Received: 14 December 2020 | Accepted: 4 November 2021

DOI: 10.1002/jso.26749

RESEARCH ARTICLE

Journal of SURGICAL ONCOLOGY WILEY

Tumor margins that lead to reoperation in breast cancer: A retrospective register study of 4,489 patients

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Funding information

Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital and Pirkanmaa Hospital District, Grant/Award Numbers: 9AA057, 9v044, 9x040; Cancer Foundation of Finland, Grant/Award Number: Kauppaneuvos Satu Tiivolan rahasto; The Finnish Medical Foundation, Grant/Award Numbers: 2167, 4038; Noncompetitive Research Funding of the Expert Responsibility Area of Pirkanmaa Hospital District, Grant/Award Number: 9AA049

Abstract

Background and Objectives: Optimal margins for ductal carcinoma in situ (DCIS) remain controversial in breast-conserving surgery (BCS) and mastectomy. We examine the association of positive margins, reoperations, DCIS and age.

Methods: A retrospective study of histopathological reports (4489 patients). Margin positivity was defined as ink on tumor for invasive carcinoma. For DCIS, we applied 2 mm anterior and side margin thresholds, and ink on tumor in the posterior margin.

Results: The incidence of positive side margins was 20% in BCS and 5% in mastectomies ($p < 0.001$). Of these patients, 68% and 14% underwent a reoperation ($p < 0.001$). After a positive side margin in BCS, the reoperation rates according to age groups were 74% (<49), 69% (50–64), 68% (65–79), and 42% (80+) ($p = 0.013$). Of BCS patients with invasive carcinoma in the side margin, 73% were reoperated on. A reoperation was performed in 70% of patients with a close (≤1 mm) DCIS side margin, compared to 43% with a wider (1.1–2 mm) margin ($p = 0.002$). The reoperation rates were 55% in invasive carcinoma with close DCIS, 66% in close extensive intraductal component (EIC), and 83% in close pure DCIS ($p < 0.001$).

Conclusions: Individual assessment as opposed to rigid adherence to guidelines was used in the decision on reoperation.

KEYWORDS

breast-conserving surgery, DCIS, mastectomy, positive margins, reoperation

Abbreviations: BCS, breast-conserving surgery; CI, confidence intrerval; DCIS, ductal carcinoma in situ; EIC, extensive intraductal component; ER, estrogen receptor; ESMO, European Society for Medical Oncology; OR, odds ratio; PgR, progesterone receptor; SSO-ASTRO, Society of Surgical Oncology–American Society for Radiation Oncology; TUCH, Turku University Hospital.

1 | INTRODUCTION

Breast cancer is the most commonly diagnosed cancer worldwide, with an estimated 2.3 million new cases annually.[1] Breast-conserving surgery (BCS) is currently considered the primary treatment for the majority of patients, yet roughly 40% of patients continue to undergo mastectomy.[2] The goal of BCS is to remove the tumor with sufficient margins, as involved margins increase the risk of local recurrence and necessitate a reoperation.[3–5] The global BCS reoperation rate is up to 30%, with high variation between institutions and surgeons.[6,7] Finnish studies report BCS reoperation rates of 8%.[8,9] Among patients undergoing mastectomy, involved or close margins are reported in 8%–10%.[10,11]

The pursued margins affect the need for reoperations. Wide margins do not decrease local recurrences after BCS in invasive carcinoma,[12] and a no ink on tumor practice is justified. For ductal carcinoma in situ (DCIS), no ink on tumor clearly reduces the risk of local recurrence, but the benefit of wider margins is controversial, particularly in patients who undergo radiation therapy.[13–15] The increased risk of positive margins is well established in patients with an extensive intraductal component (EIC),[4,16,17] but positive margins and residual disease upon reoperation has also been reported with less extensive DCIS.[18,19]

The age of the patient affects the treatment strategy, as surgeons may opt for wider margins or mastectomy or be more tolerant of close margins, depending on the patient's age.[20] Although young age is an independent risk factor for local recurrence[5,15] and a reoperation after BCS,[21] the reports on the effect of age on positive margins are conflicting, and their interpretation suffers from varying definitions of positive margins.

International guidelines have uniform recommendations on the desired margins for invasive disease and pure DCIS.[2,12,13,22,23] Finnish guidelines have recommended a no ink on tumor approach for invasive carcinoma since 2007.[24] In line with the ESMO guidelines, a 1 mm margin for DCIS was recommended before 2015, after which it was extended to 2 mm.[22,25] This is in accordance with the current SSO-ASTRO guidelines.[12,13] The guidelines are not uniform in regard to DCIS as a component of invasion. The SSO-ASTRO guidelines recommend no ink on tumor as an adequate margin,[12] whereas European guidelines do not univocally address this issue.[22,23]

The majority of studies focus on reoperation rates and do not provide a detailed description of margins. However, reoperation rates do not equal positive margin rates, as defined by current guidelines and determined by pathologists, and there is considerable variation in reoperation practices.[26] Herein, we provide a detailed assessment of histopathology reports to better understand the factors that lead to reoperation.

2 | MATERIALS AND METHODS

2.1 | Data management

Women diagnosed with breast cancer were identified from the Finnish Cancer Registry according to their personal identification number. Histopathological reports and structured tables from 1995 to 2017 were collected from the laboratory information system (Qpati) of Auria Biobank, which operates in connection with TUCH. We obtained permission to collect and analyze the data from the Finnish institute for Health and Welfare (THL/1414/5.05.00/2019).

Data management was conducted with Microsoft Excel for Office 365 ProPlus MSO, and additional pre-processing was carried out with Pandas 1.0.1 in Python 3.5.8. The entire cohort consisted of 5996 participants. The data management process is described in Figure 1. All operations, including reoperations to ensure complete removal of residual tumor with no histological detection of malignancy, were recorded. The data management was followed by the exclusion of irrelevant data. The exclusion criteria were: histopathological reports and tables that were assessed to be irrelevant to the study (e.g., unrelated organ or procedure for a benign tumor; $n = 2373$); missing data leading to a possible misinterpretation of results ($n = 627$); limited data on the operation and unavailable margin status ($n = 847$); and a structured histopathological table with missing data and no related histopathological reports ($n = 135$). Also, data concerning local recurrence in the mastectomy scar were excluded ($n = 98$).

