgeons, more non-surgeons indicated that patients' lack of awareness of NAST (60% vs 41%, $p=0.016$), other clinicians' disinterest in NAST (43% vs 13%, $p<0.001$), and lack of NAST clinical trials (41% vs 7%, $p<0.001$) to be important barriers.

Interest in offering NAST in routine care and in clinical trials

Of 165 responses to this question, 74 (45%) and 96 (58%) indicated a preference to increase the number of patients who receive NAST as part of routine care and as part of a clinical trial respectively. Ninety-one (55%) felt that the number of their patients given NAST in routine care was appropriate, and 69 (42%) felt that the right number of patients are accessing NAST clinical trials. Importantly, there were no respondents who believed that NAST is being given too often, as routine care or in clinical trials. Fifty-eight (35%) had enrolled one or more patients on a NAST clinical trial. Considering only the 45 respondents who did not routinely offer NAST for operable breast cancer, 20 (44%) were interested in offering more of their patients NAST in routine care, and 29 (64%) were interested in offering more patients NAST in a clinical trial. In sum, 193/207 (93%) of respondents demonstrated interest in offering NAST to at least some of their patients with operable breast cancer.

Supplementary questionnaire

NAST patient workup and treatment

In the supplementary questionnaire, 77/80 (96%) respondents indicated that a core biopsy was required to make treatment decisions, and for 64 (80%), a core biopsy was done as the first diagnostic biopsy for these patients. Fifty-six (70%) place a radio-opaque or other marker in the breast primary, while only two (3%) place a marker in involved or suspicious lymph nodes. For staging of clinically node negative patients, 42/80 (53%), 45 (56%), 1 (1%) and 14 (18%) would order a bone scan, CT chest abdomen and pelvis, PET scan and breast MRI respectively. For those with clinically involved nodes, the proportions were 61/80 (76%), 61 (76%), 2 (3%) and 13 (16%) respectively. In clinically node negative patients at the time of diagnosis, a sentinel node procedure was done routinely prior to NAST by 26 (33%) and after NAST by 47 (59%). Six (8%) respondents would always recommend an axillary dissection for NAST patients. Seventy-one

(89%) felt that it was acceptable for up to 14 days to elapse after diagnosis before a treatment decision was made, and 50 (62%) felt that treatment should start within 14 days of that decision.

Patient selection for clinical trials

Respondents were more likely to offer NAST if a clinical trial was available for patients with the following characteristics: smaller primary tumour (51/78 [65%] of respondents); oestrogen receptor positive (62 [80%]) cancer; and candidates for breast conserving surgery (63 [81%]).

Decision-making and patient experience

Patients were presented at the multidisciplinary team meeting (MDT) in every NAST case by 29/76 (38%) of respondents, most of the time by 19 (25%), some of the time by 24 (32%) and never presented at the MDT by 4 (5%). The decision about whether to have NAST was made at the time of the initial specialist consultation (43/76 [56%]), the MDT (24 [31%]), at a follow-up appointment (8 [11%]) or over the phone (2 [3%]). Seventy-six percent of respondents had not identified greater rates of anxiety in patients receiving NAST compared to those receiving adjuvant systemic therapy. Eighty-six percent (66/76) stated that they would offer a decision aid developed specifically for women with operable breast cancer who were candidates for NAST.

Discussion

The majority of clinicians in this sample reported interest in NAST for operable breast cancer, offering and in some instances recommending NAST to their patients. Reasons included: to facilitate immediate breast reconstructive surgery and to downstage locally advanced or larger breast cancer. However, barriers were also identified. To improve access to this treatment option, these patient, clinician, system and clinical trial-related barriers will need to be addressed.

Our survey could not directly ascertain the total proportion of patients being offered NAST, however an indirect estimate is 6-7%, based on the proportion who were offered, agreed to see a medical oncologist, and then went on to receive NAST. While respondents reported 'routinely' offering NAST to operable patients, the proportion was low, suggesting that only highly selected patients are offered this treatment strategy. Read et al. report that 2.75% of Australian and New Zealand women with operable breast cancer receive NAST, based on an unpublished quality audit⁷. Our estimated rate is likely to be spuriously high due to overrepresentation by respondents with an interest in NAST.

Read et al. reasonably assert that any woman who is clearly a candidate for chemotherapy should have the option to receive it before surgery. Increasingly, the decision about chemotherapy is strongly influenced by tumour subtype as indicated by hormone receptors, HER expression and in some cases multiparametric gene expression profiling. Patients with triple negative and HER2 positive tumours are more likely to receive chemotherapy compared with those hormone receptor positive tumours⁹. Whilst these factors are all assessable in the pre-operative setting to allow a judgement about whether neoadjuvant chemotherapy is indicated, lack of routine universal hormone and HER2 receptor testing on diagnostic core biopsies may deter surgeons from considering NAST. An Australian single institution retrospective study found that chemotherapy was recommended for 99% of lymph node positive patients, and 90% of patients with tumours >2cm in size¹⁵. Patients who are candidates for adjuvant chemotherapy may prefer to receive their chemotherapy pre-operatively if given the opportunity.

