Published in final edited form as:

Ann Surg Oncol. 2016 October ; 23(10): 3239–3246. doi:10.1245/s10434-016-5397-7.

Early Adoption of the SSO-ASTRO Consensus Guidelines on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Stage I and II Invasive Breast Cancer: Initial Experience from Memorial Sloan Kettering Cancer Center

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Abstract

Background—Re-excision rates in patients undergoing breast-conserving surgery (BCS) for early-stage invasive breast cancer are highly variable. The Society of Surgical Oncology (SSO) and American Society for Radiation Oncology (ASTRO) published consensus guidelines to help standardize practice. We sought to determine re-excision rates before and after guideline adoption at our institution.

Methods—We identified patients with stage I or II invasive breast cancer initially treated with BCS between 06/01/2013–10/31/2014. Margins were defined as positive (tumor on ink), close (≤1 mm), or negative (>1 mm), and were recorded for both invasive cancer and ductal carcinoma in situ (DCIS) components. Re-excision rates were quantified, characteristics were compared between groups, and multivariable logistic regression was performed.

Results—1205 patients were identified; 504 pre-, and 701 post-guideline adoption (01/01/2014). Clinical and pathologic characteristics were similar between time periods. Re-excision rates significantly declined from 21.4% to 15.1% (p=0.006) after guideline adoption. A multivariable model identified extensive intraductal component (odds ratio (OR)=2.5,95% CI 1.2–5.2), multifocality (OR=2.0, 1.2–3.6), positive (OR=844.4, 226.3–5562.5) and close (OR=38.3, 21.5–71.8) DCIS margin, positive (OR=174.2, 66.2–530.0) and close (OR=6.4, 3.0–13.6) invasive margin, and time period (OR=0.5, 0.3–0.9 for post- versus pre-) as independently associated with re-excision.

Conclusion—Overall re-excision rates declined significantly after guideline adoption. Close invasive margins were associated with higher rates of re-excision than negative invasive margins in

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Disclosures: This study was funded in part by NIH/NCI Cancer Center Support Grant P30 CA008748 and presented in poster format at the 2016 American Society of Breast Surgeons Annual Meeting, April 13–17, Dallas, TX. The authors have no conflict of interest disclosures to report.

both time periods; however, the effect diminished in the post-guideline adoption period. Thus we expect continued decline in re-excision rates as adherence to guidelines becomes more uniform.

Keywords

breast-conserving surgery; invasive breast cancer; re-excision

INTRODUCTION

Re-excision rates in patients undergoing breast-conserving surgery (BCS) for early-stage invasive cancer are highly variable.[1–4] Until recently, there was no widely accepted standardized definition of an adequate margin, which contributed to significant practice variability in re-excision rates.[1–3] Reported rates vary widely (2%–38%)[2,4], with variability found at the inter- and intra- institution level, and surgeon level, with variation present even amongst high-volume surgeons (11–20%).[2,3] On average, about 25% of women require a second surgical procedure in an attempt to obtain a "clear" margin.[3,4]

There has been considerable debate and controversy regarding the definition of a negative margin, adequate margin widths, and indications for re-excision. In a recent population-based survey of surgeons on what defines an adequate margin for avoidance of re-excision in a unicentric T1b cancer, only 11% of surgeons endorsed no ink on tumor. The majority of surgeons (42%) required 1–2 mm, 28% required ≥ 5 mm, and 19% reported a need for a > 1 cm margin.[1] In a large, multi-center study, this wide variability led to two or more re-excisions in roughly 10% of patients.[3]

Multiple operations to obtain adequate margins add substantial psychological stress for the patient, increase health care costs, and have a potential cosmetic disadvantage. Additionally, approximately 10% of women will opt for a completion mastectomy when presented with the need for re-excision[3,4], and a prior failed attempt at breast conservation has also been shown to be an independent predictor of patient choice of bilateral mastectomy.[5]