2.2 | Variable definition

We collected the data from structured histopathological tables and supplemented missing data manually from histopathological reports. The data included age; the tumor type, diameter (mm), and histological grade; the prognostic markers estrogen receptor, progesterone receptor, proliferation marker (Ki-67), HER2 immunohistochemistry, and dual in situ hybridisation; as well as multifocal/multicentric tumor; the smallest distance (mm) from the invasive and DCIS components to the surgical margin; and the presence of DCIS/EIC.

The overall margin status was judged from the margin status of the invasive and DCIS components. The BCS technique at TUCH follows standard principles recommended by international guidelines.[27,28] For invasive carcinoma, no ink on tumor is applied. No reoperation is mandated if the posterior margin is histologically involved and the tumor is in touch with the pectoral fascia but does not grow beyond, according to the operative report. Therefore, posterior margins of DCIS not touching ink are considered adequate. Otherwise, for all DCIS types, 2 mm anterior and side margin thresholds were applied.

A reoperation is more often a necessity after a positive side margin. Therefore, separate analyses were conducted on reoperation rates among participants who had a positive side margin. For other comparisons, all margin orientations were considered.

2.3 | Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics Version 27 and Statsmodels 0.11.0 in Python 3.5.8.[29] In the univariate

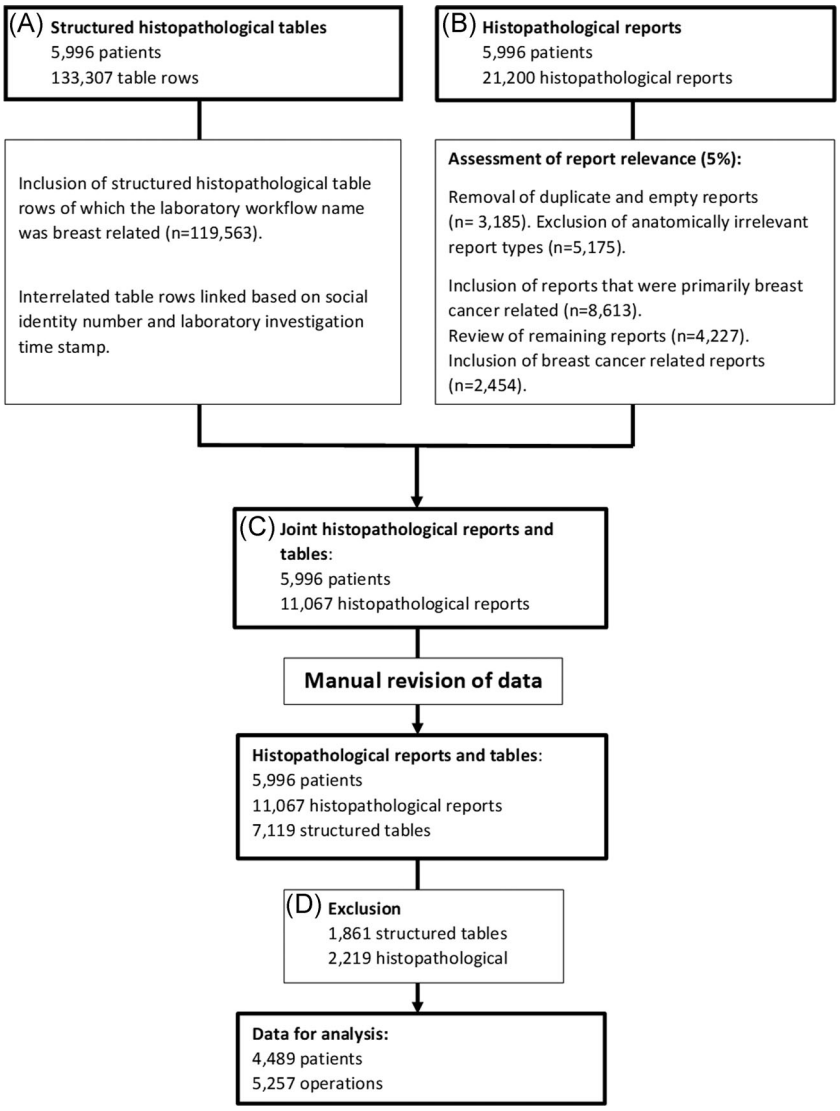

FIGURE 1 Flow chart of data management. (A) Structured histopathological tables were named based on laboratory workflow: 46 different consultation types (n = 133,307). All breast-related consultation types were included. (B) Histopathological reports were classified in 91 categories according to anatomical site (n = 21,200). A random sample from each category (5% of reports) was collected and reviewed from the viewpoint of study relevance. Relevant reports were included. (C) Relevant histopathological reports were manually reviewed, and the data in the structured tables were supplemented accordingly. (D) Irrelevant data were excluded (n = 4080)

analyses, Fischer's exact test was applied with small sample sizes, and the Chi-Square test was used on binominal variables for other comparisons. Binary logistic regression analyses were performed to test for associations between clinicopathologic features, positive margins encompassing all margin orientations (anterior, posterior, and side), side margin status, and reoperation status. The reported p values are derived from two-tailed tests.

3 | RESULTS

We collected data on 5257 breast cancer-related operations from 4489 participants (Table 1). Thirty-two percent (n = 1690) of the procedures were mastectomies and 54% (n = 2857) resections. In 14% of the cases (n = 710), the operation type was not defined. The number of operations per patient varied between one and five: one procedure was performed in 85% (n = 3807) and more than one in 15% (n = 682) of the cases. Of the resections, 86% (n = 2443) were primary BCSs. The remaining procedures were reresections or BCSs on the contralateral breast. Eighty percent (n = 1359) of the mastectomies were primary operations. The annual number of operations varied significantly, and the majority were performed between 2004 and 2013 (Figure 2).

3.1 | Temporal change

We classified the operations into two groups of 2833 (2000–2009) and 2424 (2010–2018) patients, respectively, to assess temporal change (Table 2). The relative number of mastectomies increased from 24% to 41%, while that of resections remained constant. The cases in which the operation type was not identified decreased from 22% to 4%, suggesting a more comprehensive data set in the latter group. The comparison was statistically significant (p < 0.001).

