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Changes in Reoperation After Publication of Consensus Guidelines on Margins for Breast-Conserving Surgery
A Systematic Review and Meta-analysis

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IMPORTANCE The 2014 publication of the Society of Surgical Oncology–American Society for Radiation Oncology (SSO-ASTRO) Consensus Guideline on Margins for Breast-Conserving Surgery recommended a negative margin definition of no ink on tumor. Adoption of this guideline would represent a major change in surgical practice that could lower the rates of reoperation.

OBJECTIVE To assess changes in reoperation rates after publication of the SSO-ASTRO guideline.

DATA SOURCES A systematic search of Embase, PREMEDLINE, Evidence-Based Medicine Reviews, Scopus, and Web of Science for biomedical literature published from January 2014 to July 2019 was performed. This search was supplemented by web searches and manual searching of conference abstracts.

STUDY SELECTION Included studies compared the reoperation rates in preguideline vs postguideline cohorts (actual change), retrospectively applied the SSO-ASTRO guideline to a preguideline cohort (projected change), or described the economic outcomes of the guideline.

DATA EXTRACTION AND SYNTHESIS Study characteristics and reoperation rates were extracted independently by 2 reviewers. Odds ratios (ORs) were pooled by random effects meta-analysis. Analyses were stratified by study setting (institutional or population) and preguideline accepted margins. The economic outcomes of the guideline were summarized narratively. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline was followed.

MAIN OUTCOMES AND MEASURES Odds ratios for postguideline vs preguideline reoperation rates.

RESULTS From 1114 citations, 30 studies (with 599 016 participants) reported changes in reoperation rates. Studies included a median (range) of 487 (100-521 578) participants, and 20 studies were undertaken in the US, 6 in the UK, 3 in Canada, and 1 in Australia. Among 21 studies of actual changes, pooled ORs showed a statistically significant reduction in reoperation, with an OR lower in institution-based studies than in population-based studies (OR, 0.62 [95% CI, 0.52-0.74] vs 0.76 [95% CI, 0.72-0.80]; *P* = .04 for subgroup differences). Among 9 studies of projected changes, the pooled OR was lower for preguideline margin thresholds of 2 mm or more compared with 1 mm (OR, 0.47 [95% CI, 0.40-0.56] vs 0.85 [95% CI, 0.79-0.91; *P* < .001 for subgroup differences). Projected changes were likely to overestimate actual changes. Six studies that estimated the postguideline economic outcome found the guideline to be potentially cost saving, with a median (range) saving of US $3540 ($1800-$25 650) per woman avoiding reoperation.

CONCLUSIONS AND RELEVANCE This study found a decrease in reoperation rates after the publication of the SSO-ASTRO guideline; this reduction was greater at an institutional level than a population level, the latter reflecting the differences in guideline adoption between centers. These early outcomes may be conservative estimates of longer-term implications.

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Supplemental content

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Breast-conserving surgery (BCS) is a standard treatment for early-stage breast cancer that involves the removal of the cancer along with a margin of normal tissue. Although no ink on tumor was the only microscopic margin width defined in the prospective randomized clinical trials that established the safety of BCS, over time a wide variation in surgeon attitudes regarding the adequate negative margin emerged,[1] with frequent use of reexcision to obtain margins more widely clear than no ink on tumor.[2] In the absence of prospective randomized clinical trials examining the implication of negative margin width for local recurrence, numerous guidelines with variable scientific quality were developed that specified margin widths ranging from no ink on tumor to 5 mm or greater, with some guidelines concluding that the heterogeneity of the evidence base precluded the definition of a standard margin width.[3]

The debate about margin width began at a time when tumor burden was thought to be the primary determinant of local control. The recognition that tumor biology was a major determinant of local control, coupled with the recognition that systemic therapy substantially reduced locoregional recurrence,[4-6] led the Society of Surgical Oncology (SSO) and the American Society for Radiation Oncology (ASTRO) to develop an evidence-based consensus guideline on margins for BCS for early-stage invasive breast cancer. The SSO-ASTRO guideline was published in 2014.[7] It was underpinned by meta-analyses[8,9] that found that the use of wider threshold distances to define negative margins did not statistically significantly decrease the rates of local recurrence beyond those observed with a minimal negative margin width. In recommending a no-ink-on-tumor definition of a negative margin, the SSO-ASTRO guideline sought to standardize surgical practice and to reduce overtreatment associated with obtaining larger margin distances (ie, excessive resection at initial BCS, reoperation to achieve more widely clear margins, or conversion from BCS to mastectomy).

The adoption of the SSO-ASTRO guideline for invasive cancer could represent a major change in surgical practice given that before the guideline only 11% to 15% of surgeons reported that they accepted a margin of no ink on tumor for a lumpectomy.[1,10] The primary purpose of this systematic review and meta-analysis was to assess changes in reoperation rates after publication of the SSO-ASTRO guideline for surgical management of breast cancer. In addition, we sought to identify the potential economic outcomes of the guideline.