In response to the wide variability in re-excision rates, the Society of Surgical Oncology (SSO) and the American Society for Radiation Oncology (ASTRO) assembled a multidisciplinary expert panel to provide evidence based consensus guidelines. A meta-analysis of the relationship between margin width and ipsilateral breast tumor recurrence (IBTR) was performed from a systematic review of 33 studies including 28,162 patients.[6] This identified that a positive margin (ink on tumor) was associated with at least a 2-fold increase in IBTR, thus requiring re-excision. However, margins more widely clear than no ink on tumor did not further decrease the risk of IBTR obviating the need for further excision. This recommendation did not change for those omitting adjuvant systemic therapies, was not dependent on tumor biology or subtype, young patient age, tumor histology, or the presence of an extensive intraductal component.[6]

While these guidelines were published in March 2014, they were presented beginning in October 2013 after the consensus recommendations were finalized. Our breast disease management team adopted these recommendations in January 2014. Prior to release of these guidelines, the 12 surgeons in our group did not have a specific guideline margin standard.

In this study, we analyzed the rates of re-excision before and after the adoption of the SSO-ASTRO margin guidelines and sought to identify factors associated with re-excision.

METHODS

Data Source

After study approval by the Memorial Sloan Kettering Cancer Center Institutional Review Board for Human Subjects Research, data were obtained from prospectively maintained institutional databases and electronic medical records. A cohort of patients treated with BCS for stage I or II invasive breast cancer, with planned subsequent whole breast irradiation, from June 1, 2013 through October 31, 2014 was identified. Patients who received neoadjuvant chemotherapy, and those with bilateral invasive breast cancers, a personal history of prior breast cancer, or who had their index operation at another institution were excluded. Patients in this cohort did not receive intraoperative irradiation, partial-breast irradiation, or brachytherapy. Patients were grouped into 2 study periods; patients preceding the SSO-ASTRO guideline adoption (January 1, 2014), and those undergoing surgery after. This date of guideline adoption at our institution divided the cohort of BCS patients into a pre- (June 1, 2013–December 31, 2013) and post-guideline (January 1, 2014–October 31, 2014) adoption time period.

Clinical and Pathologic Factors

Patient age, breast density, and histopathologic characteristics, including tumor size, histology, associated ductal carcinoma in situ (DCIS), receptor subtype (estrogen receptor [ER], progesterone receptor [PR], HER2/neu), nuclear grade, presence of lymphovascular invasion (LVI), extensive intraductal component (EIC), and multifocality were identified for each specimen. Final pathologic tumor size (pT), nodes (pN), and lymph node metastases (0, 1–3, ≥ 4), were also recorded. The receipt of adjuvant chemotherapy, and endocrine, anti-HER2, and whole breast irradiation was recorded in a binary fashion (received/omitted).

During the study period, all surgeons at our institution routinely utilized a seed-localization technique for non-palpable lesions and practiced a cavity-shave margin technique as previously described.[7–9] This technique does not orient the primary lumpectomy specimen but marks the new margin of each cavity shave margin, which is inked separately. If tumor is identified in this separately submitted margin, a measurement is provided to the inked margin. These practices did not change during the study period. Margins were defined as positive if tumor was present at the inked margin, close if ≤ 1 mm, or negative if > 1 mm or when there was no tumor in the separately submitted cavity margins. Margin status was recorded for invasive cancer and DCIS separately. Surgeon-level data were recorded to determine case volume and re-excision rates in the pre- and post-guideline periods.

Statistical Analysis

Demographics, and operative, detailed pathologic, and outcome data were summarized by study period using median and range for continuous covariates, and frequency and percent for categorical covariates. Comparison between the study period using Wilcoxon rank-sum tests and Fisher’s exact tests was performed. Statistical analyses were performed using R

version 3.1.1 (R Foundation, Vienna, Austria). Univariate logistic regression was used to identify factors associated with re-excision following initial BCS. Variables of interest were included in a multivariable logistic regression model in order to identify factors independently associated with re-excision, with interaction terms to evaluate whether the effect of margins on re-excision changed at the time of guideline adoption. P-values < 0.05 were considered significant.