The positive margin rate, including all margin orientations, decreased from 26% to 24% in primary BCSs. Negative margins increased concordantly. The cases in which margin status could not be identified remained constant (p = 0.028). Similarly, the positive margin

TABLE 1 Clinical characteristics of participants with invasive carcinoma and/or DCIS ($n = 4917$)

Characteristics		Number of patients	Percentage (%)
Age (years)	<35	59	1.1
	35–49	695	13.2
	50–64	2323	44.2
	65–79	1644	31.3
	80+	536	10.2
Tumor type	Ductal carcinoma	2992	60.8
	Lobular carcinoma	670	13.6
	Other	266	5.4
	Pure DCIS	453	9.2
	Not available	536	10.9
Grade: invasive carcinoma	Low	815	18.3
	Intermediate	2091	46.8
	High	1257	28.2
	Not available	301	6.7
Grade: DCIS[a]	Low	374	16.5
	Intermediate	884	39.0
	High	850	37.5
	Not available	156	3.0
Tumor size[b]	T1mi (≤1 mm)	6	0.13
	T1a (1–5 mm)	181	4.0
	T1b (5–10 mm)	635	14.2
	T1c (1–2 cm)	1555	34.8
	T2 (2–5 cm)	1519	34.0
	T3/T4 (>5 cm)	245	5.5
	Not available	323	7.2
ER[c]	Negative	630	14.1
	Positive	3390	75.9
	Not available	444	9.9
PgR[d]	Negative	935	20.9
	Positive	3081	69.0
	Not available	448	10.0
Ki-67	Low (≤15%)	1642	36.8
	High (>15%)	2361	52.9
	Not available	461	10.3
HER2	Negative	3477	77.9
	Positive	468	10.5
	Not available	519	11.6
Multifocal/ multicentric tumor	No	3422	69.6
	Yes	955	19.4
	Not available	540	11.0

Note: Patient age is reported for all operations including benign operations ($n = 5257$). Proliferation marker (Ki-67), HER2 status, and tumor size are only reported for patients with invasive carcinoma ($n = 4464$).

Abbreviations: DCIS, ductal carcinoma in situ; EIC, extensive intraductal component; ER, estrogen receptor; PgR, progesterone receptor.

[a]All DCIS types included: invasive carcinoma with DCIS/EIC and pure DCIS.

[b]Greatest dimension (mm).

[c]ER: negative 0%–10% and positive >10%.

[d]PgR: negative 0%–10% and positive >10%.

rate in mastectomies decreased from 10% to 9%. Cases in which margin status was not identified increased from 1% to 3%, which was likely reflected in the decrease in negative margins. The result reached statistical significance ($p = 0.025$).

The rate of positive side margins after primary BCS increased from 17% to 22% ($p = 0.001$). Patients were more frequently re-operated on after primary BCS during the later observation period (78%) than the earlier period (58%) ($p < 0.001$).

3.2 | Margin status encompassing all margin orientations

To maximize comparability with other publications, we report the positive margin rate encompassing all margin orientations (anterior, posterior, and side). In primary BCS, this rate was 26% ($n = 613$), whereas the corresponding rate in mastectomies was 10% ($n = 152$) ($p < 0.001$). The positive margin rate was 7% ($n = 49$) for procedures in which the operation type was not identified.

The orientation in which the invasive and DCIS tumor components reached the surgical margin is presented in Table 3. In resections, the invasive carcinoma and DCIS usually reached the side margin (56% and 81%, respectively). In mastectomies, invasive carcinoma was generally present in the posterior (61%) and DCIS in the side margin (46%). Both results reached statistical significance ($p < 0.001$).

In primary BCS, positive margins were distinctly more common in participants with DCIS (37%) as opposed to invasive carcinoma only (15%) ($n = 2371$; $p < 0.001$). In mastectomy patients, these rates were 11% and 9%, respectively, but the result was not statistically significant ($n = 1543$; $p = 0.11$). The rate of positive margins increased

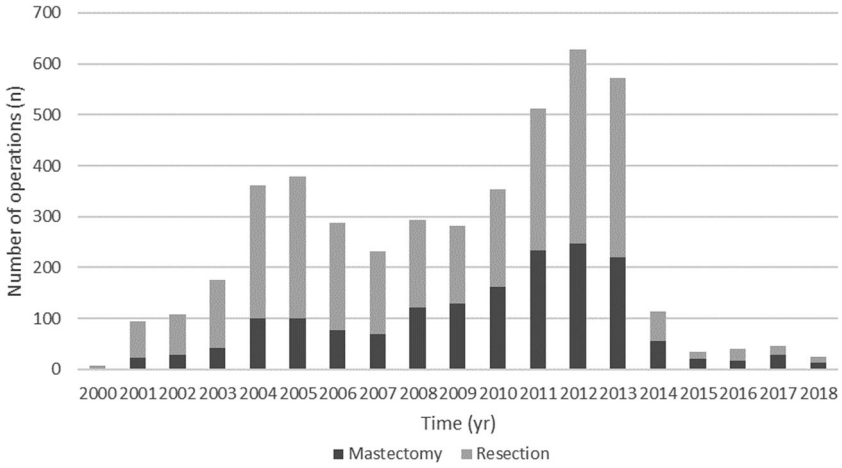

FIGURE 2 Annual distribution of mastectomies and resections (primary BCS and reresections) included in the study sample. The number of procedures varied significantly each year. BCS, breast-conserving surgery

TABLE 2 Temporal change in operation type and margin status from 2000 to 2009 and from 2010 to 2018

		2000–2009		2010–2018		
		n	%	*n*	%	*p* value
Operation type	Mastectomy	692	24.4	998	41.2	<0.001[a]
	Resection[b]	1530	54.0	1327	54.7	
	Not available	611	21.6	99	4.1	
Primary BCS: margin status[c]	Negative	990	72.2	783	73.5	0.028[a]
	Positive	361	26.3	252	23.6	
	Not available	21	1.5	31	2.9	
Mastectomy: margin status[c]	Negative	558	89.1	843	88.0	0.025[a]
	Positive	63	10.1	89	9.3	
	Not available	5	0.8	26	2.7	
Primary BCS: side margin status	Negative	1117	81.4	803	75.3	0.001[a]
	Positive	234	17.1	232	21.8	
	Not available	21	1.5	31	2.9	
Reoperation status after positive side margin[d]	No reoperation	98	41.9	52	22.4	<0.001[a]
	Reoperation	136	58.1	180	77.6	

Abbreviation: BSC, breast-conserving surgery.