Key Points

Question Was the publication of the Society of Surgical Oncology–American Society for Radiation Oncology (SSO-ASTRO) margins guideline associated with a change in reoperation rates?

Findings In this systematic review and meta-analysis of 30 studies involving 599 016 participants, the odds of reoperation after a breast-conserving surgical procedure were statistically significantly lower after publication of the SSO-ASTRO guideline. Decreases in reoperation were greater at the institutional level than at the population level and when a larger negative margin was used in the preguideline period.

Meaning This study suggests that the SSO-ASTRO guideline is associated with a significant reduction in reoperation rates, an outcome that may improve with further adoption of SSO-ASTRO guideline recommendations.

Methods

Identification of Studies

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline. We undertook a systematic search of the biomedical literature published from January 2014 (the year of publication of the SSO-ASTRO guideline) through July 2019, to identify studies that assessed the potential implications of the margin guideline for invasive cancer. Embase, PREMEDLINE, and Evidence-Based Medicine Reviews (including Cochrane Database of Systematic Reviews) were searched through Ovid (the full search strategy is available in eTable 1 in the Supplement). Keywords and medical subject headings included breast cancer, surgical margin, guideline, and practice guideline. In addition, we performed a forward citation search for the guideline and the supporting meta-analysis on Scopus and Web of Science, and we conducted internet searches to identify conference materials that were not indexed in citation databases. When conference abstracts were identified by electronic searches, the full conference proceedings containing those abstracts were obtained and searched manually. Reference lists were searched and content experts were consulted to identify additional studies.

Review of Studies, Eligibility Criteria, and Data Extraction

One of us (M.L.M.) initially screened all abstracts for eligibility using broad exclusion criteria (eTable 2 in the Supplement). Briefly, citations were excluded if they did not relate to stage I or II invasive breast cancer, did not address margin guidelines, cited or summarized guidelines without an evaluative component, or were a duplicate or superseded publication. Another one of us (N.N.) independently assessed a random sample of 25% to ensure the consistent application of the eligibility criteria. Studies that reported changes in reoperation either by comparison of preguideline and postguideline periods (actual change) or by retrospective application of the SSO-ASTRO guideline to a preguideline cohort (projected change) were included for systematic synthesis in this review. Studies that described the economic outcomes of the guideline were included for narrative synthesis. Key excluded papers assessing the outcome of a 2016 SSO-ASTRO-American Society for Clinical Oncology (ASCO) consensus guideline for ductal carcinoma in situ[11] and related meta-analysis[12] are described in eTable 3 in the Supplement.

One of us (M.L.M.) reviewed potentially eligible citations in full to determine their eligibility, in consultation with a second author (N.H. or N.N.) as required. The screening and inclusion process is summarized in eFigure 1 in the Supplement.

Two of us (M.L.M. and N.N.) independently extracted information on reoperation rates, costs, study design, study setting, and patient characteristics using a prespecified data extraction form. Disagreements were resolved by discussion and consensus, with arbitration by a third author (N.H.) when required.

Statistical Analysis

We summarized study characteristics using median values and their associated ranges. Estimates of reoperation rates in preguideline and postguideline periods (and their difference) were calculated for each study, and exact 95% CIs were computed. For studies estimating actual changes, we computed SEs of the difference for independent proportions. For studies estimating projected changes, we used PROC GENMOD in SAS, version 9.4 (SAS Institute Inc), to take account of the pairing of results within an individual when computing the SEs. Log odds ratios (ORs) for reoperation and their SEs were also computed within studies, and each subgroup of studies defined by study design (actual vs projected changes in reoperation) was pooled separately using the inverse variance method with random effects for study (DerSimoneon and Laird method as implemented in Revman 5.3 [Cochrane Collaboration]).[13] We stratified studies by setting (institutional vs population) and the preguideline margin threshold recommendation for reoperation (1 mm vs ≥2 mm). The magnitude of statistical heterogeneity was assessed by the I^2 statistic.[13]

All tests of statistical significance were 2-sided, and the level chosen for statistical significance was $P = .05$. Data analysis was performed from July 2019 to December 2019.

Results

Eligible Studies and Study Characteristics

In total, 1114 citations were identified. Thirty studies were eligible for inclusion in the meta-analysis on changes in reoperation rate,[14-43] reporting data on 599 016 participants enrolled between January 1, 1998, and December 31, 2018. Studies included a median (range) of 487 (100-521 578) participants (**Table 1**). Most studies (n = 20) were undertaken in the US[15-18,20,21,23,25-30,32-34,36-38,40]; the remainder were conducted in the UK (n = 6),[22,24,31,32,35,42] Canada (n = 3),[14,19,39] and Australia (n = 1).[41] Fifteen studies[14,15,18,20,25,26,29,32-35,37-39,41] were full-text publications, and 15 studies[16,17,19,21-24,27,28,30,31,36,40,42,43] were reported as conference abstracts.