RESULTS

Between June 1, 2013 and October 31, 2014, 1205 patients were identified, 504 in the pre-guideline and 701 in the post-guideline adoption groups. The overall cohort had a median age of 58 years, a tumor size of 1.2 cm, and was predominantly stage I (72%), with the remainder being stage IIA (21%) and IIB (7%). All clinical and pathologic factors evaluated were similar between time periods except nuclear grade (TABLE 1, TABLE 2). The post-guideline group included a significantly higher proportion of patients with nuclear grade III tumors.

The re-excision rate declined from 21.4% to 15.1% (p = 0.006) in the post-guideline adoption time period, though the percentage of negative, close, and positive margins did not differ significantly (TABLE 3). Of patients attempting BCS in the post-guideline era, 85% had a single procedure. Of those who required a re-excision, the vast majority required 1 re-excision with only 0.9% of initial BCS attempts requiring 2 re-excisions, and less than 0.3% requiring 3 or more. Conversion to mastectomy was a rare event, with less than 1% of patients needing or electing for mastectomy following an initial attempt at BCS. We reviewed the re-excision rates for each margin category (negative, close, positive) for invasive and DCIS in both the pre- and post-guidelines adoption study period, and found that across all groups the re-excision rate fell in the post-guideline period (TABLE 4).

We examined pathology characteristics (specifically, presence of EIC and multifocality) among patients who underwent re-excision in the post-guideline period despite *no positive margins*, for either the DCIS or invasive component. We found that among 37 patients with a close DCIS margin and a negative invasive margin, 21 had neither EIC nor multifocality. These data suggest ongoing uncertainty or concern regarding a close DCIS margin. Re-excision rates remained low in the final aspect of this study, and three-month re-excision rates steadily declined (January–March 2014: 20.6%; April–June 2014: 14.2%; July–September 2014: 13.5%). The final month of this dataset (October 2014) had a re-excision rate of 8.0%, indicating stability of guideline acceptance.

Surgeon-level data revealed all surgeons were active in both time periods and performed similar relative volume of operations in the pre- and post-guideline periods, indicating that differences in re-excision rates between the time periods were not due to surgeon variability. Individual surgeon (N=12) re-excision rates for the post-guideline period ranged from 6% to 25%. Although the distribution of surgeon did not change over time, we performed a sensitivity analysis accounting for potential surgeon variability in decision making by adding a surgeon-level random effect to the models for re-excision. We found the effect of time period (pre- vs post- guideline) was not affected by whether or not a surgeon effect was

included in the model. The odds ratio for time period in a univariable model was 0.65 (0.49, 0.88) without, and 0.64 (0.49, 0.87) with the surgeon effect.

Factors independently associated with re-excision by univariate and multivariate analysis are shown in TABLE 5. Of the variables analyzed, 9 factors were significant by univariable analysis, including: age, time period (post-guideline adoption), close and positive invasive or DCIS margin, receptor subtype, EIC, LVI, multifocality, and presence of associated DCIS. Using these 9 factors, a multivariable model identified EIC, multifocality, positive and close DCIS margins, as well as positive and close invasive margins, as independently associated with increased re-excisions. The post-guideline time period was found to be independently associated with fewer re-excisions (OR 0.53, 95% confidence interval [CI] 0.32–0.88, $p = 0.014$) (TABLE 5).

There was a significant association between the invasive margin and the DCIS margin ($p \leq 0.001$). A total of 154 cases were identified in which the margin was *negative* for *invasive* cancer but *close* for *DCIS*. The re-excision rate in this subgroup in the post-guideline adoption group trended toward significantly fewer re-excisions ($p = 0.078$), indicating acceptance of the consensus guideline for invasive cancer even in the setting of isolated close margins of DCIS.

