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Title page

Factors Influencing Reoperation Following Breast Conserving Surgery

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Abstract

Introduction: Reoperation rates after breast conserving surgery are highly variable and the best techniques for optimising margin clearance are being evaluated. The aim was to identify the reoperation rate at our centre and identify influential factors, including a change in guidelines on margin recommendations and the introduction of in-theatre specimen x-ray.

Methods: A retrospective review of medical records was undertaken to identify 562 patients who underwent breast conservation at The Royal Melbourne Hospital and Royal Women's Hospital between 2013-2015. All cases that underwent subsequent re-excision or total mastectomy were captured and factors influencing margin excision recorded.

Results: Reoperation was undertaken in 19.5% of patients (110; 86 re-excisions, 24 total mastectomies). There was a reduction in reoperation rate from 25% to 17% (p=0.01) with adoption of the margin guidelines in 2014, but no significant reduction with the introduction of in-theatre specimen x-ray in 2015 (21% vs. 16%, p=0.14). On multivariate analysis, factors that significantly influenced reoperation rates were the presence of multifocality on mammogram (OR 5.3, 95% CI 1.6-16.7, p<0.01); lesion size of mammogram (OR 2.2 per 10mm, 95% CI 1.4-3.6, p<0.01); smaller excision specimen weight (OR 0.5 per 25g of resection, 95% CI 0.3-0.8, p<0.01); and pure DCIS on final pathology (OR 5.9, 95% CI 1.9-16.7, p<0.01).

Conclusion: Optimising reoperation rates following breast conserving surgery remains a surgical challenge, particularly in patients with *in situ* or multifocal disease. Adoption of international margin guidelines reduced reoperation rates at our centre; however, introduction of intraoperative specimen x-ray had no influence.

Introduction

Breast conserving surgery (BCS) is usually the preferred surgical option for early breast cancer and ductal carcinoma *in situ*, providing comparable results to total mastectomy, when used in combination with radiotherapy. Successful BCS requires negative margins, and many patients undergo reoperation to achieve adequate margins[1, 2]. As involved margins are known to adversely affect local recurrence rates[3], surgical practice had been to recommend reoperation to ensure wide margins where the initial margin is close or involved. There has been great variability in practice between institutions and individual practitioners[2]. To address this variability, the Society for Surgical Oncology (SSO) and American Society for Radiation Oncology (ASTRO) developed consensus guidelines in 2014 and 2016, which respectively recommended that 'no ink on tumour' is an acceptable margin for invasive cancer and 2mm the required margin for *in situ* carcinoma[4, 5].

Re-excision may be anxiety provoking for patients and may threaten a major goal of BCS, which is good cosmesis[6-8]. It is also expensive for the health system[9]. Patient, cancer and surgical factors impact margin status and reoperation rates following BCS. Factors cited to increase the likelihood of involved margins and re-excision include younger patient age, non-palpable tumours, lack of pre-operative diagnosis, neo-adjuvant chemotherapy, mammographic microcalcifications, multifocal lesions, lobular histology, hormonal status, cancers with a ductal carcinoma *in situ* (DCIS) component and resection volume[10-16]. The use of intraoperative radiography[17, 18], ultrasound[19-22], frozen section[23], imprint cytology[23] and cavity shave[24, 25] have improved margin status and reduced the re-excision rate in some studies.

Prior to 2014, our general policy was to consider re-excision when cancer or *in situ* carcinoma was within 1mm of the surgical margin. In 2014 our service adopted the guidelines and in 2015 installed a machine allowing in-theatre specimen radiography.

The aim of this study was to determine the rate of reoperation following BCS and identify factors associated with reoperation, including the effect of introduction of the margin guidelines and in-theatre specimen radiography.

Methods

All patients who underwent BCS for core-biopsy proven *in situ* or invasive breast cancer at the combined breast service of The Royal Melbourne Hospital (RMH) and Royal Women's Hospital (RWH) between 2013-2014 were reviewed. In January 2015, we introduced routine use of Faxitron intraoperative specimen x-ray (Faxitron Bioptics, Tucson, USA) at the Royal Melbourne Hospital site and this year was included in the analysis.