Twenty-one studies[15-21,23,24,26,28-30,32,33,36-41] reported actual changes in reoperation, in which reoperation rates in the preguideline and postguideline cohorts were compared. Most of these studies (n = 17)[16-21,26,28-30,32,33,36-38,40,41] were conducted in institutional settings, but 4 studies were based on the following large population data sets: the Surveillance, Epidemiology, and End Results Program[26]; the American Society of Breast Surgeons Mastery database[33]; the National Cancer Database[37]; and the MarketScan database.[17] The accepted margin distance in the preguideline period was not consistently reported in studies of actual changes in reoperation (Table 1); therefore, we did not attempt to stratify by margin threshold. Most of these studies (n = 17)[16-21,26,28-30,32,33,36-38,40,41] examined changes in reoperation that occurred within 2 years of the SSO-ASTRO guideline publication.

An additional 9 studies[14,22,25,27,31,34,35,42,43] assessed projected changes in reoperation, in which a margin of no ink on tumor was retrospectively applied to a preguideline cohort and avoidance of reoperation was estimated. All 9 studies were undertaken in institutional settings (hence stratification by study setting was not possible). Three studies[31,35,43] applied a 1 mm threshold margin in the preguideline period, and the other 6 studies[14,22,25,27,34,42] applied a threshold of 2 mm or more (Table 1).

In addition, 6 studies[14,34,38,44-46] of the economic outcomes of the SSO-ASTRO guideline were eligible for narrative synthesis. All studies were undertaken in North America (5 in the US,[34,38,44-46] and 1 in Canada[14]) and included institutional cost estimates (n = 4)[34,38,45,46] and decision analytic modeling (n = 2).[14,44] Five studies were full-text publications,[14,34,38,44,46] and 1 was reported as a conference abstract.[45]

Change in Reoperation

Study-specific data for reoperation rates, stratified by study design (actual vs projected change), are described in **Table 2**. Corresponding pooled ORs for postguideline vs preguideline reoperation are presented in **Figure 1** and **Figure 2**.

Pooled estimates for actual change in reoperation showed a statistically significant reduction in ORs for reoperation in both institution-based[15,16,18-21,23,24,28-30,36,38-41] and population-based studies[17,26,33,37] (Figure 1). The pooled OR for institution-based studies (OR, 0.62; 95% CI, 0.52-0.74; I^2 = 48%) was statistically significantly lower than that for population-based studies (OR, 0.76; 95% CI, 0.72-0.80; I^2 = 75%) (test for subgroup differences, $P = .04$). Moderate to substantial heterogeneity was present in both subgroups,[13] which was likely associated with differences in preguideline margin thresholds between studies and the resulting baseline reoperation rates (Table 1).

Of the 7 studies[15,17,21,24,32,39,40] that reported actual changes in reoperation according to whether the second operation was a mastectomy or repeat BCS (eTable 4 in the Supplement), 6 reported reductions in ORs of conversion to mastectomy after guideline vs before guideline publication (OR range, 0.10-0.93).[15,17,21,24,39,40] A single study[32] reported a nonsignificant increase in the odds of conversion to mastectomy (OR, 2.17; 95% CI, 0.44-10.78); however, the rate of mastectomy in this study remained less than 1% in the preguideline (0.4%) and postguideline (0.9%) periods. Reductions in ORs of repeat BCS were observed in all 7 studies (OR range, 0.09-0.90).[15,17,21,24,32,39,40]

Pooled estimates for projected change showed a statistically significant reduction in ORs for reoperation, with a lower pooled OR in studies that used a preguideline margin threshold of 2 mm or more (OR, 0.47; 95% CI, 0.40-0.56; I^2 = 79%)[14,22,25,27,34,42] vs studies that used a threshold of 1 mm (OR, 0.85; 95% CI, 0.79-0.91; I^2 = 51%)[31,35,43] (test for subgroup differences, $P < .001$) (Figure 2). Substantial heterogeneity was present in both subgroups. Heterogeneity was greater

Table 1. Study, Patient, and Testing Characteristics of Included Studies of Changes in Reoperation

Variable	Studies, No.	Patients, No. (%)	Study-level estimates, median (range)
All included studies			
No.	30	599 016 (100.0)	487 (100-521 578)
Publication type			
Full text	15	559 723 (93.4)	846 (201-521 578)
Conference abstract	15	39 293 (6.6)	417 (100-33 966)
Country			
United States	20	590 947 (98.7)	449 (100-521 578)
Canada	3	2223 (0.4)	599 (512-1112)
United Kingdom	6	5284 (0.9)	457 (317-2858)
Australia	1	562 (0.1)	562
Study design, change			
Actual	21	592 348 (98.9)	599 (100-521 578)
Projected	9	6668 (1.1)	450 (317-2858)
Studies of actual change in reoperation rates			
Years of recruitment (midpoint)			
Preguideline	20[a]	151 178 (25.5)	2012 (2006-2013)
Postguideline	20[a]	441 170 (74.5)	2014 (2014-2016)
Study setting			
Institutional	17	8726 (1.5)	463 (100-1205)
Population	4	583 622 (98.5)	30 034 (1976-521 578)
Preguideline margin			
1 mm	3[b]	1645 (31.8)	562 (237-846)
≥2 mm	6[b]	3534 (68.2)	572 (119-1112)
Studies of projected change in reoperation rates			
Years of recruitment (midpoint)			
Preguideline	9[c]	6668 (100.0)	2012 (2005-2016)
Study setting			
Institutional	9	6668 (100.0)	450 (317-2858)
Population	0	NA	NA
Preguideline margin			
1 mm	3	3592 (53.9)	417 (317-2858)
≥2 mm	6	3076 (46.1)	456 (436-779)

Abbreviation: NA, not applicable.

[a] One study[21] did not report sufficient information to derive midpoints of recruitment.

[b] Twelve of 21 studies (57.1%)[17,19,21,23,26,28,30,32,33,37,38,40] of actual changes in reoperation did not report the preguideline margin threshold.

[c] Two studies[35,43] of projected changes included women in the postguideline period. The Society of Surgical Oncology–American Society for Radiation Oncology guideline was not used in this period.

in the subgroup with a threshold of 2 mm or more, reflecting the range of potential thresholds applied in these studies.

All 3 studies of projected change that applied a 1 mm preguideline threshold were conducted in the UK[31,35,43]; 4 of 6 studies that applied a 2 mm or more threshold were from North America (US or Canada),[14,25,27,34] with the remaining 2 studies being from the UK.[22,42] In a post hoc subgroup analysis, differences in ORs persisted when pooled analyses were stratified by country (eFigure 2 in the Supplement), with a lower pooled OR in North American studies (OR, 0.45; 95% CI, 0.36-0.58; I^2 = 86%) than in UK studies (OR, 0.69; 95% CI, 0.57-0.84; I^2 = 93%) (test for subgroup differences, P = .007).

When estimates were pooled as risk differences (preguideline reoperation rates subtracted from postguideline reoperation rate), the results were consistent with those for pooled ORs; however, greater statistical heterogeneity was observed for pooled risk differences (larger I^2 value for each subgroup).[13] These pooled risk differences are presented in eFigures 3 and 4 in the Supplement for comparison with pooled ORs.

Economic Outcomes

Studies that estimated the potential economic outcome of the guidelines are summarized in **Table 3**.[14,34,38,44-46] All 5 US studies found the SSO-ASTRO guideline to be potentially cost saving,[34,38,44-46] with a median (range) saving of US $3540 ($1800-$25 650) per woman from avoiding reoperation,[34,38,45,46] whereas the Canadian study estimated a cost saving of CAD $698 (US $680) per woman from undergoing BCS.[14] One additional US study estimated an annual national cost saving of US $18.8 million from the avoidance of reoperation for close margins.[44] This cost saving was considered to be a conservative estimate owing to the exclusion of hospital costs and costs of surgical complications and the use of Medicare reimbursement rates in decision analytic models.

Table 2. Study-Level Reoperation Rates Stratified by Studies of Actual vs Projected Changes

Source	Preguideline			Postguideline			Postguideline vs preguideline	
	No.	Reoperation No.	Reoperation % (95% CI)	No.	Reoperation No.	Reoperation% (95% CI)	Difference in % (95% CI)	Odds ratio (95% CI)
Actual change in reoperation								
Bhutani et al,[15] 2018	126	46	36.5 (28.1 to 45.5)	111	10	9.0 (4.4 to 15.9)	−27.5 (−37.5 to −17.5)	0.17 (0.08 to 0.36)
Cate et al,[16]2015	102	11	10.8 (4.8 to 16.8)	103	1	1.0 (0.0 to 5.3)	−9.8 (−16.1 to −3.5)	0.08 (0.01 to 0.64)
Chavez-MacGreggor et al,[17] 2018	20 159	5100	25.3 (24.7 to 25.9)	13 807	2982	21.6 (20.9 to 22.3)	−3.7 (−4.6 to −2.8)	0.81 (0.77 to 0.86)
Chung et al,[18] 2015	597	115	19.3 (16.1 to 22.4)	249	32	12.9 (8.7 to 17.0)	−6.4 (−11.6 to −1.2)	0.62 (0.40 to 0.94)
Drohan et al,[19] 2018	188	26	13.8 (9.2 to 19.6)	411	32	7.8 (5.4 to 10.8)	−6.0 (−11.6 to −0.5)	0.53 (0.30 to 0.91)
Heelan Gladden et al,[20] 2017	395	42	10.6 (7.8 to 14.1)	286	29	10.1 (6.9 to 14.2)	−0.5 (−5.1 to 4.1)	0.95 (0.58 to 1.56)
Heidrich et al,[21] 2016	124	40	32.3 (24.1 to 41.2)	42	1	2.4 (0.1 to 12.6)	−29.9 (−39.3 to −20.5)	0.05 (0.01 to 0.39)
Israel et al,[23] 2018	110	22	20.0 (13.0 to 28.7)	150	20	13.3 (8.3 to 19.8)	−6.7 (−15.9 to 2.6)	0.62 (0.32 to 1.19)
Jiwa et al,[24] 2015	225	48	21.3 (16.2 to 27.3)	238	32	13.4 (9.4 to 18.5)	−7.9 (−14.8 to −1.0)	0.57 (0.35 to 0.94)
Kantor et al,[37] 2019[a]	402 678	NR	NR	118 900	NR	NR	−3.6 (NR)	0.76 (0.75 to 0.78)
Mamtani et al,[40] 2019	312	98	31.4 (26.3 to 36.9)	433	100	23.1 (19.2 to 27.4)	−8.3 (−14.8 to −1.8)	0.66 (0.47 to 0.91)
Monaghan et al,[39] 2019	523	118	22.6 (19.1 to 26.4)	589	110	18.7 (15.6 to 22.1)	−3.9 (−8.7 to 0.9)	0.79 (0.59 to 1.05)
Morrow et al,[26] 2017[b]	851	232	27.3 (24.3 to 30.4)	1125	205	18.2 (16.0 to 20.6)	−9.0 (−12.8 to −5.3)	0.59 (0.48 to 0.74)
Parma et al,[28] 2018	15	3	20.0 (4.3 to 48.1)	85	11	12.9 (6.6 to 22.0)	−7.1 (−28.5 to 14.4)	0.59 (0.14 to 2.45)
Patten et al,[29] 2017	402	82	20.4 (16.6 to 24.7)	552	90	16.3 (13.3 to 19.7)	−4.1 (−9.1 to 0.1)	0.76 (0.55 to 1.06)
Pawloski et al,[30] 2016	123	42	34.1 (25.8 to 43.2)	148	34	23.0 (16.5 to 30.6)	−11.2 (−21.9 to −0.4)	0.58 (0.34 to 0.98)
Philpott et al,[41] 2018	204	51	25.0 (19.2 to 31.5)	358	59	16.5 (12.8 to 20.7)	−8.5 (−15.6 to −1.4)	0.59 (0.39 to 0.90)
Rosenberger et al,[32] 2016	504	108	21.4 (17.9 to 25.3)	701	106	15.1 (12.5 to 18.0)	−6.3 (−10.8 to −1.9)	0.65 (0.49 to 0.88)
Schulman et al,[33] 2017[c]	13 297	2482	18.7 (18.0 to 19.3)	12 805	1851	14.5 (13.9 to 15.1)	−4.2 (−5.1 to −3.3)	0.74 (0.69 to 0.79)
Van Den Bruele et al,[38] 2018	116	23	19.8 (13.0 to 28.3)	85	13	15.3 (8.4 to 24.7)	−4.5 (−15.1 to 6.0)	0.73 (0.35 to 1.54)
Wall et al,[36] 2015	53	7	13.2 (5.5 to 25.3)	66	12	18.2 (9.8 to 29.6)	5.0 (−8.1 to 18.0)	1.46 (0.53 to 0.74)
Projected change in reoperation								
Baliski and Pataky,[14] 2017	512	126	24.6 (20.9 to 28.6)	512	82	16.0 (12.9 to 19.5)	−8.6 (−11.1 to −0.1)	0.58 (0.50 to 0.68)
Bell,[43] 2018	417	78	18.7 (15.1 to 22.8)	417	62	14.8 (11.6 to 18.7)	−3.8 (−5.7 to −2.0)	0.76 (0.66 to 0.87)
Hogan et al,[22] 2014	450	111	24.7 (20.7 to 28.9)	450	70	15.6 (12.2 to 18.9)	−9.1 (−11.8 to −6.5)	0.56 (0.47 to 0.67)
Merrill et al,[25] 2016	437	139	31.8 (27.5 to 36.4)	437	77	17.6 (14.2 to 21.5)	−14.2 (−17.5 to −10.9)	0.46 (0.38 to 0.55)
Nayyar et al,[27] 2018	436	143	32.8 (28.4 to 37.4)	436	56	12.8 (9.9 to 16.3)	−19.9 (−23.7 to −16.2)	0.30 (0.24 to 0.38)
Pickard et al,[31] 2015	317	62	19.6 (15.3 to 24.4)	317	55	17.4 (13.3 to 22.0)	−2.2 (−3.8 to −0.1)	0.86 (0.78 to 0.96)
Singer et al,[34] 2016	462	149	32.3 (28.0 to 36.7)	462	88	19.0 (15.6 to 22.9)	−13.2 (−16.3 to −10.1)	0.49 (0.42 to 0.58)
Tang et al,[35] 2017	2858	493	17.2 (15.9 to 18.7)	2858	441	15.4 (14.1 to 16.8)	−1.8 (−2.3 to −1.3)	0.88 (0.84 to 0.91)
Truda,[42] 2019	779	102	13.1 (10.8 to 15.7)	779	50	6.4 (4.8 to 8.4)	−6.7 (−8.4 to −4.9)	0.46 (0.37 to 0.56)

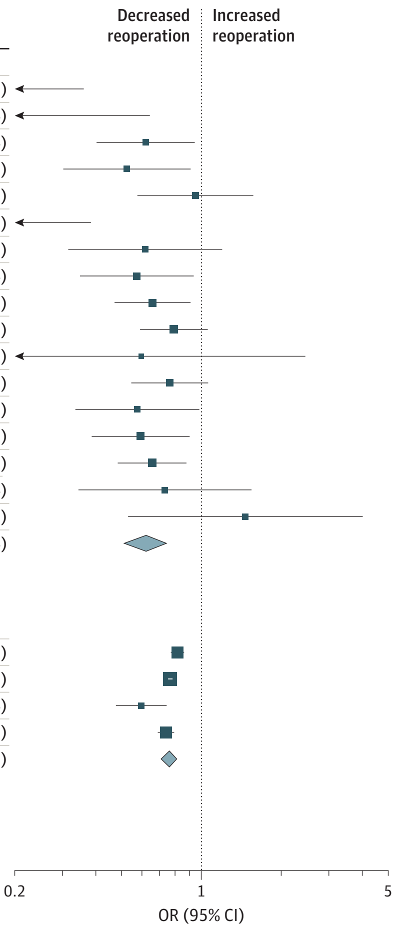
[a] Preguideline and postguideline numerators and percentages were not reported (NR) in the publication.

[b] Data provided by study authors.

[c] Preguideline and postguideline percentages were derived from numerators and denominators reported in the publication (these differ from the reported percentages).

Figure 1. Actual Changes in Reoperation, Stratified by Study Setting

Source	Postguideline total, No.	Preguideline total, No.	OR (95% CI)	Weight, %
Institution-based studies				
Bhutiani et al,[15] 2018	111	126	0.17 (0.08-0.36)	4.1
Cate et al,[16] 2015	103	102	0.08 (0.01-0.64)	0.7
Chung et al,[18] 2015	249	597	0.62 (0.40-0.94)	7.9
Drohan et al,[19] 2017	411	188	0.53 (0.30-0.91)	6.1
Heelan Gladden et al,[20] 2017	286	395	0.95 (0.58-1.56)	6.7
Heidrich et al,[21] 2016	42	124	0.05 (0.01-0.39)	0.7
Israel et al,[23] 2015	150	110	0.62 (0.32-1.19)	4.8
Jiwa et al,[24] 2015	238	225	0.57 (0.35-0.94)	6.9
Mamtani et al,[40] 2019	433	312	0.66 (0.47-0.91)	9.7
Monaghan et al,[39] 2019	523	589	0.79 (0.59-1.05)	10.4
Parma et al,[28] 2018	85	15	0.59 (0.14-2.45)	1.4
Patten et al,[29] 2017	552	402	0.76 (0.55-1.06)	9.6
Pawloski et al,[30] 2016	148	123	0.58 (0.34-0.98)	6.2
Philpott et al,[41] 2018	358	204	0.59 (0.39-0.90)	7.9
Rosenberger et al,[32] 2016	701	504	0.65 (0.49-0.88)	10.3
Van Den Bruele et al,[38] 2018	85	116	0.73 (0.35-1.54)	4.1
Wall et al,[36] 2015	66	53	1.46 (0.53-4.02)	2.5
Subtotal	4541	4185	0.62 (0.52-0.74)	100
Heterogeneity: $\tau^2 = 0.06$; $\chi^2_{16} = 30.82$ ($P = .01$); $I^2 = 48\%$				
Overall effect: $z = 5.26$ ($P < .001$)				
Population-based studies				
Chavez-MacGregor et al,[17] 2017	13 807	20 159	0.81 (0.77-0.86)	30.0
Kantor et al,[37] 2019	118 900	402 678	0.76 (0.75-0.78)	37.8
Morrow et al,[26] 2017	1125	851	0.59 (0.48-0.74)	6.2
Schulman et al,[33] 2017	12 805	13 297	0.74 (0.69-0.79)	26.1
Subtotal	146 637	436 985	0.76 (0.72-0.80)	100
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_3 = 12.13$ ($P = .007$); $I^2 = 75\%$				
Overall effect: $z = 9.37$ ($P < .001$)				
Subgroup differences: $\chi^2_1 = 4.41$ ($P = .04$); $I^2 = 77.3\%$				



OR indicates odds ratio.

Discussion

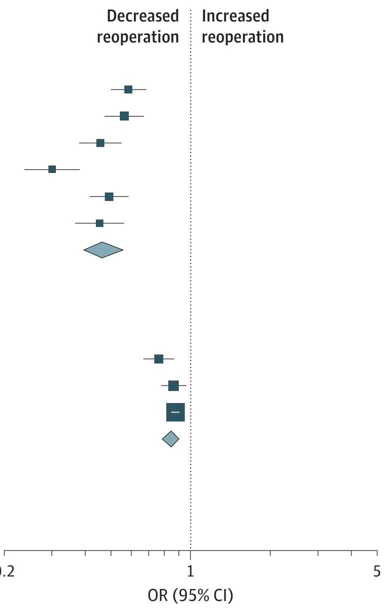
The 2014 SSO-ASTRO guideline[7] and related meta-analysis[8,9] for early-stage invasive breast cancer heralded an opportunity to change the entrenched practice of resecting more breast tissue than warranted to achieve local control in BCS. Although the recommendation of no ink on tumor generated mixed discussion,[47,48] it was generally endorsed by societies such as ASCO and the American Society of Breast Surgeons.[49-51] The main objective of this systematic review was to assess whether these guidelines have translated into changes in breast cancer surgical practice. This meta-analysis found strong evidence of an early change in reoperation rates after the initial BCS following the introduction of the SSO-ASTRO guideline based on data from 30 studies (collectively involving 599 016 participants).

Pooled estimates showed a statistically significant reduction in the odds of reoperation in studies that reported actual change in reoperation rate (preguideline vs postguideline) for both institution-based (OR, 0.62) and population-based (OR, 0.76) studies. Although these pooled estimates differed in magnitude, there was consistency in the direction of change. The smaller reduction in the odds of reoperation observed in the population-based studies likely reflects a variation in practice among different institutions captured in these data sets, both in the timeliness and/or extent of guideline adoption and in the definition of an adequate margin used in the preguideline period. Because these studies primarily assessed the changes in reoperation within 2 years of publication of the guideline, these may be conservative estimates of the long-term implication for reducing the rates of reoperation.

Similarly, studies that projected the change in reoperation (had the guideline been applied) showed a significant reduction in the odds for reoperation, although the estimates differed across analyses stratified by preguideline margin threshold. The marked reduction in reoperation in studies that used a preguideline margin threshold of 2 mm or more (OR, 0.47) highlights the potential for greater change in settings in which wider margins were required before the diffusion of the guideline. As anticipated, in studies that already used a narrower margin threshold of 1 mm, a smaller change was observed (OR, 0.85). However, studies of projected changes in reoperation assumed that all women with close margins would

Figure 2. Estimated Changes in Reoperation, Stratified by Preguidelines Margin Definition

Source	Postguideline total, No.	Preguideline total, No.	OR (95% CI)	Weight, %
Preguideline margin: ≥2 mm				
Baliski and Pataky,[14] 2017	512	512	0.58 (0.50-0.68)	17.9
Hogan et al,[22] 2014	450	450	0.56 (0.47-0.67)	17.3
Merrill et al,[25] 2016	437	437	0.46 (0.38-0.55)	16.8
Nayyar et al,[27] 2018	436	436	0.30 (0.24-0.38)	14.7
Singer et al,[34] 2016	462	462	0.49 (0.42-0.58)	17.4
Truda et al,[42] 2019	779	779	0.46 (0.37-0.56)	15.8
Subtotal	3076	3076	0.47 (0.40-0.56)	100
Heterogeneity: $\tau^2 = 0.03$; $\chi^2_5 = 24.30$ ($P < .001$); $I^2 = 79\%$				
Overall effect: $z = 8.87$ ($P < .001$)				
Preguideline margin: 1 mm				
Bell,[43] 2018	417	417	0.76 (0.66-0.87)	20.0
Pickard et al,[31] 2015	317	317	0.86 (0.78-0.96)	26.1
Tang et al,[35] 2017	2858	2858	0.88 (0.84-0.91)	53.8
Subtotal	3592	3592	0.85 (0.79-0.91)	100
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_2 = 4.12$ ($P = .13$); $I^2 = 51\%$				
Overall effect: $z = 4.48$ ($P < .001$)				
Subgroup differences: $\chi^2_1 = 40.17$ ($P < .001$); $I^2 = 97.5\%$				



OR indicates odds ratio.

Table 3. Economic Outcomes of the Society of Surgical Oncology–American Society for Radiation Oncology Consensus Guideline

Source (country)	Design	Cost saving?	Estimate, $[a]
Baliski and Pataky,[14] 2017 (Canada)	Decision tree model	Yes	CAD $698 (US $680) per patient undergoing BCS
Yu et al,[46] 2017 (US)	Institutional cost estimate	Yes	2360 per patient avoiding reexcision
Van Den Bruele et al,[38] 2018 (US)	Institutional cost estimate	Yes	25 654 per patient avoiding reexcision
Singer et al,[34] 2016 (US)	Institutional cost estimate	Yes	1802 per patient avoiding reexcision
Arora et al,[45] 2015 (US)	Institutional cost estimate	Yes	4721 per patient avoiding reexcision
Abe et al,[44] 2015 (US)	Decision tree model	Yes	18.8 million per year (nationally)

Abbreviation: BCS, breast-conserving surgery.

[a] Estimates are shown in US dollars unless otherwise specified.

avoid reoperation by the application of a no-ink-on-tumor threshold. The SSO-ASTRO guideline acknowledged that in the postguideline period, clinical judgment based on patient and tumor factors would sometimes result in reexcision even when a margin of no ink on tumor was obtained. This means that studies that use a predictive approach are likely to overestimate reductions in reoperation compared with studies that document actual changes. We did not undertake similar stratification of studies of actual change in reoperation, in which margin thresholds in the preguideline period were incompletely or inconsistently reported because many practices did not routinely use a single margin width.

A previous meta-analysis[52] of studies on the SSO-ASTRO guideline showed a statistically significant reduction in actual reoperation in 7 studies (pooled OR, 0.65). However, because of the larger number and broader range of studies included in the present meta-analysis, we were able to explore the significant statistical heterogeneity noted in that earlier review. This analysis highlighted the differences in guideline outcomes by both study setting and accepted margins in the preguidelines era, allowing our estimates to be applied to specific institutional or population-level scenarios. In addition, this review highlighted the economic outcome of the guideline. All eligible studies estimated substantial cost savings through the avoidance of reoperation, ranging from US $1800 to $25 650 per woman avoiding reoperation.

An investigation of longer-term outcomes is warranted to explore the degree to which changes in practice are sustained or become more widely disseminated. Similarly, additional research into changes in reoperation rates after the 2016 publication of SSO-ASTRO-ASCO guideline for ductal carcinoma in situ (with particular reference to positive, close, or negative margin status) is required to define its outcome. Overall, the SSO-ASTRO guideline has had a favorable outcome for surgical practice in early-stage invasive breast cancer, playing a substantial role in reducing overtreatment.

Limitations

This study has several limitations. Because most of the studies conducted a preguideline vs postguideline comparison of reoperation rates, potential confounding factors could not be excluded. An increase in the use of cavity-shave margins in the postguideline era has been suggested as an alternative explanation of reductions in reoperation.[53] However, institutional studies in which cavity shaves were performed routinely both before and after the guidelines (with no change in practice over the study period) reported significant reductions in reoperation, with ORs comparable to the pooled estimates of the present study.[18,32] A study of 316 114 patients who underwent BCS for stage 0, 1, and 2 breast cancer between 2004 and 2010 observed only a 2.7% decrease in reexcision during that time period, emphasizing the stability of reexcision rates in the preguideline era.[54] In their population-based study, Morrow et al[26] controlled for patient and tumor factors in the preguideline and postguideline periods and reported an OR of 0.59 for reoperation in the postguideline period for patients with invasive cancer. In contrast, in patients with ductal carcinoma in situ to whom the guideline did not apply, no change in reoperation was observed.[26] Other studies have noted no other major changes in breast oncology practice associated with the preguideline and postguideline periods that could account for the consistent reduction in reoperation rates observed in the included studies.[37] These factors, coupled with surveys showing substantial increases in endorsement by surgeons of a no-ink-on-tumor margin after vs before the guidelines,[1,26] suggest that the SSO-ASTRO guideline was the primary factor in reduced reoperation rates observed in this meta-analysis.

The follow-up period of included studies was insufficient to assess rates of local recurrence. Even with a longer postguideline follow-up, assessing the potential changes in recurrence rate will be challenging. Given the low recurrence rates (currently 2% to 3% at 10 years for estrogen receptor–positive cancers) and a small expected effect of the change in margin definition,[8,9,12] large sample sizes are required. Furthermore, because tumor burden is just 1 of multiple factors recognized to reduce local recurrence, controlling for the confounding effects of tumor subtype and changes in systemic and hormone therapies over time would require detailed data not typically available in retrospective studies.

Conclusions

In this systematic review and meta-analysis, we assessed the changes in reoperation rates after publication of the SSO-ASTRO margins guideline for invasive breast cancer. Findings of this study show a significant reduction in the odds of reoperation after publication of the guideline. These findings were complemented by reports of substantial cost savings through the avoidance of reoperation. These changes were observed over a relatively short time frame after the publication of the guideline.

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Concept and design: Marinovich, Houssami.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Marinovich, Houssami.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Marinovich.
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