In a model run with interaction terms between margin status and time period, close invasive margin was associated with 13.0 times the odds of re-excision prior to guideline adoption, which decreased to 4.2 after adoption; however, this difference did not reach significance ($p = 0.331$). Similarly, a close DCIS margin was associated with 68.4 times the odds of re-excision for DCIS before guideline adoption, decreasing to 24.6 following adoption ($p = 0.205$). As neither was found to be significantly different, interaction terms were omitted in the final model for simplicity.

DISCUSSION

The SSO-ASTRO margin guidelines were developed in response to a lack of consensus regarding the definition of a negative margin as well as highly variable rates of re-excision among surgeons. In this study, we examined our re-excision rates in the time period immediately before and after adoption of the SSO-ASTRO margin guidelines. In our large cohort of 1205 consecutive BCS patients, we noted a significant decline in overall re-excision rates from 21.4% (June–December 2013) to 15.1% (January–October 2014). The time period following the guideline adoption was independently associated with fewer re-excisions, with roughly half the odds of requiring a re-excision in the post-adoption time period. This suggests surgeon adoption of the guideline and a change in practice pattern, with fewer return trips to the operating room for close but negative margins.

Since publication of the SSO-ASTRO guidelines, an American Society of Breast Surgeons (ASBrS) survey was performed presenting a sample of clinical scenarios and querying the likelihood of re-excision.[10] Overall, they reported significant familiarity with the consensus guidelines; however, wide acceptance remains uncertain. In non-controversial examples, such as a 2 mm margin, with a favorable tumor subtype, 95% of surgeons responded they

would never or infrequently re-excise the margin. However, highly variable responses were obtained for more complex cases, such as those with margins closer than 1 mm, multiple close margins, presence of extensive DCIS, or more aggressive subtypes; these likely reflect a hesitation to adopt the guidelines as more complex decision-making becomes necessary.[10]

Similarly, in our series, we noted a close invasive margin was associated with a higher re-excision rate than a negative invasive margin; however, the effect of close versus negative was smaller in the post-guideline adoption period, demonstrating a greater adoption of the guidelines. We noted a similar finding with a close versus negative DCIS margin. A close DCIS margin increased the chance of re-excision more than a close invasive margin (OR 38.3 versus 6.35). These data suggest ongoing uncertainty about the optimal margin for DCIS, as was also seen in the ASBrS survey. However, the SSO-ASTRO guidelines specifically note that re-excision is appropriate for negative margins in clinical circumstances where the likelihood of a heavy residual tumor burden is high, so some of this variation is reflective of reasonable clinical judgment.

Other factors independently associated with re-excision in our series were EIC and multifocality. In the SSO-ASTRO guidelines, EIC was highlighted as a cautionary area, as it reflects a large DCIS burden and may be associated with residual DCIS following BCS. Historical data in studies performed in an era without margin assessment found a significantly higher rate of IBTR with EIC-associated invasive breast cancer.[11,12] However, more contemporary studies do not note an increase in IBTR with EIC-associated invasive cancers when margins are negative, and thus no ink on tumor remains a negative margin even in the presence of EIC.[13]

While we know a positive margin is associated with at least a doubling of the risk of an in-breast tumor recurrence (IBTR), increasingly wider margins have not been shown to reduce IBTR.[14,15] This principle holds true even in the triple-negative subset known to have one of the highest rates of local recurrence. A recent study evaluated the impact of margin width on IBTR for triple-negative breast cancer and found margin width > 2 mm was not associated with reduced rates of IBTR when compared to smaller margins.[16] Notably, the IBTR for this subset was remarkably low, with only 5% of those with < 2 mm margins having an IBTR at 60 months of median follow-up. These extremely low rates of recurrence are likely attributed to advancements in radiation and systemic therapies providing improved local control. There is a growing body of literature supporting the concept that bad tumor biology is the driver of recurrence, not tumor left behind, and larger surgical excisions do not alter this factor.[17–19] In our study, we found triple-negative histology to be associated with re-excision on a univariate analysis, but not to be significant on multivariable analysis again supporting no ink on tumor as defining a negative margin regardless of receptor subtype.

