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Title:
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Date:
2018-07-01

Citation:
Pattanasri, M., Elder, K., Nickson, C., Cooke, S., Machalek, D., Rose, A., Mou, A., Collins, J. P., Park, A., De Boer, R., Phillips, C., Pridmore, V., Farrugia, H. & Mann, G. B. (2018). Uptake of adjuvant breast cancer treatments recommended by multi-disciplinary meetings. ANZ Journal of Surgery, 88 (7-8), pp.745-750. https://doi.org/10.1111/ans.14368.

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Running title: Uptake of adjuvant breast cancer therapy

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Number of tables: 3

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ans.14368

Word Count (Abstract): 246

Word Count (Text): 2606

Word Count (References): 396

ABSTRACT

Purpose: Adjuvant therapy for breast cancer is routinely discussed and recommended in multidisciplinary meetings (MDMs). Current literature explores how treatments received by patients differ from national guidelines, however does not explore whether treatment is concordant with MDMs. This study provides an Australian perspective on the uptake of MDM recommendations and reasons for non-concordance.

Methods: A retrospective cohort study of patients with breast cancer presented at The Royal Melbourne Hospital MDM in 2010 and 2014 to investigate the concordance between MDM recommendations and treatment received.

Results: The study group comprised 441 patients (161 from 2010 and 280 from 2014). 375 patients were included in the analyses. Overall, 82% of patients had perfect concordance between recommended and received treatment for all modes of adjuvant therapy. Concordance to endocrine therapy was higher for invasive cancers than DCIS (97% versus 81%, $p<0.0001$). Concordance to radiotherapy was high and did not differ according to type of cancer or surgery (ranging from 88% to 91%). Concordance to chemotherapy recommendations was high overall (92%) and did not vary with nodal status. Women aged

over 65 years were least likely to be recommended for adjuvant therapy but most likely to concordant with the recommendation.

Conclusions: Uptake of MDM-recommended treatments is high. There is a minority of patients in whom MDM recommendations are not followed, highlighting that there are extra steps between recommendations at an MDM and decisions with patients. More attention to this issue is appropriate, and the reasons for non-concordance warrant further study.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in Australian women and currently the second most commonly diagnosed cancer in Australia.[1] Breast cancer outcomes have improved significantly over recent decades, due partly to earlier diagnosis but significantly to better treatments. Appropriate use of adjuvant therapies is a major contributor to improved treatments.

National guidelines for breast cancer treatments play a fundamental role in ensuring effective treatment. Concordance between guidelines and received treatments has been shown to vary greatly (45% to over 90%).[2-5] Several US studies have found that concordance rates for systemic adjuvant therapy to the National Comprehensive Cancer Network Guidelines (NCCN) are low to modest, with 45-63% of patients receiving the recommended therapies.[2,3] One study of 844 invasive breast cancer and DCIS patients found modest concordance for

adjuvant chemotherapy (63%) and adjuvant hormonal therapy (78%) but high concordance for radiotherapy (81%).[4] In the UK an audit of 194 invasive breast cancer patients found high concordance of radiotherapy treatments to guidelines (90%) but modest concordance for chemotherapy (74%).[5]

Multidisciplinary meetings (MDMs) have been developed in an effort to ensure that all breast cancer patients are recommended and receive appropriate adjuvant therapy, becoming the standard of care throughout the UK and Australia.[6] Harrison and colleagues[7] showed that the majority of respondents in a survey of 294 participants (including breast surgeons, oncologists and breast care nurses) regarded MDM meetings as effective. Decisions made by MDMs conform to evidence based guidelines, offer a more tailored individual treatment approach and result in increased patient satisfaction.[6,8] Previous research into levels of concordance has focused on issues such as patient age, comorbidities and patient choice as contributing factors.[2,5,9] A multi-disciplinary approach to breast cancer treatment often considers these factors and may choose not to recommend adjuvant therapy in the best interests of the patient.[10]

However, not all patients undergo treatment recommended by MDMs. Comparing treatments received to those recommended in MDMs may reveal another variant in the pathway between breast cancer treatment guidelines and clinical practice.

The aim of this study is to measure the concordance of treatment recommended at MDMs with treatments received for the three main forms of adjuvant treatment: radiotherapy, chemotherapy and endocrine therapy. This study will provide the first Australian perspective on the uptake of MDM recommendations amongst breast cancer patients.

METHODS

This was a retrospective cohort study of all patients who received breast cancer treatment at The Royal Melbourne Hospital (RMH) following breast cancer diagnoses in 2010 and 2014. These years were selected to allow comparison over time and to ensure adequate follow up and documentation would be available.

