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Project Title: Retrospective study of the adequacy of surgical margins post breast conservation surgery in Manitoba.

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SUMMARY: (no more than 250 words single spaced)

The objectives of this study are; 1- To identify the rate of re-excisions for a positive or close margins in Manitoba after original lumpectomy for invasive or non-invasive breast cancer between 2009 and 2012 2- To identify factors that could potentially predict no residual cancer in subsequent surgery. Patients with these factors could potentially avoid an unnecessary second surgery.

The cohort for this retrospective study consisted of Manitoban patients with invasive or non-invasive breast cancer who underwent a lumpectomy between January 2009 and December 2012 with a positive or a close margin (<2mm) that led to a re-excision.

The rate of re-excision because of close or positive margins after BCS between 2009-2012 is 17.0%. We have identified Invasive tumour size, N stage, Invasive grade, and margin status to be related with residual disease after re-excision. Surprisingly, Her2, lymphovascular invasion, and location of cancer were not found to be correlated with the status of residual disease in subsequent surgery.

Student Signature **Supervisor Signature**

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Retrospective study of the adequacy of surgical margins post breast conservation surgery in Manitoba.

Introduction:

Breast conservation surgery (BCS) is the standard of care for the treatment of early stage breast cancer including non-invasive and invasive malignancies. BCS with radiation therapy results in survival equal to mastectomy for early-stage breast cancer [1–3].

A safety margin of normal tissue around the cancer is required to ensure complete resection. There are currently no studies which confidently define what constitutes an adequate surgical margin. This controversy can lead to increased rates of re-excision among BCS patients, as well as increased costs, risk of complications, and the delay of adjuvant treatment [1,4]. Moreover, the impact of width of resection margins on recurrence and survival is not certain [5].It is estimated that 20 to 60% of women who undergo BCS require additional breast surgery (re-excision) because of positive or inadequate margins after the initial lumpectomy [4,6,7].

Lack of consensus on what constitutes adequate negative margins in BCS has led to variability in practice between centers and surgical oncologists [8]. Some argue that re-excisions for close or positive margins are mandatory. Gatek J et al showed that a margin width of >5 mm is required to ensure no residual cancer [9]. On the other hand, Jaffré I et al stated that re-excision for close or focally involved margins had no impact on local relapse-free survival. The decision to perform a surgical re-excision for an involved margin should not be systematic but should take multiple risk factors into consideration, such as patient age or diffuse margin involvement [10]. A similar finding was reported by Russo et al, who stated that in an era of routine adjuvant systemic therapy, close surgical margins and maximally resected close/positive margins were not associated with an increased risk of local recurrence compared to widely negative margins [5]. In other words, minimizing the sub-clinical tumour burden is not critical for reducing local recurrence after multiple forms of adjuvant treatment.

This is supported by a meta-analysis of 21 retrospective studies, which examined the effect of various margin widths on local recurrence in patients with breast cancer, and showed an odds ratio for local recurrence of 2.42 ($P<0.001$) with positive margins. However, it did not identify a statistically significant difference in local recurrence rates associated with margin widths of more than 1 mm, more than 2 mm, or more than 5 mm after adjustment for the use of a radiation boost or endocrine therapy [7].

Lupe K et al attempted to rationalize the approach for re-excision by identifying the subgroup of patients who may benefit from re-excision. Upon univariate analysis, subsets with close or positive margins, in combination with age <45 years, grade 3, lymphovascular space invasion, and ≥4 positive nodes, have 5-year local recurrence >10% despite whole breast plus boost radiation therapy. These patients should be considered for more definitive surgery [11].

Furthermore, literature reveals that a significant number of patients undergoing re-excision for positive or unclear margins had no residual disease in the re-excised specimen. In a study by Russo et al of 377 patients who underwent re-excision, 63.5% had no residual cancer [5]. This observation is shared by Adams BJ et al, which showed that there appeared to be no correlation between close or positive margins and the presence of residual disease in the re-excision specimen [1]. Interestingly, a study by Jaffré et al found that the probability of finding residual disease was significantly related to the margin being involved with an intraductal component [10].