[a]Chi-Square test.

[b]All resections included (primary BCS, reresections).

[c]Margin status encompassing all margin orientations (anterior, posterior and side).

[d]Reoperation status after a positive side margin in primary BCS.

with the extent of DCIS in patients treated with primary BCS or mastectomy and was the highest, at 43%, in EIC (Figure 3).

Positive margins were more frequent in young patients. The positive margin rates in primary BCS according to age group were 34% (<49 years), 24% (50–64 years), 25% (65–79 years), and 25% (80+) ($n = 2386$; $p = 0.004$). In mastectomy patients, the respective rates were 15%, 10%, 7%, and 10% ($n = 1553$; $p = 0.004$).

The association of operation type, the extent of DCIS, and age with margin status was further explored with binary logistic regression in patients treated with primary BCS or mastectomy (Table 4). The odds ratio (OR) for a positive margin was 3.9-fold (95% confidence interval [CI]: 3.2–4.8) in primary BCS when compared to mastectomy ($p < 0.001$). Positive margins were most frequent among young participants (<49 years) ($p < 0.001$). The extent of DCIS was associated with positive margins, with the highest OR of 6.1 in EIC (95% CI: 4.7–7.8) ($p < 0.001$).

3.3 | Side margin status

The clinical practice concerning reoperation due to positive side margins differs from other margin orientations. Therefore, we went

TABLE 3 The orientation in which the invasive carcinoma and DCIS tumor components reached the surgical margin presented according to operation type

Carcinoma component	Operation type	Anterior		Posterior		Side		Multiple		*p* value
		n	%	*n*	%	*n*	%	*n*	%	
Invasive carcinoma	Resection[a]	6	2.0	101	34.7	162	55.7	22	7.6	<0.001[b]
	Mastectomy	4	4.1	59	60.8	25	25.8	9	9.3	
DCIS	Resection[a]	1	0.2	43	10.6	330	81.1	33	8.1	<0.001[b]
	Mastectomy	10	15.4	13	20.0	30	46.2	12	18.5	

Note: Margin positivity was defined as ink on tumor for invasive carcinoma. For DCIS, posterior margins of no ink on tumor were adequate. Otherwise, 2 mm anterior and side margin thresholds were applied.

Abbreviations: BSC, breast-conserving surgery; DCIS, ductal carcinoma in situ.

[a]All resections included (primary BCS and reresections).

[b]Fischer's exact test.

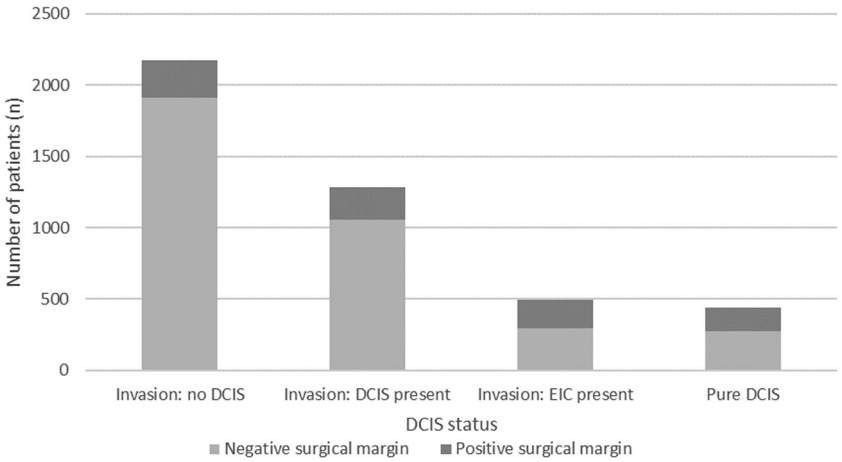

FIGURE 3 The relative number of positive surgical margins increased as the extent of DCIS increased. The positive margin rate was 13% in invasive carcinoma, 18% in invasive carcinoma with DCIS, 43% in invasive carcinoma with EIC, and 38% with pure DCIS ($n = 3914$; $p < 0.001$). Margin status encompasses all margin orientations (anterior, posterior, and side). DCIS, ductal carcinoma in situ; EIC, extensive intraductal component

on to focus on their management with a reoperation. In primary BCS, the positive side margin rate was 20% ($n = 466$), while the rate in mastectomies was 5% ($n = 70$) ($p < 0.001$). Young age associated with positive side margins in mastectomy, and the rates by age group were 7% (<49 years), 6% (50–64 years), 3% (65–79 years), and 3% (80+ years) ($n = 1553$; $p = 0.049$). After primary BCS, the corresponding rates were 24%, 19%, 18%, and 21%, respectively, but this comparison was not statistically significant ($n = 2386$; $p = 0.12$).

In a multivariate analysis of patients treated with primary BCS or mastectomy, the operation type and young age were both associated with side margin status (Table 4). In primary BCS, the OR for a positive side margin was 5.1 (95% CI: 3.9–6.7) in comparison to mastectomy ($p < 0.001$). The OR for a positive side margin decreased while transitioning from the youngest to the older age groups ($p = 0.027$).

3.4 | Surgical management of positive side margins

A reoperation was performed in 68% ($n = 316$) of participants with a positive side margin after primary BCS, compared to only 14% ($n = 10$) in the mastectomy group ($p < 0.001$). Accordingly, the reoperation rate due to a positive side margin in primary BCS was 13%.

Young age was associated with reoperations. The reoperation rate after a positive side margin in primary BCS decreased with advancing age and was the lowest, at 42%, in patients over 80 years of age (Table 5) ($p = 0.013$). The trend was similar in mastectomies, but the result was not statistically significant.

The side margin is positive if there is ink on invasive carcinoma and/or DCIS located within 2 mm of the margin. To investigate the management of positive side margins, we examined (1) which tumor components were present in the side margin and (2) whether the distance from these components to the margin guided the decision regarding a reoperation. The results are presented in Table 5.

In primary BCS, reoperations were most frequent if both invasive carcinoma and DCIS were present in the side margin (78%), followed by invasive carcinoma only (73%). Mere DCIS within 2 mm of the side margin led to a reoperation in 65% of the cases. However, DCIS most often caused side margin positivity ($n = 295$ vs. $n = 171$), but the result did not reach statistical significance ($p = 0.11$). Reoperations after mastectomy were infrequent. DCIS was usually the cause of side margin positivity ($n = 38$) but led to a reoperation in only 5% of the cases. Reoperations were most common (50%) if both invasive carcinoma and DCIS were present in the margin. The result reached statistical significance, but the cases were few ($p = 0.018$).