MDM recommendations and information regarding treatment received was obtained from electronic and/or paper sources at RMH. Recommendation for and concordance to adjuvant therapy was determined separately for endocrine therapy, radiotherapy, and chemotherapy. For radiotherapy and chemotherapy, treatment was assumed delivered if the patient had a treatment commencement date planned; endocrine therapy was assumed to have been delivered if the patient had accepted a prescription. Only planned treatment was captured in this study, adherence was not assessed.

Four key measures were examined for each therapy type: recommendation rates, concordance (treatment recommended by the MDM (yes or no) matching treatment delivered to the patient (yes or no)), negative predictive values (NPVs, the proportion of patients for whom treatment not recommended and not received) and positive predictive values (PPVs, the proportion of patients for whom treatment was both recommended and received).

These rates were assessed according to year, type of cancer (invasive/Ductal Carcinoma in Situ (DCIS)), type of surgery (mastectomy/Breast Conserving Surgery (BCS)), nodal status and age at diagnosis. Specifically, endocrine therapy was assessed separately for patients with DCIS and invasive cancer. Radiotherapy was compared separately for post-BCS and post-mastectomy patients, and according to DCIS and invasive cancer. Chemotherapy was assessed according to nodal involvement, for invasive breast cancer patients only. Age groups were split by <50, 50-64 and >65. This was selected due to the varied clinical recommendations amongst these age groups.

Non-concordance to MDM recommendations was further assessed, defined as treatment recommended but not delivered to the patient. The reason for non-concordance was categorised as patient choice (definitively written in the notes), patient comorbidities (statement about patient age/frailty/other comorbidities), patient circumstance (defined as when treatment course changed depending on patient circumstance/reassessment of situation) or other unknown reasons.

We report summary statistics and apply Fisher's Exact tests for differences between groups, using Stata/SE 14.2[11]. This study was approved by the Human Research Ethics Committee at the Royal Melbourne Hospital (QA2013163, February 2016).

RESULTS

A total of 441 patients from 2010 and 2014 (161 and 280 respectively) were identified. Sixty-six patients (15%) were removed from the analysis due to partial or completely missing data (44 from 2010 and 22 from 2014). Of the patients that were excluded, 56 had invasive cancer (35 from 2010, 21 from 2014) whilst 10 had DCIS (9 from 2010, 1 from 2014).

This left a total of 375 (85%) patients with complete information for analysis (Table 2). Approximately half of the diagnoses were screen-detected cancers, and half were diagnosed outside the screening program (diagnosed in the community). Most patients (79%) were treated for invasive cancer; this rate was higher in 2014 than 2010 (86% versus 76%, p = 0.02). Most patients received BCS (72%).

Recommendation and concordance to adjuvant therapy

Overall, 82% (95% CI 78%-85%) of patients had perfect concordance between recommended and received treatment for all treatments (Table 2) and this did not vary by year or age group.

Endocrine therapy

Patients with invasive cancers were more likely than DCIS patients to be recommended adjuvant endocrine therapy (91% vs 77%, p=0.003); recommendation rates were higher in 2014, but not to statistical significance.

Concordance was higher among invasive breast cancer patients (97% versus 81%, p<0.0001). Concordance was significantly lower for 2014 than 2010 for invasive cancer (95% versus 100%, p=0.03), but the difference was not statistically significant for DCIS patients (79% versus 88%,). The lower concordance among DCIS patients was driven largely by patients not taking up the recommended treatment (PPV 77%) rather than patients commencing treatment contrary to MDM recommendation (NPV 94%); this held for all age groups. There was no difference in concordance for invasive cancers amongst age groups.

Radiotherapy

Post BCS patients with invasive cancer were most likely to be recommended radiotherapy (87%), followed by those with DCIS (60%) then post-mastectomy patients with invasive disease (31%) (p<0.0005 between each group).

Radiotherapy was less likely to be recommended for women aged 65 or older (Table 3), with statistically significant differences for invasive breast cancer post-BCS patients

($p<0.001$) and invasive breast cancer post-mastectomy patients ($p=0.006$) but not for the 58 DCIS post-BCS patients. The lower than expected rate of RT recommendation in those over 65 is likely due to the opening of a local clinical trial- Post-Operative Radiotherapy Omission in Selected Patients with Early Breast Cancer Trial (PROSPECT) in 2010. Of the 20 DCIS patients who underwent mastectomy, one patient was recommended post-mastectomy radiotherapy.