It is our observation that a significant number of re-excision specimens in Manitoba for positive or close resection margins are actually negative for residual disease. This raises concern about the value of another surgery in some patients and calls for better identification of the subgroup of patients who will not benefit from further surgery.

Objectives:

The objectives of this study are; 1- To identify the rate of re-excisions for positive or close margins in Manitoba after original lumpectomy for invasive or non-invasive breast cancer between 2009 and 2012. 2- To identify factors that could potentially predict absence of residual cancer in subsequent surgery. Patients with these factors could potentially avoid an unnecessary second surgery.

Materials and Methods:

Patient Cohort and Database Construction:

The cohort for this retrospective study consisted of Manitoban patients with invasive or non-invasive breast cancer who underwent a lumpectomy between January 2009 and December 2012 with a positive or a close margin (<2 mm) that led to a re-excision.

The study was approved by both the Health Research Ethics Board at the University of Manitoba and the Research Resource Impact Committee at CancerCare Manitoba. Data collection started in May 2014 and continued through to June 2015. Patients were identified through the CancerCare Manitoba Cancer Registry, a population based registry that capture all cases of breast cancer diagnosed in the province. Electronic patient charts were reviewed, and information that was not contained in electronic charts was reviewed from paper charts within the department of Health Records at CancerCare Manitoba. To ensure confidentiality, anonymization of patient data was achieved through establishing unique study I.D. numbers for each patient, which enabled reference between the Master list provided by the Department of Epidemiology and Cancer Registry at CancerCare Manitoba and the study database itself. All Cancer Registry numbers were confined to the Master list and were not included in the study database. The study database was constructed using Microsoft Excel. This database was password protected and accessed only by the small group of individuals responsible for the study.

Collected Data:

A. Demographics and treatment information

Patient information such as age, date of birth, and vital status at time of data collection was obtained from the CancerCare Manitoba Cancer Registry. Past malignancy and adjuvant therapy was determined by electronically accessing patient information from the CancerCare Manitoba Cancer Registry. Adjuvant radiation and chemotherapy information for the instance of malignancy being examined was determined by electronically accessing patient information from the CancerCare Manitoba Cancer Registry.

B. Surgical and Pathological Details

Data regarding acting surgeon, location, date, and type of surgery were collected from the CancerCare Manitoba Cancer Registry.

TNM staging was obtained from the CancerCare Manitoba Cancer Registry. Staging was determined according to the American Joint Committee on Cancer (AJCC) guidelines . Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) status were collected from pathology reports.

Surgical margins and descriptions of the malignancy such as tumour grade were identified from pathology reports. Margins of invasive and in situ cancer were reported separately if known. Unreported margins were recorded as negative if pathology reports did not comment on them. Each of the 6 anatomical margins was reported for margin status (focally positive, positive, close, negative, or unknown), margin width (if close), and the pathology type at that margin. A close margin was defined as a margin width of less than 2 mm, while a negative margin was defined as a margin width of 2 mm or more.

In cases where multiple foci of cancer where apparent, the largest size and highest grade were reported.

C. Statistical Analysis

Univariate analysis was conducted on variables of interest. Variables of interest were identified by conducting a literature review and discussion with surgical and radiation oncologists and speaking with clinicians. Chi-square testing was applied to study the correlation of different categorical variables with the status of residual disease. This test is used to determine significant association between two variables. Fisher's exact test was used when binary data was analyzed. Variables with p-values <0.05 were considered statistically significant. The software used to perform these calculations was SAS by SAS Institute Inc.

Results:

Re-excision Rate:

Of 2488 patients from 2009-2012, we identified 422 patients who underwent a re-excision within a year due to close of positive margins with an available first pathology report confirming the

margin status. Thus, we identified the re-excision rate for close or positive margins during this period to be 17.0%. Patients without pathology report of first surgery were excluded even if pathology reports of subsequent surgeries were available.