TABLE 4 Binary logistic regression analyses on the association of DCIS, operation type and age with margin status encompassing all margin orientations (anterior, posterior, and side), side margin status and reoperation status

Dependent variable (*n*)[a]	Explanatory variables		Multivariate model OR (95% CI)	*p* value
Primary BCS and mastectomy				
Margin status[b] (3914)	DCIS extent	No DCIS	1.0	<0.001
		Small DCIS	1.48 (1.21–1.82)	
		EIC	6.05 (4.72–7.76)	
		Pure DCIS	4.95 (3.79–6.46)	
	Operation type	Mastectomy	1.0	<0.001
		Primary BCS	3.91 (3.18–4.81)	
	Age	<49	1.0	<0.001
		50–64	0.61 (0.48–0.77)	
		65–79	0.62 (0.48–0.81)	
		80+	0.75 (0.53–1.06)	
Side margin status (3939)	Operation type	Mastectomy	1.0	<0.001
		Primary BCS	5.13 (3.93–6.68)	
	Age	<49	1.0	0.027
		50–64	0.76 (0.58–0.99)	
		65–79	0.64 (0.48–0.86)	
		80+	0.68 (0.45–1.02)	
Reoperation status (536)	Positive side margin cause	Invasion	1.0	0.029
		DCIS	0.62 (0.41–0.95)	
		Both	1.48 (0.56–3.91)	
	Operation type	Mastectomy	1.0	<0.001
		Primary BCS	13.70 (6.73–27.88)	
	Age	<49	1.0	0.015
		50–64	0.90 (0.52–1.57)	
		65–79	0.89 (0.49–1.63)	
		80+	0.28 (0.12–0.65)	
Primary BCS				
Reoperation status (320)[c]	DCIS distance[d]	0 mm	1.0	0.003
		0.1–1.0 mm	0.78 (0.43–1.40)	
		1.1–2.0 mm	0.30 (0.15–0.60)	
	DCIS extent	DCIS	1.0	0.002
		EIC	1.54 (0.87–2.73)	
		Pure DCIS	3.22 (1.67–6.18)	
	Age	<49	1.0	0.032
		50–64	1.15 (0.56–2.34)	
		65–79	1.16 (0.53–2.53)	
		80+	0.28 (0.10–0.83)	

(Continues)

TABLE 4 (Continued)

Dependent variable (*n*)[a]	Explanatory variables		Multivariate model OR (95% CI)	*p* value
	Grade: DCIS	Low	1.0	0.27
		Intermediate	0.97 (0.46–2.05)	
		High	1.50 (0.71–3.16)	

Abbreviations: BSC, breast-conserving surgery; CI, confidence interval; DCIS, ductal carcinoma in situ.

[a]Number of cases included in the binary logistic regression.

[b]Margin status encompassing all orientations (anterior, posterior, and side).

[c]The reoperation status of patients diagnosed with a positive side margin.

[d]The distance from the DCIS component to the surgical side margin (mm).

Next, we examined the smallest distance (mm) from the invasive carcinoma and DCIS components to the side margin in primary BCS (Table 5). Ink on invasive carcinoma led to a reoperation in 74% of the patients, in comparison to only 55% among the cases where the invasive component was located further away from the margin ($p < 0.001$). As no ink on tumor is adequate for invasive carcinoma, the participants with invasive disease located further away simultaneously had DCIS within 2 mm of the side margin. Approximately 70% of the participants with close (≤1 mm) DCIS side margins underwent a reoperation, compared to only 43% of those with a wider DCIS margin ($p = 0.002$).

The following step in our study was to examine which DCIS components were located close (≤1 mm) to the side margin and whether this affected the reoperation rates in primary BCS. We also assessed the association of reoperation status and the grade of DCIS (Table 5). To reflect the significance of DCIS alone, we excluded patients who also had ink on an invasive carcinoma. The reoperation rates were 55% in invasive carcinoma and close DCIS, 66% in close EIC, and 83% in close pure DCIS ($p < 0.001$). There was no difference in reoperation rates among patients with low, intermediate or high-grade DCIS ($p = 0.64$).

The association between reoperation status, the cause of positive side margins, age, and operation type in patients treated with primary BCS or mastectomy was further explored in a multivariate model (Table 4). The OR for a reoperation after primary BCS was almost 14-fold compared to mastectomy ($p < 0.001$). Young age was associated with reoperations—the OR in the oldest group was 0.3 (95% CI: 0.1–0.7) when compared to the youngest age group ($p = 0.015$). However, the confidence intervals were wide. Reoperations were fewer with only DCIS present in the side margin (OR: 0.6; 95% CI: 0.4–1.0) than with invasive carcinoma. The OR was 1.5-fold with both components in the margin, but the CI exceeded one. The result was statistically significant ($p = 0.029$).

The results achieved in the univariate analyses concerning the association of reoperation status with DCIS extent, distance from the side margin, DCIS grade, and age persisted in multivariate analysis (Table 4). Primary BCS cases with a positive side margin and DCIS were included in this comparison ($n = 320$). Compared to involved margins, DCIS located within 1.1–2.0 mm from the side margin was often accepted (OR: 0.3; 95% CI: 0.2–0.6). The OR for a reoperation in close (0.1–1.0 mm) margins was 0.8, but the CI exceeded one. The result was statistically significant ($p = 0.003$). Pure DCIS and EIC in the side margin resulted in a reoperation more often than regular DCIS ($p = 0.002$). Reoperations were rare among participants over 80 years of age (OR: 0.3; 95% CI: 0.1–0.8), but the reoperation rates were similar in the other age groups ($p = 0.032$). The OR for a reoperation in high grade DCIS was 1.5, but the CI exceeded one. The result did not reach statistical significance ($p = 0.27$).

4 | DISCUSSION

Our results show that positive margins, as defined by guidelines, do not automatically lead to a reoperation. The positive margin and reoperation rates are in line with the literature. The examination of margin status and reoperations sheds light on the different treatment patterns along the path to optimal surgical practice.