Concordance to radiotherapy recommendations was high overall and did not vary with cancer or surgery type. Of note, invasive breast cancer patient concordance to adjuvant radiotherapy was similar following BCS or mastectomy (91% vs 88%). For post-mastectomy invasive breast cancer patients, non-concordance was driven largely by low uptake in the 31% of women recommended for radiotherapy (PPV=67%) rather than commencement of radiotherapy contrary to MDM recommendation (NPV=98%) and this was consistent across age groups and years. For post-BCS patients, both PPV and NPV contributed to non-concordance (e.g. for invasive breast cancer post-BCS patients, PPV=91% and NPV=93%). This was consistent by year and by age group, except possibly for DCIS patients younger than 50, although this was a small group for analysis (n=11).

Chemotherapy

Chemotherapy was recommended for 45% of invasive breast cancer patients and as expected more commonly for node-positive than node-negative patients (69% versus 32%, $p<0.0001$). No patient with DCIS was recommended for or received chemotherapy.

Older patients were less likely to be recommended chemotherapy (e.g. 64% of women younger than 50 years compared to 51% of women aged 50-64 and 28% of women aged 65 or older, $p<0.001$), and this difference remained within node-positive patients ($p<0.001$) or node-negative patients ($p=0.008$).

Concordance did not vary significantly with nodal status, year or age. However, uptake of recommended chemotherapy was lower in older women (PPV = 68% in women aged 65 years or older, compared to 92% in women aged under 50 years and 86% in women aged 50-64, $p=0.02$); these differences were significant within node-positive patients ($p=0.045$) but not node-negative patients.

Given the variation of chemotherapy recommendations to cancer subtype, which tend to vary with age, these results are difficult to interpret.

Reasons for patients not receiving treatments recommended by MDMs.

For the 64 patients who did not receive recommended treatments, our detailed patient record review showed that patient choice was the largest contributor for all therapies. Most

of these patients declined adjuvant therapy after having an informed discussion about risks and benefits with their clinician. Patient circumstance and patient co-morbidities played lesser roles (Table 3). In our study patient circumstance mainly included patients who initially had local disease which became metastatic and patients who developed other illnesses during their treatment course.

DISCUSSION

While many studies have compared treatments received to guidelines, few have assessed the concordance of recommendations at MDMs to treatment received. On the assumption that treatments recommended by the MDM will be individualised to each patient, we expected that rates of concordance for MDM recommended treatment would be higher than concordance to practice guidelines. The rates of concordance to adjuvant therapy obtained in this study were high. Overall perfect concordance to all adjuvant therapy recommendations was 82%, with concordance rates ranging from 81% to 95%. These rates were higher than previously published rates of concordance to national guidelines. This highlights the importance of considering individual patient factors when making treatment decisions, therefore studies that focus on compliance with guidelines must take this in to account when setting goals.

We hypothesized that with certain characteristics of illness there would be increased concordance to the recommended adjuvant therapy. For endocrine therapy and for post-BCS radiotherapy, those with invasive cancer were significantly more likely to be concordant with MDM recommendations than those with DCIS. For chemotherapy we found a higher

concordance rate in node negative as compared to node positive cancers. This is most likely a reflection of cancer subtype with recommendations for chemotherapy in triple negative or HER2 positive breast cancer being very strong, even if the cancer is node negative, whereas with ER positive HER2 negative cancer, even if node positive, the chemotherapy recommendation may be less definite, with the option of endocrine therapy alone.

It is likely that the varying rates of concordance for adjuvant therapy depending on the characteristics of illness may be due to shared decision making, with the patient making the final decision after adding her personal perspective while considering the MDM recommendation.

When comparing concordance between age groups we found that, despite a decreasing recommendation rate for endocrine therapy and radiotherapy for those over the age of 65, concordance rates in this age group remained similar if not greater than other age groups. MDM decisions are likely to reflect competing comorbidities in an older age group and as such will only recommend treatment where there is a more absolute benefit. Patients in this age group are also more likely to follow the advice and recommendations of health practitioners.

We did find however that uptake of recommended chemotherapy was lower in older women. Chemotherapy guidelines are often unclear in older women.[12] Buist et al[12] found that the majority of women with high risk early stage breast cancer over the age of 65 did not

receive chemotherapy. The majority of these women did have a discussion and/or referral to a medical oncologist but did not receive chemotherapy, highlighting the importance of the patient-doctor discussion in the patient's final decision.[12]

Non-concordance to MDM recommendation for adjuvant therapy

We found a minority of patients in whom MDM recommendations are not followed, demonstrating that there are extra steps between treatment recommendations at an MDM and treatment decisions. Patient choice was the largest reason for MDM recommendations not being concordant with treatment received, especially with endocrine and chemotherapy. This has been highlighted in previous research,[13] showing that patients were more likely to refuse adjuvant drug treatment, rather than radiation or surgery. As this study looked at post surgery MDM recommendations concordance to the MDM recommended surgery was not explored. It may be useful to expand on this in future studies.