The breast service database was retrospectively reviewed to identify patients who underwent reoperation (re-excision or total mastectomy) within 100 days of their primary procedure. Data were manually extracted from: medical records (patient demographics, examination findings and surgical details), hospital imaging (ultrasound and mammographic lesion characteristics where applicable) and pathology databases (excision specimen weight, histological characteristics, margin and hormonal status).

Intraoperative re-excisions were guided by palpation alone in 2013-2014 and by a combination of palpation and Faxitron in 2015. Intraoperative re-excisions were classified into four categories:

1. No lesion present, ineffective – margin was already histopathologically satisfactory and additional healthy tissue was taken
2. No lesion present, effective – margin was initially involved or <2mm from *in situ* disease and additional healthy tissue was taken producing a new satisfactory margin
3. Lesion present, ineffective – lesion was present in additional specimen but new margins were still involved
4. Lesion present, effective – lesion was present in additional specimen and new margins were satisfactory

Statistical analyses were performed using STATA12 (StataCorp, College station, TX, USA). Patients' demographic and clinical data were summarised and reported as N (%) (Table 1). Differences between groups were determined using Chi-Square or Fisher's exact tests. Two-sided p-values <0.05 were considered statistically significant. Factors significantly associated with the 100 days re-excision on univariate analysis were entered into a stepwise multivariate logistic regression model to identify variables that independently predicted reoperation. Patients with incomplete data were excluded from multivariate analysis and this left 195 patients for analysis. Intraoperative re-excision effectiveness was calculated by dividing the number of effective intraoperative re-excisions by the total number of intraoperative excisions undertaken in that year.

Results

Patient, disease and surgical demographics

There were 562 patients that underwent BCS for biopsy-proven *in situ* or invasive carcinoma. Patient, lesion and surgical characteristics are outlined in Table 1. Median primary excision specimen weight was 51 (IQR, 33-80) grams.

Reoperation rate

The reoperation rate within 100 days of primary breast conserving surgery was 19.5% (110 patients). Re-excision was undertaken in 86 patients and total mastectomy in 24 patients. The median weight of re-excision specimens was 14 (IQR, 8-29) grams and total mastectomy specimens were 400 (IQR, 237-697) grams. Disease was present in 54% of re-excisions and 73% of total mastectomies.

On univariate analysis there was a reduction in re-excision rate from 25% to 17% (p=0.01) with the introduction of SSO/ASTRO guidelines (Table 2). There was no significant reduction with the introduction of the Faxitron (21% vs. 16%, p=0.14) (Table 2). Significant predictors of reoperation on stepwise multivariate analysis are displayed in Table 3.

Intraoperative re-excisions

Intraoperative resection of an additional margin was undertaken during the primary procedure in 29% (164) of patients. In eight cases pathology reports failed to document additional margin tissue separately to the primary excision specimen. The effectiveness of the additional

margin in these cases was therefore unable to be classified. The remaining 156 intraoperative additional margin resections were analysed. The median weight of additional margin was 7 (IQR, 4-14) grams. Median total resection weight during the primary operation was 53 (IQR, 34-83) grams.

Intraoperative selective margin re-excisions were effective in 18% and ineffective in 82% (Table 4). The introduction of the Faxitron did not improve the effectiveness of intraoperative selective margin excision (Pre: 19% vs. Post: 14%, p=0.42). Faxitron guided 37 selective intraoperative margin re-excisions: 14% (5) of re-excisions successfully cleared previously unsatisfactory margins; 70% (26) had no lesion present and had no impact on margin status; and 8% (3) contained a lesion but margins continued to be unsatisfactory. Faxitron had a false negative rate of 13% (22 patients) and these patients required subsequent reoperation.

Discussion

This large retrospective cohort study identified a reoperation rate of 19.5% at a tertiary referral breast cancer centre. Significant predictors of reoperation in the cohort were the presence of multifocality on mammogram, lesion size of mammogram, smaller surgical resection and pure DCIS lesions. Faxitron did not improve the effectiveness of intraoperative margin re-excision nor did it reduce reoperation at our centre.