Study Cohort:

Out of these 422 patients, we excluded 8 patients due to lack of pathology reports from subsequent surgeries. Additionally, 5 patients with phyllodes type pathology were excluded. Of the remaining 409 patients, only one underwent 4 surgeries, while the remaining underwent either 2 or 3. 4 patients with invasive pathology had an unknown invasive tumour size. In the group of patients that had no residual cancer in their second surgery specimen, 1 consequently underwent an elective mastectomy.

Table 1 shows the demographics and cancer details of our cohort by the variables outlined earlier. Patients were further grouped by whether or not they had residual cancer after re-excision. In our study, 37.9% (155/409) of patients had no residual disease identified, and 62.1% (254/409) patients had residual disease identified in the second surgery's pathology report.

In the original lumpectomy, 311 (76.0%) patients had disease apparent at the margin. Patients who had at least one positive or focally positive margin after initial lumpectomy accounted for 214 (52.3%) and 97 (23.7%) of the 409 total patients respectively. At least one close margin (< 2 mm) after initial lumpectomy, as the nearest disease to the specimen's margin, was apparent in the remaining 98 (24.0%) patients.

Analytical Statistics:

The following variables were studied in relation to presence or absence of residual disease: anatomical location of cancer, status of invasive pathology, pathology type, grade, size, margin status, lymph node status, age, HER2 status, ER status, PR status, and the presence of lymphovascular space invasion. The results from univariate analysis are summarized in Table 2. Invasive tumour size, nodal stage, invasive grade, and margin status were correlated with the status of residual disease in the second surgery with p-values of 0.0009, 0.0469, 0.0356, and <0.0001 respectively.

Anatomical location of cancer, status of invasive pathology, pathology type, age, HER2 status, ER status, PR status, and the presence of lymphovascular space invasion did not show a statistically significant correlation with the finding of residual disease in the second surgery.

Discussion:

The first objective of this study was to identify the rate of re-excisions in Manitoba after original lumpectomy for invasive or non-invasive breast cancer between 2009 and 2012. We identified the re-excision rate during this period to be 17.0%. This finding is slightly lower than literature, which has estimated a re-excision rate between 20-60% [4,6,7].

Current literature has looked extensively at breast cancer recurrence rates in relation to margin width. However, there is a paucity of literature that has attempted to predict those who do not have residual disease after re-excision despite its apparent importance in potentially saving patients from an unnecessary operation including its risks and costs.

The second objective of this study was to identify factors that could potentially predict no residual cancer in patients requiring a subsequent surgery. In our study, 37.9% (155/409) of patients had no residual disease identified in the second surgery's pathology report. This is considerably lower than the previously noted studies by Russo et al and Jaffré et al, in which 63.5% and 75%, respectively, had no residual disease in their re-excision specimen [5,10]. Nevertheless, in our cohort 30 patients with no residual cancer underwent a mastectomy as a second surgery. This excessive surgery could potentially be avoided if we could predict the probability of residual cancer in subsequent surgery. Our data agrees with a study which looked at factors predictive of residual tumour after lumpectomy by Joste et al, in which a similar rate of 37% was reported [12].

Literature supports re-excision in cases of positive margins, and this is widely practiced [9,13]. As noted earlier, the impact of width of resection margins on recurrence and survival is not certain [5]. The general interpretation is that negative margins of excision are desirable, but the width of the negative margin does not influence outcome [14]. In this study, margin status was defined as either focally positive, positive, close (< 2 mm) or negative (2 mm or more). Univariate analysis determined margin status, as per these definitions, to show a statistically significant (p=<0.0001) correlation with status of residual disease.

71.03% of patients with one or more positive margins had residual disease identified in the second surgery. To a lesser extent, 44.9% of patients with one or more close margins had residual disease in the second surgery. This finding of a higher probability of identifying residual disease if original margin was positive compared to close, is consistent with previously published literature [12].