In previous research reluctance to use adjuvant therapy in the elderly, ambiguity of certain criteria, patient choice and medical reasons accounted for a significant proportion of non compliance to guidelines. We found that the rate of treatment recommendation reduced for all forms of adjuvant therapy in patients over 65, which is consistent with this.

Literature exploring reasons for non-concordance to adjuvant therapy in breast cancer patients has demonstrated the significant role that clinicians and their relationships with the

patients play.[9] As suggested by Bickel and colleagues,[9] a patient's beliefs about the efficacy of a particular therapy and the adverse effects associated with it have been shown to be associated with receiving such therapy. Our study was unable to capture the conversations between the patient and clinician regarding the role of adjuvant therapy. It is possible therefore that the strength of the MDM recommendation and/or an individual clinician's level of commitment to the recommendation may have been portrayed in the discussions, leading to less inclination from the patient to accept the recommendation. This has been highlighted by Bhatta et al[14] demonstrating that in their cohort, perceived importance of adjuvant hormone therapy and the degree to which they valued their doctor's opinion correlated with overall compliance.

In light of these findings, the RMH MDM has moved away from a Yes/No model for each modality to a 5 level scale – Recommend, Discuss/Recommend, Discuss, Discuss/Not recommend, Not recommend. We expect that this should assist in the subsequent consultation with the patients. Further research on how the implementation of this new model translates into MDM concordance will be useful.

Limitations

There were limitations in our research. We excluded 15% of patients from our original data set in the final analyses, a large proportion of these from 2010 (67%). This resulted in a much smaller sample size for 2010 as compared to 2014.

For our statistical analyses, we combined patients from 2010 and 2014 despite finding some statistical differences. For example, there was a significant difference between the concordance rate for endocrine therapy for invasive cancers in 2010 as compared to 2014. We postulate this is likely due to a change in the MDM policy over the time course, in that in 2014 our MDM changed to recommending that endocrine therapy should be considered in most cases of DCIS but that this recommendation would not be strong.

Our study focused on the decision of the patient to accept the MDM recommendation and did not look at adherence to therapies. Research into how this translates into adherence to adjuvant therapy overall will be interesting for future clinical practice.

Conclusion

In this single centre study, concordance to adjuvant endocrine therapy, radiotherapy and chemotherapy in breast cancer treatment as recommended by MDMs is high (81% - 95%). These concordance rates appeared to differ depending on the cancer characteristics. A minority of patients did not receive the recommended treatment with most common reason for both invasive cancer and DCIS being due to patient choice.

Overall, our study provide key information to aid in the understanding of the steps between the recommendations of these adjuvant therapies and the actual receipt of these recommendations.

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Tables

Table 1: Patient Demographics according to age at diagnosis, type of cancer (DCIS or invasive), method of detection (screening versus otherwise in the community) and type of surgery (BCS versus mastectomy). Figures show N(%) unless stated otherwise.

	2010	2014	Combined
N (%)	117 (35%)	258 (65%)	375 (100%)
Age mean (range)	60 (29-94)	59 (28-90)	59 (28-94)
DCIS	61 (48-72)	58 (37-89)	59 (37-89)
Invasive	60 (29-94)	60 (28-90)	60 (28-94)
Type of cancer			
DCIS	16 (14%)	62 (24%)	78 (21%)
Invasive	101 (86%)	196 (76%)	297 (79%)
Method of Detection			
Community	60 (51%)	137 (53%)	197 (53%)
DCIS	4 (3%)	24 (9%)	28 (8%)
Invasive	56 (48%)	113 (44%)	169 (45%)
Screen	57 (49%)	120 (47%)	177 (47%)
DCIS	12 (10%)	38 (15%)	50 (13%)
Invasive	45 (39%)	82 (32%)	127 (34%)
Type of surgery			
Breast Conserving Surgery (BCS)	88 (75%)	183 (71%)	271 (72%)
DCIS	13(11%)	45 (17%)	58 (15%)
Invasive	75 (64%)	138 (54%)	213 (57%)
Mastectomy	29 (25%)	75 (29%)	104 (28%)
DCIS	3 (3%)	17 (66%)	20 (5%)
Invasive	26 (22%)	58 (23%)	84 (22%)

Table 2: For each adjuvant therapy examined, rates of recommendation, concordance, and positive and negative predictive values. Shown separately for age at diagnosis and year of diagnosis. Figures show N(%) unless stated otherwise.