Re-excision lumpectomy rates (RELR) following BCS are variable between 0- 50%, with a mean of 20-23% in several large national databases[1, 2, 10]. Reduced reoperations could theoretically minimise psychological distress, delays in adjuvant therapy and additional healthcare costs

associated with reoperation[6, 26]. However, RELR alone is an imperfect outcome measure. It is influenced by patient selection, resection volume and the surgeon's decision to reoperate. Its use has been cautioned as a quality measure due to a lack of evidence of its negative effect and the possible impact it may have on resection volumes[27, 28]. Two-thirds of participants at the recent American Society of Breast Surgeons (ASBrS) Collaborative Attempt to Lower Lumpectomy Reoperation Rates (CALLER) conference, agreed that by 2020 reoperation rates should be <20%[29].

In this series, more generous resection was associated with significantly reduced reoperation rates; for each additional 25g of tissue resected, the odds of reoperation reduced by 0.5 ($p<0.01$). This has been demonstrated by some[13] but not all[2] studies. Impaired cosmetic outcomes and reduced patient satisfaction with larger resection volumes[30], and more specifically, higher percentage of breast volume excised have been reported[31]. Cochrane et al. demonstrated a marked difference in patient satisfaction when less than 10% of breast volume was excised in comparison with those greater (83% vs. 37%)[31]. This highlights the dilemma whereby reducing excision specimen volume to improve cosmetic outcomes is associated with an increased likelihood of re-excision.

The presence of pure DCIS on final histopathology and the presence of multifocality on mammogram were independently associated with an increased rate of reoperation in this study. Patients with pure DCIS were 5.9 times more likely to have reoperations compared to those with invasive carcinoma. Patients with multifocal lesions were 5.3 times more likely to require reoperation than patients with unifocal disease. Presence of *in situ* carcinoma[10-12] and multifocal disease[11, 13, 32] have previously been identified as risk factors for margin involvement and reoperation and remains a significant surgical challenge. Younger patient age[10, 11, 33], mammographic

microcalcifications[32], lobular cancers[32] and hormonal status[13] have each been associated with increased reoperation rates in the literature but failed to reach significance in the multivariate analysis of this cohort.

Lack of clarity as to adequate resection margins led to the development of the 2014 ASTRO/SSO consensus guideline[4]. The guideline was based on a meta-analysis of 33 studies involving 28,162 patients that found no increased risk of local recurrence for invasive cancer in the presence of close margins, but a two-fold increased risk in the presence of positive margins[3]. The guideline recommendation of "no ink on tumour" as the acceptable margin could significantly reduce reoperation rates[34-36] and healthcare costs[9]. A reduction in reoperation rates from 2013 to 2014/15 (25% vs. 17%, p=0.01) with the introduction of the guideline was demonstrated in this study. The impact of the more recent 2016 ASTRO/SSO consensus guideline advocating 2mm margins for DCIS in BCS is yet to be seen.

Intraoperative selective margin re-excisions were undertaken in 29% of patients and successfully cleared a previously unacceptable margin in 18% (28/156) of these cases. The 2015 ASBrS CALLER conference recommended that intraoperative imaging be used to allow identification of close margins and allow immediate shave of the particular margin[29]. Intraoperative specimen radiography[17, 18] and cavity ultrasound [19-22] have been the most widely studied to date.

The introduction of Faxitron did not improve the effectiveness of intraoperative re-excision compared to palpation alone (Palpation: 19% vs. Faxitron: 14%, p=0.43), nor did it significantly reduce reoperation rates (21% vs. 16%, p=0.14). False negatives occurred in 13% of patients and

these patients required subsequent reoperation. Some studies have shown more encouraging results. Bathla et at. found Faxitron to identify unsatisfactory margins and guide effective intraoperative clearance in 23/24 patients[17]. McCormick et al. found Faxitron to lower the incidence of inadequate margins from 7% to 5% in patients undergoing BCS for invasive cancer[18]. In contrast to these studies, the present study compared palpation to radiographically guided intraoperative re-excision. Regardless which method was used there was a 7% trend in reduction in reoperation rate for patients who underwent intraoperative selective margin re-excisions (22% vs. 15%, p=0.06). Critics of intraoperative specimen radiography have highlighted its low specificity and inability to exclude margin involvement[37]. Furthermore it is of limited use in radiographically occult disease. A meta-analysis conducted by Gray et al. found insufficient evidence to recommend its use[38].