The size of invasive tumour identified in the first surgery was found to be statistically significant by univariate analysis (p=0.0009). Invasive tumour size smaller than 0.5 cm and larger than 2 cm had a higher chance of residual disease. Interestingly, tumour size from 0.5 cm to 2 cm showed similar probability of residual cancer and no residual cancer. Potential reasons for smaller sized tumours showing this trend include difficulty localizing smaller tumours during surgical procedures. Furthermore, there may be interplay between the size of an associated ductal carcinoma in situ (DCIS), which might be difficult to appreciate during BCS for a small invasive cancer [10]. This may lead to positive margins with DCIS for small sized invasive cancer that leads to residual disease detected upon re-excision.

Whether or not a patient had residual disease was related to grade of invasive pathology in initial lumpectomy (p=0.0356). A past study by Jaffré et al did not find grade to be related to residual disease upon re-excision [10].

Nodal stage was found to be related to residual disease upon re-excision. Univariate analysis using the Fisher's exact test looking at two-sided probability rendered a p value of 0.0469 which

is statistically significant. We identified that of the 409 patients, 321 (78.48%) had negative lymph nodes and 88 (21.52%) had positive lymph nodes. This finding is consistent with a meta-analysis by Houssami et al [7]. Of the 88 patients with positive node status, 63 (71.59%) had residual disease and 25 (28.41%) had no residual disease after re-excision.

Other studies identified location of cancer as a predictor for residual disease upon re-excision [13]. We did not find location of cancer to be statistically significant by univariate analysis. Similarly, age was identified as a predictor of residual disease upon re-excision [13]. Again, univariate analysis did not show this to hold true in our study.

Literature has shown HER2 status to be a predictor of recurrence [15]. Interestingly, in our study HER2 status was not found to be related to residual disease after re-excision. We believe that the biological behaviour of HER2 positive cancers is the factor to drive risk of recurrence rather than the size or excision status.

We found lymphovascular space invasion was not related to residual disease status after re-excision despite the fact that it is widely accepted to be predictive of recurrence [11].

In the future, we would like to report patient information about multifocality as literature has shown this to be predictive for re-excision [16]. We would also like to group patients by number of positive margins. Furthermore, it would be interesting to group patients by type of pathology, invasive or non-invasive, is found in their specimens' margins.

Limitations:

It is important to note that our study did not include the cohort of patients who had close or positive margins but did not undergo further surgery. This subgroup is not required to answer the main questions of our study. Nevertheless, it would give a better overview of the overall rate of positive or close margin after lumpectomy.

Missing patient data is a common weakness in retrospective studies. There were cases of patients known to have surgeries but no pathology reports were available for viewing to report on pathology and margin status. Furthermore, in cases with both an invasive and non-invasive component, often pathology reports would focus almost entirely on the invasive component. Thus, unreported non-invasive grade, size, and margin status was of common occurrence.

Conclusion:

The rate of re-excision in Manitoba because of close or positive margins after BCS between 2009-2012 is 17.0%, which is lower than what is reported in other retrospective studies. We have identified invasive tumour size, nodal stage, invasive grade, and margin status to be related with residual disease after re-excision. Surprisingly, HER2 status, lymphovascular space invasion, and location of cancer were not found to be related to the presence of residual disease in subsequent surgery. The statistically significant variables identified in this study need to be examined in a multivariate regression model to assess the independent importance of each in predicting status of residual disease after re-excision. Based on this, a subgroup of patients could potentially be saved an unnecessary surgery.

Table 1: Description of the Study Cohort

Variables	All Patients	No Residual Cancer in 2nd Surgery	Residual Cancer in 2nd Surgery
Age[1]			
<50	88	27	61
≥50	321	128	193
Total:	409	155	254
Tumour Size Invasive[1]			
Tis	119	43	76
T1mi	13	7	6
T1a	37	9	28
T1b	35	20	15
T1c	85	43	42
T2	98	30	68
T3	18	3	15
Unknown	4	0	4
Total:	409	155	254
Nodal Stage			
Positive	88	25	63
Negative	321	130	191
Total:	409	155	254
Grade Invasive[1]			
Grade 1	78	40	38
Grade 2	115	35	80
Grade 3	77	29	48
Unknown	20	8	12
N/A (Non-invasive)	119	43	76
Total:	409	155	254
Status of Invasive Pathology[1]			
Invasive and Non-invasive	249	97	152
Invasive Only	41	15	26
Non-invasive Only	119	43	76
Total:	409	155	254
Invasive Pathology[1]			
Other	9	3	6
Lobular	36	9	27
Ductal	225	91	134
Mixed	15	7	8
Unknown	5	2	3
Non-invasive	119	43	76
Total:	409	155	254