We found a very low rate of mastectomy following BCS, with only 8 patients proceeding with completion mastectomy following an initial attempt at BCS (< 1%). One possible explanation for our low rate of mastectomy following BCS may be because only 1% of patients required 2 or more re-excisions, allowing fewer opportunities for patients to reconsider mastectomy as a treatment option.

Our rate of conversion to mastectomy is low compared to other published reports. For example, in a large published series of 1468 patients undergoing BCS, 11.9% of patients proceeded to mastectomy.[4] Another recent study by Isaacs et al also reported more than 10% of patients proceeded to mastectomy following initial BCS attempt.[20] That study included 89,448 patients attempting BCS in New York State and reported highly variable re-excision rates of 0–100%. The majority of the surgeons in this study were low-volume surgeons, with 90.8% of surgeons performing a mean of less than 14 primary cases per year. Low-volume surgeons were independently associated with higher re-operation rates, had an unadjusted re-operation rate of 35.2%, and had a 50% higher risk for re-excision compared to higher-volume surgeons.[20] However, the commentary by Nag and Hwang appropriately highlighted the multiple elements that contribute to this variability beyond the surgeon alone, specifically including intraoperative radiographic evaluation, pathologic processing and assessment, and proficiency of preoperative breast radiologists' localization.[21]

Our study has some notable strengths and limitations. This is a very large dataset including over 1200 BCS cases from a single institution. Advantages include a uniform surgical technique using the cavity-shave method by all 12 surgeons, the consistency of the pathologic analysis, and a practice agreement to adopt the guidelines. As a retrospective series, this study is limited in its ability to decipher information regarding surgeon and patient-level decision making. We did not collect information regarding intraoperative specimen radiographs, post-excision mammography, MRI, and how these factors may influence the surgeon's recommendations regarding re-excision.

In summary, following adoption of the SSO-ASTRO guidelines, re-excision rates fell significantly, from 21.4% to 15.1%. We anticipate further reduction in re-excision rates with closer adherence to guidelines and expanded comfort level. We also await further guidelines regarding DCIS that will help address the need for re-excision in the group where the invasive component margin is negative and DCIS is close. Follow-up studies are indicated to follow long-term outcomes following the widespread implementation of these guidelines.

Acknowledgments

This study was funded in part by NIH/NCI Cancer Center Support Grant P30 CA008748 and presented in poster format at the 2016 American Society of Breast Surgeons Annual Meeting, April 13–17, Dallas, TX. The authors have no conflict of interest disclosures to report.

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Synopsis

Re-excision rates in patients undergoing BCS for early-stage invasive breast cancer are highly variable, with about 25% of women requiring a re-excision to achieve negative margins. Following SSO-ASTRO guideline adoption, our center found a significant decline in re-excision rates.

TABLE 1

Clinical factors by time period in the pre- and post-guideline study periods

Factors	Overall	Pre-Study Period (n = 504)	Post-Study Period (n = 701)	p-value
Age in years (range) *	58.5 (29.0, 90.4)	57.9 (29.0, 86.7)	58.7 (30.1, 90.4)	0.330
Breast density †				0.750
- Fatty	91 (7.6)	42 (8.3)	49 (7.0)	
- Scattered	451 (37.4)	191 (37.9)	260 (37.1)	
- Heterogeneous	570 (47.3)	231 (45.8)	339 (48.4)	
- Extremely Dense	93 (7.7)	40 (7.9)	53 (7.6)	
Chemotherapy/Anti-HER2 therapy	542 (45.9)	236 (46.9)	306 (45.1)	0.555
Radiation therapy	1065 (89.6)	453 (90.2)	612 (89.1)	0.565
Endocrine therapy	908 (84.5)	404 (83.5)	504 (85.4)	0.397