One might consider more recently qualified, metropolitan, or academic clinicians to be more likely to offer NAST, however we could not identify predictors of offering NAST. This may be due to respondents having a high average level of interest in NAST, and a relatively small sample size. The large proportion of clinicians who present their NAST patients at the MDT prior to surgery

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indicates that interdisciplinary communication is occurring in this area. Still, 27% felt that other clinicians' disinterest in NAST was an important barrier.

Compared with surgeons, medical oncologists' workflow may require a greater fundamental change to adapt to routine NAST. Proffered reasons for offering NAST included allowing time for surgical planning and for genetic testing. In some areas, the coordination of immediate breast reconstruction is complex, and may require more planning time than routine breast cancer surgery^{16,17}. Also, decision-making about breast reconstruction is complex due to the range of options available, and patients may benefit from additional time to make a decision about their preferred option¹⁸. The use of NAST in these situations shifts the immediacy of treatment from surgeons to medical oncologists, who are used to having time after surgery before giving adjuvant chemotherapy. Potential solutions include allocating neoadjuvant-specific new patient appointments, having a combined clinic with medical oncologists and surgeons, or having a rapid response system for NAST referrals. In Germany, the pathway to NAST is more straightforward, as breast surgeons also prescribe chemotherapy for their patients. Having one clinician present both sides of the story means that biases towards offering one's own treatment first are less likely to be a factor in the discussion, whether overt or implied.

Considering the large proportion of patients in our study who, when offered NAST, were willing to see a medical oncologist and then went on to receive it, patient willingness does not appear to be a major barrier¹³. Despite this, clinicians indicated that patient-related barriers were the biggest impediment to NAST use. Barriers such as lack of prior awareness or unfounded concern about progression on chemotherapy may be addressed through increased awareness about NAST as an option, via breast cancer advocacy organisations and the media. More widespread use of NAST will increase awareness via discussions amongst patients, their families and the broader

healthcare community. The use of a decision aid has been shown to increase knowledge and improve decision-related outcomes, and may be warranted in this situation^{19,20}.

Clinical trials have accelerated the use of NAST, due to the promise of pCR acting as a surrogate endpoint for more rapid approval of new drugs and indications⁶. A lack of available neoadjuvant clinical trials was a commonly cited barrier, particularly for medical oncologists. The NeoSphere trial demonstrated a significantly higher pCR rate in patients who received pertuzumab along with standard chemotherapy and trastuzumab, leading to FDA approval and a change in clinical practice²¹. This finding is controversial due to the lack of a significant difference between trastuzumab and trastuzumab/lapatinib in the adjuvant ALTTO trial disease-free survival²², despite a 21% difference in pCR rate in the similar (but not identical) neoadjuvant NeoALTTO trial²³.

Statistical modelling has, however, demonstrated that a large difference in pCR would be required to show a small difference in disease-free survival, concluding that the neoadjuvant model remains an important drug development model²⁴. More than half of the clinicians we surveyed wanted to increase the number of patients treated on a NAST trial, and were willing to treat patients with lower risk characteristics such as smaller tumour size, candidates for breast conserving surgery and hormone receptor positive tumours. Access to clinical trial was limited, with only 35% reporting ever having a patient enrolled on a NAST clinical trial.

Patients who achieve pCR in the breast and lymph nodes have a better prognosis than those who do not achieve pCR, irrespective of immunohistochemical subtype⁴. This may be of value to clinicians and patients, however thus far no trial has demonstrated an advantage to additional adjuvant therapy in patients who did achieve pCR. Lack of pCR is an entry criterion for a number of clinical trials, such as the PenelopeB trial (NCT01864746), due to the need for novel treatment strategies in these poor prognosis patients.

Our study is limited by its low response rate, which is likely to be artificially low due to double counting of recipients who are members of multiple groups and survey invitations sent to non-breast cancer clinicians, thus inflating the denominator. It is not possible to quantify the number of non-responders who did not treat breast cancer patients and would have been ineligible.

Missing data increased with later questions, particularly the last set, regarding barriers.

Respondents typically had extensive experience treating breast cancer, and may have been more up-to-date on current evidence for breast cancer treatment. Rural and private practitioners were under-represented, which may bias the reported barriers. Techniques attempting to increase the response rate by identifying and removing ineligible participants from the denominator were unsuccessful.

Conclusion

This group of Australian and New Zealand breast cancer specialists are interested in offering their patients NAST in both routine clinical care and in clinical trial settings. There are patient and system related barriers that should be addressed in order for clinicians to be able to offer their preferred optimal treatment to their patients, and for patients to be able to access a treatment option that they may prefer. We are currently evaluating a decision aid for women with operable breast cancer who have been offered NAST, which may reduce patient-related barriers.