	Age at diagnosis			Year of diagnosis		Total
	<50	**50-64**	**≥65**	**2010**	**2014**	
N (%)	76 (20)	165 (44)	134 (38)	**117 (35)**	**258 (65)**	**375 (100)**
OVERALL CONCORDANCE	80	82	83	83	81	82
ENDOCRINE THERAPY						
Invasive Cancer (%)	*n* = 61 (21)	*n* = 125 (42)	*n* = 111 (37)	*n* = 101 (34)	*n* = 196 (56)	*n* = 297 (100)
Recommendation rate	90	92	89	87	92	91
Concordance rate	97	97	97	100	95	97
PPV	96	97	97	100	95	97
NPV	100	100	100	100	100	100
DCIS (%)	*n* = 15 (19)	*n* = 40 (51)	*n* = 23 (30)	*n* = 16 (21)	*n* = 62 (79)	*n* = 78 (100)
Recommendation rate	73	85	65	63	81	77
Concordance rate	80	78	87	88	79	81
PPV	73	74	88	64	69	77
NPV	100	100	90	100	92	94

RADIOTHERAPY						
Invasive cancer post-BCS (%)	*n* = 40 (19)	*n* = 99 (46)	*n* = 74 (35)	*n* = 75 (35)	*n* = 138 (65)	*n* = 213 (100)
Recommendation rate	95	96	72	89	86	87
Concordance rate	88	91	91	93	89	91
PPV	90	93	89	94	89	91
NPV	83	91	96	88	94	93
Invasive cancer post-mastectomy (%)	*n* = 21(25)	*n* = 26 (31)	*n* = 37 (44)	*n* = 26 (31)	*n* = 58 (69)	*n* = 84 (100)
Recommendation rate	38	50	14	46	24	31
Concordance rate	86	85	92	81	91	88 (
PPV	63	69	67	69	64	67
NPV	100	100	97	93	100	98
DCIS post-BCS (%)	*n* = 11 (19)	*n* = 30 (52)	*n* = 17 (29)	*n* = 13 (22)	*n* = 45 (78)	*n* = 58 (100)
Recommendation rate	82	57	53	69	58	60
Concordance rate	64	93	100	92	89	90
PPV	56	94	100	89	85	86
NPV	100	93	100	100	95	96
CHEMOTHERAPY						

Invasive cancer (%)	*n* =61 (21)	*n* =125 (42)	*n* =111 (37)	*n* =101 (34)	*n* =196 (66)	*n* =297 (100)
Recommendation rate	64	51	28	45	45	45 (
Concordance rate	95	91	91	94	91	92
PPV	92	86	68	89	81	84
NPV	100	97	100	98	99	99
Node positive invasive cancer (%)	*n* =28 (27)	*n* = 43 (41)	*n* = 33 (32)	n=39 (38)	n=65 (62)	*n* =104 (100)
Recommendation rate	79	84	42	72	68	69
Concordance rate	93	91	85	90	90	89
PPV	91	91	64	86	87	86
NPV	100	90	100	100	96	98
Node negative invasive cancer (%)	*n* = 33 (17)	*n* = 82 (43)	*n* = 78 (40)	*n* =62 (32)	*n* =131 (68)	*n* =193 (100)
Recommendation rate	52	34	22	29	34	32
Concordance rate	97	91	94	97	92	93
PPV	94	79	71	95	75	81
NPV	100	98	100	98	100	99

Table 3: Non-concordance to MDM recommendation (N (%))

	Patient comorbidities	Patient choice	Patient circumstance	Total known	*Unknown*
Invasive Cancer					
Endocrine therapy	0 (0)	6 (100)	0 (0)	6 (100)	*3 (33)*
Radiotherapy	3 (19)	9 (56)	4 (25)	16 (100)	*7 (30)*
Chemotherapy	3 (25)	8 (67)	1 (8)	12 (100)	*3 (20)*
DCIS					
Endocrine therapy	0 (0)	7 (88)	1 (13)	8 (100)	*6 (43)*
Radiotherapy	0 (0)	3 (100)	0 (0)	3 (100)	*0*
Total	**6 (13)**	**33 (73)**	**6 (13)**	**45 (100)**	***19 (30)***