4.1 | Primary BCS and positive margins

Our findings emphasize individual assessment as opposed to rigid adherence to guidelines in regard to BCS margins. As Finnish datasets show similar local control after BCS and mastectomy, foregoing a reoperation is likely justified in some cases.[30,31]

Even though the definition of positive margins in the literature is not uniform, our findings confirm that the rates of positive margins are higher than reoperation rates.[16,26] A recent Canadian study defined margin positivity in primary BCS as ink on invasive carcinoma or DCIS and reported a positive margin rate of 26%. Among the reported patients, 84% underwent a reoperation. In 5% of the cases, the final margin status remained positive.[16] The positive margin rate would likely have been higher if 2 mm margins for DCIS had been applied. Morrow et al.[26] reported a positive margin rate of 33% after BCS, with a 14% reoperation rate after the implementation of the no ink on tumor guideline for invasive carcinoma. Yet, only 59% of the cases had invasive carcinoma present on the inked margin. Neither of these studies reported the interpretation of margin orientations. In

TABLE 5 First, the association of reoperation status with the cause of side margin positivity and age in mastectomy and primary BCS. Next, the association of reoperation status with the smallest distance (mm) from the invasive and DCIS components to the side margin in primary BCS. Last, the association of reoperation status with the grade of DCIS and the extent of close DCIS (0–1.0 mm from the side margin)

		Reoperation		No reoperation		
		n	%	*n*	%	*p* value
Mastectomy						
Positive margin cause	Invasive carcinoma	6	21.4	22	78.6	0.018[a]
	DCIS	2	5.3	36	94.7	
	Both	2	50.0	2	50.0	
Age	<49	2	12.5	14	87.5	0.70[a]
	50–64	5	16.7	25	83.3	
	65–79	3	18.8	13	81.3	
	80+	0	0	8	100	
Primary BCS						
Positive margin cause	Invasive carcinoma	105	72.9	39	27.1	0.11[b]
	DCIS	190	64.4	105	35.6	
	Both	21	77.8	6	22.2	
Age	<49	55	73.3	20	26.7	0.013[b]
	50–64	161	69.4	71	30.6	
	65–79	87	68.0	41	32.0	
	80+	13	41.9	18	58.1	
Distance to side margin	Invasive component					
	0 mm	126	73.7	45	26.3	<0.001[a]
	0.1–1.0 mm	7	87.5	1	12.5	
	1.1–2.0 mm	7	77.8	2	22.2	
	>2 mm	68	51.9	63	48.1	
	DCIS component					
	0 mm	132	70.2	56	29.8	0.002[b]
	0.1–1.0 mm	58	68.2	27	31.8	
	1.1–2.0 mm	21	42.9	28	57.1	
	>2 mm	1	100	0	0	
DCIS extent	DCIS	38	55.1	31	44.9	<0.001[b]
	EIC	60	65.9	31	34.1	
	Pure DCIS	73	83.0	15	17.0	
Grade: DCIS	Low	30	73.2	11	26.8	0.64[b]
	Intermediate	35	34.3	67	65.7	
	High	31	30.1	72	69.9	

Note: Participants with a positive side margin were included in the first comparisons. Participants diagnosed with a positive side margin and DCIS were included in the second comparison.Participants diagnosed with a positive side margin, DCIS and no ink on invasive carcinoma were included in the last comparison.

Abbreviations: BSC, breast-conserving surgery; DCIS, ductal carcinoma in situ; EIC, extensive intraductal component.

[a]Fischer's exact test.

[b]Chi-Square test.

our study, the BCS margin status encompassing all orientations was positive in 26% of the patients, which appears low, as we defined a negative margin as >2 mm for DCIS.

Previous Finnish studies have reported reoperation rates of 8% for reoperations due to insufficient margins after BCS.[8,9] Only one of them reported positive margin rates. The authors used a conservative negative margin definition (>5 mm for invasion and >10 mm for DCIS) early in the study before the application of the no ink on tumor approach for the invasive component and a >2 mm margin for DCIS. This potentially overestimated the rates of reoperations due to margin positivity. The authors only reported the smallest lateral margins,[8] and the results should therefore be compared to the rate of reoperations due to positive side margins after primary BCS (13%) in our study.

4.1.1 | The role of DCIS

As in previous studies, DCIS was frequently present in the side margin of patients who underwent a reoperation, and the odds for a positive margin increased with the extent of DCIS. A nationwide Dutch study on BCS for invasive carcinoma identified focally positive resection margins in 10% and extensive positive margins in a further 7% of the patients. DCIS was strongly associated with involved margins, and the odds increased along with the DCIS diameter.[32]

Kurniawan et al.[33] also reported results close to ours: the positive margin rate was 14%, and 70% of these participants underwent a reoperation. The authors defined margin positivity as ink on tumor for both DCIS and invasive carcinoma and also studied a subgroup with close (≤1 mm) negative margins, which is closer to international guidelines regarding DCIS. The incidence of close negative margins was slightly elevated when DCIS was present with invasive carcinoma, and it was twofold with pure DCIS.[33] Our study adds to these results by showing that an elevated risk of positive margins is also present with the current 2 mm margin guidelines.

Niinikoski et al.[8] identified EIC as a risk factor for reoperation in a Finnish population. In our study, EIC was evidently associated with positive margins, with almost sixfold odds compared to mere invasive disease in multivariate analysis. The positive margin rate of approximately 40% in EIC was higher than the previously reported rates and is likely to be a consequence of the positive margin definition of ≤2 mm for DCIS.[16]

In addition to positive margins, our analysis also associated DCIS and its extent with reoperations after primary BCS. Positive margins were followed by a reoperation in 68% of the cases after BCS, which is well in line with previous studies.[19,21] We found no association between the grade of DCIS and reoperations. High tumor grade has been associated with a higher risk of repeat surgery in invasive carcinoma[34,35] whereas the importance of DCIS grade in reoperations has remained ambiguous.[36] Altogether, a preoperative suspicion of DCIS should be factored into the surgical planning to reduce reoperation rates. The preoperative prediction of DCIS extent with imaging is challenging, and only anecdotal evidence has been reported on the predictive power of core needle biopsy.[37,38] This underlines the need for more research to better predict the extent of DCIS. Invasive disease with DCIS differs biologically from pure invasive disease and could thus be potentially identified with molecular panels.[39]

4.1.2 | The role of age

Previous literature on age and positive margins in primary BCS is not concordant. Most studies report no association analogous to our results,[16,21,33] but Van Deurzen et al.[32] found a higher risk of involved margins in patients aged above 50 years when compared to patients exceeding 60 years in a nationwide study in the Netherlands. Young age was a significant risk factor for reoperation after primary BCS, which is consistent with previous findings.[6,21] We hypothesize that the difference in reoperation rates is explained by the perceived low likelihood of local recurrence in older patients.

4.2 | Mastectomy and positive margins

Although there has been a shift towards BCS, many patients still require a mastectomy. The positive margin rate in our study was in concordance with previous studies. A meta-analysis reported close margins in 8% of the mastectomies. The definitions of margin positivity varied from ≤2 mm to a cut-off of 4–10 mm.[10] Another study found positive margins in 9%, defined as DCIS or invasive disease present in any margin.[11] The factors related to margin positivity differ between BCS and mastectomy. Comparable with our results, Lai et al.[21] associated young age with positive mastectomy margins. They also reported no association with the histologic subtype of DCIS and margin status, reflecting our results. Similarly, reoperations were significantly more common after BCS (70%) than mastectomy (9%). Contradictory evidence also exists, as Yu et al.[11] showed no differences between patients who had a positive margin and those who did not with respect to age or DCIS. Overall, studies on mastectomy margins are few, and margin positivity is not well defined in contemporary datasets.

4.3 | Temporal trends in surgical treatment

We detected an increase in positive side margins, which might be attributed to the pursuit of less radical primary surgical treatment. The targeted margin for DCIS has shifted during the study period, as DCIS relevance was not as well distinguished in the early guidelines.[24] This might be reflected in the observed increase, even though a trend toward less frequent reoperations has been reported.[26] The observed increase in mastectomies is probably due to bias caused by pathology reports that did not specify the type of operation in the early study period. These operations likely comprised mastectomies, as the positive margin rate in this group was corresponding, at 7%.

Despite being a weakness of the study, this does not cause notable bias because we did not resume the temporal division of data in subsequent analyses.

4.4 | Limitations

The retrospective nature can be considered a weakness of the study. We aimed to minimize bias with consistent and repeatable data management. The operations were mainly performed between 2001 and 2013. The lack of cases for the remaining years is unlikely to cause significant bias, as the study sample is representative for most of the study period. The data appear partially limited, as portrayed in Table 1. The unavailable data on prognostic markers that are consistently analyzed for each patient amount to approximately 10%. Some participants have likely been diagnosed with breast cancer before the study period, and the first operation was thus not truly performed for primary breast cancer. We did not have access to surgical and oncological reports. These could have benefited the study as regards the reasoning behind the reoperations and the oncological treatment patterns, such as boost radiation therapy and systemic treatments, when a reoperation was abstained from. Similarly, we were unable to assess factors such as preoperative techniques, surgical techniques, and reconstruction numbers, as we did not utilize the surgical reports of patients. These factors should be explored in future studies.

5 | CONCLUSIONS

Reoperation does not automatically ensue from positive margins, as defined in treatment guidelines, and margin status should be transparently presented when reporting reoperation rates. Operation type, the presence of DCIS, and age affect the rates of positive margins and reoperations. The preoperative assessment of DCIS extent is important, particularly in BCS, and the assessment methods should be improved in the future. Another important topic for further studies is whether the pursuit of 2 mm DCIS margins with a reoperation benefits the patient's prognosis.

ACKNOWLEDGEMENTS

We thank Surgical Specialist Riitta Aaltonen and Oncology Specialist Riikka Huovinen from TUCH, who provided insight into breast cancer treatment policies, and Biostatistician Mika Helminen from Tampere University Hospital (Tays) for his assistance in statistical analysis that greatly improved the manuscript.

CONFLICT OF INTERESTS

Maiju Lepomäki declares funding from the Doctoral School of Tampere University, The Finnish Medical Foundation (grant numbers 2167, 4038), and Cancer Foundation of Finland (Kauppaneuvos Satu Tiivolan rahasto). This study was also financially supported by Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital and Pirkanmaa Hospital District (Grants 9AA057, 9×040, and 9v044), and Non-Competitive Research Funding of the Expert Responsibility Area of Pirkanmaa Hospital District (Grant 9AA049). Antti Roine and Niku Oksala are shareholders and employees of Olfactomics Ltd., a medical device company that develops novel technology for intraoperative surgical margin assessment. Teemu Murtola is a consultant for Astellas, Janssen-Cilag, and Ferring and reports receiving speakers' bureau honoraria from Astellas and Janssen-Cilag, in addition to participating in congresses at the expense of Janssen-Cilag and Pfizer. He also owns stock in Arocell Ab. For the remaining authors, no conflicts of interest relevant to this study are declared.

ETHICS STATEMENT

A permission to collect and analyze data was obtained from the Finnish Institute for Health and Welfare (THL/1414/5.05.00/2019). The study was performed in accordance with the Declaration of Helsinki.

DATA AVAILABILITY SENTENCE

Research data are not shared because this could compromise participant anonymity or privacy.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
2. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2019;30(8):1194-1220.
3. Morrow M. Breast conservation and negative margins: how much is enough? *Breast*. 2009;18(3):84-86.
4. Singletary SE. Surgical margins in patients with early-stage breast cancer treated with breast conservation therapy. *Am J Surg*. 2002;184(5):383-393.
5. Kreike B, Hart AA, van de Velde T, et al. Continuing risk of ipsilateral breast relapse after breast-conserving therapy at long-term follow-up. *Int J Radiat Oncol Biol Phys*. 2008;71(4):1014-1021.
6. Van Leeuwen MT, Falster MO, Vajdic CM, et al. Reoperation after breast-conserving surgery for cancer in Australia: statewide cohort study of linked hospital data. *BMJ Open*. 2018;8(4):e020858.
7. Valero MG, Mallory MA, Losk K, et al. Surgeon variability and factors predicting for reoperation following breast-conserving surgery. *Ann Surg Oncol*. 2018;25(9):2573-2578.
8. Niinikoski L, Leidenius MHK, Vaara P, et al. Resection margins and local recurrences in breast cancer: comparison between conventional and oncoplastic breast conserving surgery. *Eur J Surg Oncol*. 2019;45(6):976-982.
9. Ojala K, Meretoja TJ, Mattson J, et al. The quality of preoperative diagnostics and surgery and their impact on delays in breast cancer treatment—a population based study. *The Breast*. 2016;26:80-86.
10. Rowell NP. Are mastectomy resection margins of clinical relevance? A systematic review. *The Breast*. 2010;19(1):14-22.
11. Yu J, Al Mushawah F, Taylor ME, et al. Compromised margins following mastectomy for stage I–III invasive breast cancer. *J Surg Res*. 2012;177(1):102-108.
12. Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast

irradiation in stages I and II invasive breast cancer. *Int J Radiat Oncol Biol Phys*. 2014;88(3):553-564.
13. Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Ductal Carcinoma In Situ. *Ann Surg Oncol*. 2016;23(12):3801-3810.
14. Dunne C, Burke JP, Morrow M, Kell MR. Effect of margin status on local recurrence after breast conservation and radiation therapy for ductal carcinoma in situ. *J Clin Oncol*. 2009;27(10):1615-1620.
15. Tadros AB, Smith BD, Shen Y, et al. Ductal carcinoma in situ and margins. *Ann Surg*. 2019;269(1):150-157.
16. Lovrics PJ, Cornacchi SD, Farrokhyar F, et al. The relationship between surgical factors and margin status after breast-conservation surgery for early stage breast cancer. *Am J Surg*. 2009;197(6):740-746.
17. Nayyar A, Gallagher KK, Mcguire KP. Definition and management of positive margins for invasive breast cancer. *Surg Clin North Am*. 2018;98(4):761-771.
18. Dzierzanowski M, Melville KA, Barnes PJ, MacIntosh RF, Caines JS, Porter GA. Ductal carcinoma in situ in core biopsies containing invasive breast cancer: correlation with extensive intraductal component and lumpectomy margins. *J Surg Oncol*. 2005;90(2):71-76.
19. Jeevan R, Cromwell DA, Trivella M, et al. Reoperation rates after breast conserving surgery for breast cancer among women in England: retrospective study of hospital episode statistics. *BMJ*. 2012;345(7869):18.
20. McGuire A, Brown JA, Malone C, McLaughlin R, Kerin MJ. Effects of age on the detection and management of breast cancer. *Cancers*. 2015;7(2):908-929.
21. Lai HW, Huang RH, Wu YT, et al. Clinicopathologic factors related to surgical margin involvement, reoperation, and residual cancer in primary operable breast cancer—an analysis of 2050 patients. *Eur J Surg Oncol*. 2018;44(11):1725-1735.
22. *Finnish Breast Cancer Group. Rintasyövän valtakunnallinen diagnostiikka- ja hoitosuositus*. Helsinki: Finnish Breast Cancer Group; 2019.
23. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up †. *Ann Oncol*. 2015;26:v8-v30.
24. *Working group set by the Finnish Medical Society Duodecim and the Finnish Breast Cancer Group. Rintasyövän hoito ja seuranta. Current Care -guideline*. Helsinki: The Finnish Medical Society Duodecim; 2007.
25. *Finnish Breast Cancer Group. Rintasyövän valtakunnallinen diagnostiikka- ja hoitosuositus*. Helsinki: The Finnish Breast Cancer Group; 2015.
26. Morrow M, Abrahamse P, Hofer TP, et al. Trends in reoperation after initial lumpectomy for breast cancer: addressing overtreatment in surgical management. *JAMA Oncol*. 2017;3(10):1352-1357.
27. The American Society of Breast Surgeons. Official statement - Consensus Guideline on Breast Cancer Lumpectomy Margins. 2017 Dec.
28. Ditsch N, Untch M, Thill M, et al. AGO Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2019. *Breast Care*. 2019;14(4):224-245.
29. Seabold S, Perktold J "Statsmodel: Econometric and statistical modeling with Python." Proceedings of the 9th Python in Science Conference. 2010.
30. Peltoniemi P, Huhtala H, Holli K, Pylkkänen L. Effect of surgeon's caseload on the quality of surgery and breast cancer recurrence. *The Breast*. 2012;21(4):539-543.
31. Siponen ET, Joensuu H, Leidenius MHK. Local recurrence of breast cancer after mastectomy and modern multidisciplinary treatment. *Acta Oncol*. 2013;52(1):66-72.
32. van Deurzen CHM. Predictors of surgical margin following breast-conserving surgery: A large population-based cohort study. *Ann Surg Oncol*. 2016;23:627-633.
33. Kurniawan ED, Wong MH, Windle I, et al. Predictors of surgical margin status in breast-conserving surgery within a breast screening program. *Ann Surg Oncol*. 2008;15(9):2542-2549.
34. O'Flynn EA, Currie RJ, Mohammed K, Allen SD, Michell MJ. Preoperative factors indicating risk of multiple operations versus a single operation in women undergoing surgery for screen detected breast cancer. *Breast*. 2012;22(1):78-82.
35. Wilke LG, Czechura T, Wang C, et al. Repeat surgery after breast conservation for the treatment of Stage 0 to II breast carcinoma: a report from the national cancer data base, 2004-2010. *JAMA Surg*. 2014;149(12):1296-1305.
36. Houvenaeghel G, Lambaudie E, Bannier M, et al. Positive or close margins: reoperation rate and second conservative resection or total mastectomy? *Cancer Manag Res*. 2019;11:2507-2516.
37. Kim HR, Jung HK, Ko KH, Kim SJ, Lee KS. Mammography, US, and MRI for preoperative prediction of extensive intraductal component of invasive breast cancer: interobserver variability and performances. *Clin Breast Cancer*. 2016;16(4):305-311.
38. Barbalaco Neto G, Rossetti C, Fonseca FL, Valenti VE, de Abreu L. Ductal carcinoma in situ in core needle biopsies and its association with extensive in situ component in the surgical specimen. *Int Arch Med*. 2012;5:19.
39. Wong H, Lau S, Yau T, Cheung P, RJE. Presence of an in situ component is associated with reduced biological aggressiveness of size-matched invasive breast cancer. *Br J Cancer*. 2010;102(9):1391-1396.

How to cite this article: Lepomäki M, Karhunen-Enckell U, Tuominen J, et al. Tumor margins that lead to reoperation in breast cancer: A retrospective register study of 4,489 patients. *J Surg Oncol*. 2021;1-12. doi:10.1002/jso.26749