*Continuous variables reported as a median (range)

†Categorical variables reported as N, %

TABLE 2

Pathologic factors by time period in the pre- and post-guideline study periods

Factors	Overall	Pre-Study Period (n = 504)	Post-Study Period (n = 701)	p-value
Size * (centimeters)	1.2 (0.1, 5.4)	1.2 (0.1, 5.4)	1.2 (0.1, 4.5)	0.601
Tumor histology †				0.511
- Invasive ductal	988 (82.0)	409 (81.2)	579 (82.6)	
- Invasive lobular	127 (10.5)	51 (10.1)	76 (10.8)	
- Mixed invasive ductal & lobular	51 (4.2)	26 (5.2)	25 (3.6)	
- Invasive other	39 (3.2)	18 (3.6)	21 (3.0)	
Associated DCIS				0.941
- Invasive only	232 (19.3)	98 (19.4)	134 (19.1)	
- Invasive + DCIS or EIC	972 (80.7)	406 (80.6)	566 (80.9)	
Extensive intraductal component (presence)	98 (8.1)	46 (9.1)	52 (7.4)	0.287
Receptor subtype				0.072
- ER/PR+, HER2−	982 (83.5)	404 (81.1)	578 (85.3)	
- ER/PR±, HER2+	100 (8.5)	44 (8.8)	56 (8.3)	
- Triple negative	94 (8)	50 (10)	44 (6.5)	
Nuclear grade				***0.041***
- I	61 (5.4)	35 (7.4)	26 (3.9)	
- II	681 (60.2)	278 (59.0)	403 (61.1)	
- III	389 (34.4)	158 (33.5)	231 (35.0)	
Lymphovascular invasion (presence/suspected)	363 (31.2)	155 (31.7)	208 (30.9)	0.798
Multifocality (Presence)	227 (18.9)	88 (17.5)	139 (19.9)	0.332
Pathologic Tumor classification (pT)				0.439
- T1	974 (81.4)	402 (80.6)	572 (82.1)	
- T2	221 (18.5)	96 (19.2)	125 (17.9)	
- T3	1 (0.1)	1 (0.2)	0 (0)	
Pathologic nodal classification (pN)				0.629
- N0	1005 (84.2)	423 (84.9)	582 (83.7)	
- N1 & N2	188 (15.8)	75 (15.1)	113 (16.3)	
Lymph node metastases				0.574
- 0	1017 (84.4)	429 (85.1)	588 (83.9)	
- 1–3	188 (15.6)	75 (14.9)	113 (16.1)	
Stage (pathologic)				0.823
- I	865 (72.4)	362 (72.5)	503 (72.3)	
- IIA	249 (20.8)	101 (20.2)	148 (21.3)	
- IIB	81 (6.8)	36 (7.2)	45 (6.5)	

*Continuous variables reported as a median (range)

†Categorical variables reported as N, %

DCIS, ductal carcinoma in situ; EIC, extensive intraductal component; ER, estrogen receptor; PR, progesterone receptor

TABLE 3

Outcome data in the pre- and post-guideline study periods

Factor/Outcome	Overall	Pre-Study Period (n = 504)	Post-Study Period (n = 701)	p-value
Margin width, invasive *				0.797
- Negative (> 1 mm)	1063 (88.2)	441 (87.5)	622 (88.7)	
- Close (≤ 1 mm)	83 (6.9)	37 (7.3)	46 (6.6)	
- Positive	59 (4.9)	26 (5.2)	33 (4.7)	
Margin width, DCIS †				0.086
- Negative (> 1 mm)	954 (79.3)	384 (76.5)	570 (81.3)	
- Close (≤ 1 mm)	196 (16.3)	90 (17.9)	106 (15.1)	
- Positive	53 (4.4)	28 (5.6)	25 (3.6)	
Number of re-excisions				***0.017***
- 0	991 (82.2)	396 (78.6)	595 (84.9)	
- 1	195 (16.2)	97 (19.2)	98 (14)	
- 2	16 (1.3)	10 (2)	6 (0.9)	
- ≥ 3	3 (0.2)	1 (0.2)	2 (0.3)	
Mastectomy †† (performed)	8 (0.7)	2 (0.4)	6 (0.9)	0.480