This study demonstrated that intraoperative selective margin re-excision remains non-specific. Involved margins were frequently not identified, margins excised were often benign without improvement to the margin status (68%) and thirdly, even when an appropriate margin was identified for re-excision the resection was often insufficient to satisfactorily clear the margin (14%).

Routine cavity shave has been proposed as a solution to the problem. Randomised control trials by Chagpar et al. and Jones et al. showed reduced incidence of positive margins and reoperation in patients who underwent routine cavity shaves with volumes of 36mL and 62mL[24, 25]. A metanalysis by Wang et al. found reduced margin involvement and reoperation, without increased resection volumes in patients undergoing lumpectomy and cavity shave in comparison to

lumpectomy alone[39]. The recent ASBrS CALLER conference recommended consideration of cavity shaves in patients with larger lesions and those lesions with an extensive *in situ* component[29].

Conclusion

This large retrospective cohort study identified a reoperation rate of 19.5% at a tertiary referral breast cancer centre. Factors that significantly predicted reoperation were the presence of multifocality on mammogram, larger lesion size of mammogram, smaller surgical resection and pure DCIS lesions. Intraoperative margin assessment remains imprecise using present technologies and patients identified at high risk of margin involvement may benefit from routine cavity shave.

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Table 1. Patient, lesion and surgery characteristics

Primary operation details	
Total patients	562
Age (years), median	58 (IQR, 51-67)
Menopause status	
Pre	112 (20%)
Peri	56 (10%)
Post	385 (69%)
Unknown	9 (2%)
Examination	
No lump (screen detected)	287 (51%)
Lump	252 (45%)
Other	7 (1%)
Unknown	16 (3%)
Year	
2013	204
2014	193
2015	165
Localisation	
None	181
Carbon localised	308
Hook-needle localised	73
Resection specimen total weight (g), median	53 (IQR, 34-83)
Faxitron specimen x-ray	
No (2013/14)	397 (71%)
Yes (2015)	165 (29%)
Primary operation histopathology	
Lesion type	
In situ	106 (19%)
Invasive cancer	420 (75%)
Other	36 (6%)
Hormone status	
ER/PR+[†]	467 (83%)
HER2+ [‡]	54 (10%)
Triple negative	33 (6%)
Unknown	8
Grade	
1	134 (25%)
2	221 (40%)
3	191 (35%)
Lymphovascular invasion (in invasive cancer lesions)	
No	345 (82%)
Yes	75 (18%)
***In situ* component present (in invasive cancer lesions)**	
No	120 (29%)
Yes	300 (71%)
Reoperation details	
No	452
Yes	110
Procedure	
Re-excision	86
Total mastectomy	24
Resection specimen weight (g), median	
Re-excision	14 (IQR, 8-29)
Total mastectomy	400 (IQR, 237-697)
Lesion present	
Re-excision	44/86 (54%)
Total mastectomy	16/22 (73%)

[†] Oestrogen/Progesterone positive
[‡] Human epidermal growth factor receptor 2 positive