Margin Status[1,2]			
Focally Positive	97	39	58
Positive	214	62	152
Close (<2 mm)	98	54	44
Negative (≥2mm)	0	0	0
Unknown	0	0	0
Total:	409	155	254
Lymphovascular Space Invasion[1,4]			
Focally Positive or Positive	47	14	33
Negative	238	99	139
Unknown	124	42	82
Total:	409	155	254
Location of Cancer:			
Central	84	26	58
Upper Outer Quadrant[3]	150	57	93
Lower Outer Quadrant	38	12	26
Upper Inner Quadrant	40	21	19
Lower Inner Quadrant	17	6	11
Unknown	42	19	23
Multiple Locations	38	14	24
Total:	409	155	254
HER2 Status[4]			
Positive	46	14	32
Negative	242	92	150
Unknown	121	49	72
Total:	409	155	254
ER Status			
Negative	72	21	51
Positive	327	128	199
Unknown	10	6	4
Total:	409	155	254
PR Status			
Negative	121	39	82
Positive	277	110	167
Unknown	11	6	5
Total:	409	155	254
Chemotherapy (CT)			
Received CT	133	39	94
No CT	276	116	160
Total:	409	155	254

Radiation Therapy (RT)			
Received RT	249	114	135
No RT	160	41	119
Total:	409	155	254
Boost Radiation			
Received Boost RT	78	35	43
No Boost RT	331	120	211
Total:	409	155	254
Hormone Therapy (HT)			
Received HT	182	80	102
No HT	227	75	152
Total:	409	155	254
Type of Re-excision- 2nd Surgery			
Lumpectomy	248	125	123
Mastectomy	161	30	131
No Surgery	0	0	0
Total:	409	155	254

[1] First Surgery.
[2] Patients were identified for this variable by their most severe margin. The order of severity from least severe to most severe followed the pattern of: negative, focally positive, positive. Thus, a patient included in the group with 1 or more positive margins may have focally positive or negative margins as well.
[3] Includes Axillary Tail.
[4] This variable is not reported in patients with no invasive disease and these patients are included with the "unknown" cohort.

Table 2: Univariate Analysis

Variable	P- Value (χ2)[1]
Age[2]	NS*
Size of Invasive Tumour[2,3]	0.0009
Nodal Stage	0.0469*
Grade Invasive[2,4]	0.0356
Status of Invasive Pathology[2]	NS
Margin Status[2,5]	<0.0001
Lymphovascular Space Invasion[2,6]	NS*
Location of Cancer	NS
HER2 Status	NS
ER Status	NS*
PR Status	NS*

NS= Not statistically significant
* Fisher's exact test- two-sided p-value
[1] Chi-square analysis unless otherwise noted.
[2] First Surgery.
[3] 119 patients with non-invasive cancers and 4 with an unknown size of invasive cancer have been excluded from this analysis. 112 of the remaining 286 patients had no residual disease.
[4] 119 patients with only non-invasive pathology were excluded from this analysis. Of the remaining 290 patients, 20 patients had an unknown invasive disease grade, 8 with no residual disease (40%) and 12 with residual disease (60%) after re-excision.
[5] Patients were identified for this variable by their most severe margin. The order of severity from least severe to most severe followed the pattern of: negative, focally positive, positive. Thus, a patient included in the group with 1 or more positive margins may have focally positive or negative margins as well.
[6] 119 patients with only non-invasive pathology and 4 patients who had unknown lymphovascular space invasion status were excluded from this analysis.

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