Conflict of interest statement

None of the authors declare a conflict of interest pertaining to this work.

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Figure

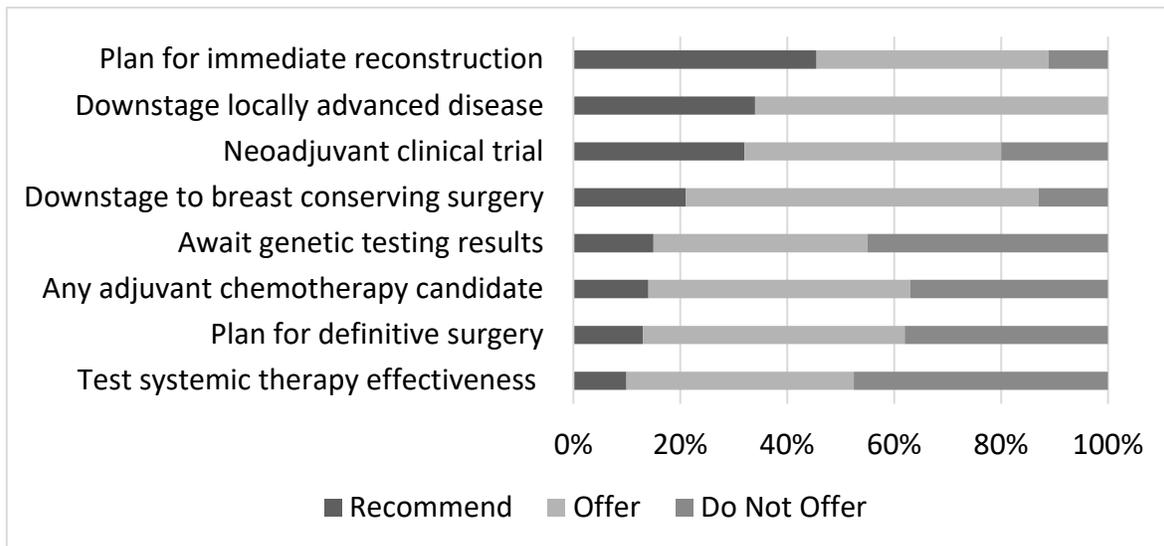


Figure 1. Clinicians' reasons for offering/recommending neoadjuvant systemic therapy

Table 1. Patient characteristics for whom clinicians would consider NAST.

		HR+/HER2-	HR+/HER2+	HR-/HER2+	TNBC	Total
		N=162†				
NAST offered to this subtype		65%	74%	76%	71%	71%
	<1cm	0%	0%	1%	1%	0%
	1-1.9cm	3%	7%	10%	12%	8%
	2-2.9cm	10%	21%	26%	22%	20%
	3-4.9cm	27%	22%	22%	23%	23%
	≥5cm	60%	50%	42%	42%	48%
Axillary lymph node status	+ or -	66%	84%	88%	89%	82%
Inoperable disease only		45%	21%	17%	20%	24%
If downstaging from mastectomy to BCS desired		51%	63%	64%	62%	60%
Any mastectomy candidate		22%	31%	33%	31%	29%
Clinical trial participants only		39%	26%	26%	32%	30%

† Respondents who reported offering NAST. BCS: breast conserving surgery; HR: hormone receptor; NAST: neoadjuvant systemic therapy; TNBC: triple negative breast cancer; +/-: positive/negative; BCS: breast conserving surgery

Table 2. Barriers to the use of neoadjuvant systemic therapy

	Important/very important, N (%)			p-value†
	Surgeon n=85	Non-surgeon n=80	Total n=165	
Patient factors				
Desire for surgery as soon as possible	54 (64)	50 (63)	104 (63)	0.891
Fear of progression on NAST	39 (46)	32 (40)	71 (43)	0.446
Not interested in downstaging	32 (38)	20 (25)	52 (32)	0.081
Lack of awareness about NAST	35 (41)	48 (60)	83 (50)	0.016
System/Clinician factors				
Other clinicians not interested	11 (13)	34 (43)	45 (27)	<0.001
Inability to obtain a timely medical oncology appointment	13 (15)	11 (14)	24 (15)	0.779
Unacceptable wait for chemotherapy	9 (11)	6 (8)	15 (9)	0.490
Too difficult to coordinate	9 (11)	9 (11)	18 (11)	0.892
Too difficult to get an appointment with other clinicians	8 (9)	5 (6)	13 (8)	0.451
Insufficient evidence for the use of NAST for operable breast cancer	7 (8)	8 (10)	15 (9)	0.694
Clinical trial factors				
No clinical trials available	6 (7)	33 (41)	39 (24)	<0.001
No institutional capacity for clinical trials	8 (9)	9 (11)	17 (10)	0.698
Competing adjuvant trials	4 (5)	3 (4)	7 (4)	0.761

†p-value (χ^2) for comparison of Surgeon and Non-surgeon for each factor. NAST: neoadjuvant systemic therapy.

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