Table 2. Univariate analysis - Predictors of reoperation within 100 days

	Total	Reoperation (%)	p value
Age			<0.01
<50yo	111	35 (32%)	
50+	451	75 (17%)	
Menopause status			0.01
Pre/peri	168	43 (26%)	
Post	385	64 (17%)	
Examination			0.54
No lump	287	62 (22%)	
Lump	252	43 (17%)	
Other	7	1 (14%)	
Unknown	16	4 (25%)	
Mammogram - Focality			<0.01
Unifocal	432	76 (18%)	
Multifocal	62	20 (32%)	
Mammogram - Finding			<0.01
Architect distortion	20	3 (15%)	
Microcalcification	141	49 (35%)	
Mass	81	9 (11%)	
Non-specific density	36	8 (22%)	
Spiculating mass	201	25 (11%)	
No finding	26	5 (19%)	
Mammogram - Size			<0.01
0-9.9mm	87	9 (10%)	
10-19.9mm	158	22 (14%)	
20-29.9mm	67	13 (19%)	
30-39.9mm	31	8 (26%)	
40mm+	26	11 (42%)	
Ultrasound - Focality			0.02
Unifocal	353	53 (15%)	
Multifocal	62	17 (27%)	
Ultrasound - Finding			0.04
Cystic	6	0 (0%)	
Indeterminant	15	3 (20%)	
Solid	384	66 (17%)	
No finding	34	12 (35%)	
Ultrasound - Size			0.31
0-9.9mm	98	12 (12%)	
10-19.9mm	172	28 (16%)	
20-29.9mm	55	8 (15%)	
30-39.9mm	19	6 (32%)	
40mm+	4	1 (25%)	
Core biopsy - Lesion type			<0.01
In situ	124	43 (35%)	
Cancer	418	67 (16%)	
Core biopsy - Hormone subtype			0.29
ER/PR +	467	88 (19%)	
HER2 +	54	15 (28%)	
Triple negative	33	7 (21%)	
Guideline			0.01
Pre guideline (2013)	204	51 (25%)	
Post guideline (2014/15)	358	59 (17%)	
Faxitron specimen x-ray			0.14
No Faxitron (2013/14)	397	84 (21%)	
Faxitron (2015)	165	26 (16%)	
Localisation			0.01
None	181	29 (16%)	
Carbon localised	308	58 (19%)	
Hook-needle localised	73	23 (32%)	
Intraoperative margin re-excision			0.06
No	406	86 (22%)	
Yes	164	24 (15%)	
Weight of excision specimen			0.01
0-25g	56	15 (27%)	
25-50g	186	49 (26%)	
50-75g	121	18 (15%)	
75-100g	74	6 (8%)	
>100g	79	10 (13%)	
Histology - Lesion type			<0.01
DCIS	106	34 (32%)	
IDC	373	58 (16%)	
ILC	47	14 (30%)	
Other	36	4 (11%)	
Histology - Grade			<0.01
1	134	16 (12%)	
2	221	41 (19%)	
3	191	51 (27%)	
Histology - Lesion size			<0.01
0-9.9mm	147	26 (18%)	
10-19.9mm	202	24 (12%)	
20-29.9mm	126	33 (26%)	
30-39.9mm	37	9 (24%)	
40mm+	38	16 (42%)	
Histology - Focality			<0.01
Unifocal	484	82 (17%)	
Multifocal	78	28 (36%)	
Histology – Lymphovascular			<0.01

invasion (in invasive cancer lesions)			
No	345	51 (15%)	
Yes	75	21 (28%)	
Histology – *In situ* component present (in invasive cancer lesions)			<0.01
No	120	9 (8%)	
Yes	300	63 (21%)	

Table 3. Multivariate analysis - Significant predictors of reoperation within 100 days

	OR (95% CI)	p value
Mammogram - Multifocal	5.3 (1.6-16.7)	<0.01
Mammogram - Lesion size (per 10mm)	2.2 (1.4-3.6)	<0.01
Weight of excision specimen (per 25g resection)	0.5 (0.3-0.8)	<0.01
Histology - Pure DCIS	5.9 (1.9-16.7)	<0.01

Table 4. Effectiveness of intraoperative margin re-excision[†]

	Total (n)	Intraoperative margin re-excision (n)	Guidance	Lesion palpable preoperatively	No lesion present		Lesion present		Overall Effectiveness
					Ineffective	Effective	Ineffective	Effective	
2013	204	62	Palpation	47% (29)	65% (40)	8% (5)	16% (10)	11% (7)	19% (12/62)
2014	193	57	Palpation	46% (26)	70% (40)	7% (4)	11% (6)	12% (7)	19% (11/57)
2015	165	37	Palpation + Faxitron	32% (12)	70% (26)	5% (2)	16% (6)	8% (3)	14% (5/37)
Total		562	156		68% (106)	7% (11)	14% (22)	11% (17)	18% (28/156)

[†] 8 Cases have been excluded from analysis due to inadequate pathology reporting of additional margin