*Width of closest margin, invasive component only

†Width of closest margin, DCIS component only

††Mastectomy performed following attempted breast-conserving surgery

DCIS, ductal carcinoma in situ

TABLE 4

Re-excision rates by margin category in the pre- and post-study periods.

	Pre-Study Period	Post-Study Period	Raw Percent Change	Relative Reduction
Invasive margin *				
Negative (> 1 mm)	66/441 (15.0)	58/622 (9.3)	−5.7	38.0%
Close (≤ 1 mm)	18/37 (48.6)	19/46 (41.3)	−7.3	15.0%
Positive	24/26 (92.3)	29/33 (87.9)	−4.4	4.8%
DCIS margin †				
Negative (> 1 mm)	24/384 (6.2)	32/570 (5.6)	−0.6	9.7%
Close (≤ 1 mm)	57/90 (63.3)	50/106 (47.2)	−16.1	25.4%
Positive	27/28 (96.4)	24/25 (96.0)	−0.4	0.4%

*Width of closest margin, invasive component only

†Width of closest margin, DCIS component only

TABLE 5

Clinical and pathologic factors associated with re-excision—univariable and multivariable associations *

Factor	Univariable Odds Ratio (95% Confidence Interval)	p-value	Multivariable Odds Ratio (95% Confidence Interval)†	p-value
Time period		***0.005***		***0.014***
- Before 1/1/14	Reference		Ref	
- After 1/1/14	0.65 (0.49, 0.88)		0.53 (0.32, 0.88)	
Age	0.977 (0.963, 0.99)	**< *0.001***	0.995 (0.972, 1.017)	0.633
Invasive margin		**< *0.001***		**< *0.001***
- Negative (> 1 mm)	Ref		Ref	
- Close (≤ 1 mm)	6.09 (3.79, 9.75)		6.35 (3.01, 13.55)	
- Positive	66.89 (30.43, 176.79)		174.21 (66.24, 529.96)	
DCIS margin		**< 0.001**		**< *0.001***
- Negative (< 1 mm)	Ref		Ref	
- Close (≤ 1 mm)	19.28 (13.13, 28.65)		38.3 (21.53, 71.80)	
- Positive	408.91 (122.72, 2540.14)		844.43 (226.26, 5562.53)	
Receptor subtype		***0.008***		0.206
- ER/PR+, HER2−	Ref		Ref	
- HER2+	2.04 (1.27, 3.21)		2.01 (0.89, 4.47)	
- Triple negative	0.87 (0.46, 1.53)		1.39 (0.54, 3.41)	
Extensive intraductal component		**< 0.001**		***0.019***
- Absent	Ref		Ref	
- Present	3.52 (2.26, 5.42)		2.45 (1.16, 5.19)	
Lymphovascular Invasion		***0.032***		**0.736**
- Absent	Ref		Ref	
- Present	1.41 (1.03, 1.92)		1.11 (0.64, 1.87)	
Multifocality		**< 0.001**		***0.013***
- Absent	Ref		Ref	
- Present	3.64 (2.62, 5.05)		2.04 (1.16, 3.58)	
Presence of DCIS		***0.001***		0.118
- Absent	Ref		Ref	
- Present	2.11 (1.37, 3.38)		0.53 (0.24, 1.20)	

* Factors ***not*** associated with re-excision (univariable associations): method of detection, breast density, tumor size, tumor histology, nuclear grade, pathologic tumor or nodal classification, number of positive nodes, pathologic stage, and planned chemotherapy, radiation therapy, or endocrine therapy

† n = 1147

DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor