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ORIGINAL ARTICLE – GUIDELINE AND META-ANALYSIS

The Association of Surgical Margins and Local Recurrence in Women with Early-Stage Invasive Breast Cancer Treated with Breast-Conserving Therapy: A Meta-Analysis

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ABSTRACT

Purpose. There is no consensus on what constitutes adequate negative margins in breast-conserving therapy (BCT). We systematically review the evidence on surgical margins in BCT for invasive breast cancer to support the development of clinical guidelines.

Methods. Study-level meta-analysis of studies reporting local recurrence (LR) data relative to final microscopic margin *status* and the threshold *distance* for negative margins. LR proportion was modeled using random-effects logistic meta-regression.

Results. Based on 33 studies (LR in 1,506 of 28,162), the odds of LR were associated with margin *status* [model 1: odds ratio (OR) 1.96 for positive/close vs negative; model 2: OR 1.74 for close vs. negative, 2.44 for positive vs. negative; ($P < 0.001$ both models)] but not with margin *distance* [model 1: >0 mm vs. 1 mm (referent) vs. 2 mm vs. 5 mm ($P = 0.12$); and model 2: 1 mm (referent) vs. 2 mm vs. 5 mm ($P = 0.90$)], adjusting for study median follow-up time. There was little to no statistical evidence that the odds of LR decreased as the distance for declaring negative margins increased, adjusting for follow-up time [model 1: 1 mm (OR 1.0, referent), 2 mm (OR 0.95), 5 mm (OR 0.65), $P = 0.21$ for trend; and model 2: 1 mm (OR 1.0, referent), 2 mm (OR 0.91), 5 mm (OR 0.77), $P = 0.58$ for trend]. Adjustment for covariates, such as use of endocrine therapy or median-year of recruitment, did not change the findings.

Conclusions. Meta-analysis confirms that negative margins reduce the odds of LR; however, increasing the *distance* for defining negative margins is not significantly associated with reduced odds of LR, allowing for follow-up time. Adoption of wider relative to narrower margin widths to declare negative margins is unlikely to have a substantial additional benefit for long-term local control in BCT.

Both tumour burden and tumour biology contribute to clinical outcomes in breast cancer (BC). The effectiveness of breast-conserving therapy (BCT) [breast-conserving surgery (BCS) and radiation therapy] for local treatment of invasive BC is well established.[1–6] Adequate local control has been shown to confer a survival benefit at long-term follow-up.[6] BCS aims to achieve a balance between complete resection of the tumour and to avoid excessive resection of breast tissue to provide good cosmetic outcome.[7,8] Many tumour and therapeutic factors influence the risk of local (in-breast) recurrence (LR) after BCT for invasive BC, including the status of surgical margins.[6–12]

There is consensus that the risk of LR is increased if the surgical margins are positive (ink on tumour cells at the resection margin), although estimates of effect vary between studies.[8,10,12,13] However, to date, there is no consensus on what constitutes an adequate negative margin for BCS.[12–17] Lack of consensus on this issue is reflected in variations in practice amongst clinicians, countries, and clinical guidelines, with the net result that reexcision to achieve more widely clear margins is commonly performed.[11,17–20]

In this work, we extend our previous systematic review on margins to provide an updated summary of the evidence

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on the association between tumour margins in invasive BC and LR, to support the development of consensus guidelines.[10] Using study-level meta-analysis, the evidence on surgical margins in women with early-stage invasive BC treated with BCT was systematically examined (a) to estimate the effect of microscopic margin status on LR, (b) to examine the effect of various thresholds to define negative (and relative positive or close) margins, and (c) to discuss whether a minimum negative distance or width can be defined for margins in relation to maximising local control.

METHODS

The methodology used in this systematic review was based on published work from Houssami et al.[10] and will be described relatively briefly.

Criteria for Study Eligibility

Studies were eligible for inclusion if they reported data allowing calculation of the *proportion of LR* in relation to margin status and the threshold width or distance used to declare a negative margin, and where the following predefined criteria also were met[10]: (1) subjects had early-stage invasive BC (clinical or pathological stages I and II in at least 90 %); (2) treatment consisted of BCT [BCS and whole-breast radiotherapy (WBR)]; (3) reported quantitatively-defined microscopic margins where negative margins, and relatively positive and/or close margins, were defined in terms of a threshold distance or width from the cut edge of the specimen (exception noted below); (4) provided age data; and (5) had a *minimum* median or mean follow-up time of 4 years.

Studies reporting LR without quantifying margins, or where all subjects had the same margin status, or using nonstandard or unclear margin definitions, or limited to small subgroups, were ineligible. For the updated meta-analysis, we also considered studies that did not declare a quantified distance for negative margins (hence not meeting criterion number 3) provided that the information in the study allowed classification of negative margins as >0 mm; however, these studies were not included in trend analysis for negative margin distance. Authors were contacted for clarification or for further information on definitions and/or data where necessary.

Study eligibility criteria considered epidemiological principles in evaluating prognostic studies—specifically, that subjects were assembled at a relatively common point in the course of disease and that adequate follow-up time was allowed for clinical endpoints to have occurred.[10,21,22] Therefore, eligibility criteria for this review integrated cancer stage and a minimum follow-up time as a quality filter and required final *microscopic* margins and WBR as inclusion criteria to reflect standards of care. Additional information to help characterize and appraise eligible studies was extracted, including design, population characteristics, follow-up, margin assessment, and treatment-related variables. These were partly adapted from a framework and recommendations for assessing the internal validity of studies dealing with prognosis in meta-analysis.[21,22]

Literature Search and Data Extraction

A systematic literature search was conducted [MEDLINE and EBM reviews, 1965 to May 2010 (initial search); Medline search updated at January 2013] for primary studies that met eligibility criteria, using the search and study identification strategy summarised in Online-Appendix 1. One investigator (NH) screened abstracts identified in the literature search ($n = 870$) and full-text of potentially relevant studies ($n = 115$). Data from eligible studies ($n = 33$) were extracted independently by two investigators (NH, MLM for updated data extraction; or as previously described) using predefined data forms.[10,23–55] The search strategy and identification of eligible studies (including information on related studies and excluded studies) are presented in Online-Appendix 1.[56–89] Where two or more papers reported the same cohort, the most recent study (that provided margin-specific LR data) was preferentially used to minimize duplicate data—additional details in Online-Appendix 1.

Extracted Variables

Descriptive and quantitative data were extracted from each study for the following: margin definition and categories, LR definition and outcomes data, duration of (and losses to) follow-up, years of study recruitment, study design, age, stage (distribution, node status, aggregate tumour size), surgery including reexcision, radiation therapy [WBR dose, boost (proportion given boost and dose), total dose to tumor bed, node irradiation], systemic therapy (endocrine or chemotherapy use), hormone receptors, tumor grade, lymphovascular invasion (LVI), and extensive intraductal component (EIC). We did not collect the following variables (HER2 status, histology distribution) because our prior data extractions indicated that few studies reported these variables.

Definitions of Variables

Margins Study-specific information on the definition of the *final* microscopic margins, from excision or reexcision, was extracted based on margin *status* (whether negative,

close, or positive) and margin *distance* (the width used as the threshold for declaring negative margins relative to positive or close). To standardize synthesis of the evidence on microscopic margins, we considered a *standard* classification for positive margins to be the presence of (invasive or in situ) cancer at the transected or inked margin. Negative margins were defined as the absence of tumour within a specified distance (mm) of the resection margin, with a close margin indicating presence of tumour within that distance *but not at* the resection margin. Studies reporting margin distance for negative relative to positive (without differentiating close from positive) also were considered. To allow for variable classification of margins across studies, two models were developed (see also "Statistical Analysis" section): *model 1* included all studies, combining positive and close (because some studies did not distinguish between these categories or did not report LR data separately for positive and close) compared with negative; and *model 2* included studies allowing comparisons across the three categories positive, close and negative.

Where an *unknown* margin category was reported, this was generally due to: specimen not being inked, specimen fragmented or removed in pieces; microscopic margins not given in the pathology report; or specimen not available (in studies where specimens were reviewed).[38,40,42,47,49] Because the unknown category cannot contribute meaningful data on the effect of margins, it has not been included in our models however data for this category were included in descriptive analyses.

Local Recurrence Definition and data for LR as endpoint was classified into two categories: *LR* (*first*), for studies reporting LR as the *first site of relapse* (including studies where LR may have occurred alone or simultaneously with regional and/or distant relapse); and *LR* (*any*), for studies reporting LR occurring at *any* time (including LR as the first site of relapse *or* concurrent with or after regional or distant relapse, *or* LR not further specified).

Covariates Extracted variables were classified based on quantitative data; additional information was categorized for stage, surgery, and losses to follow-up, for analytic purposes. Studies were classified into two categories for stage: (1) all subjects had stage I–II BC; or (2) $\geq$90 % of subjects were estimated to have had stage I–II BC, based on reported stage-distribution, or derived from tumor-size and node data distribution. Therefore, category 2 studies included some stage 0 (DCIS), stage III, or stage unknown in <10 % of subjects. Studies reporting quadrantectomy in some subjects also were examined separately.[32,35,38,40,41,43,48,50,54] Studies reporting information on losses to follow-up were compared with those not reporting any information on this variable.

Statistical Analysis

Descriptive analyses were used to examine the distribution of study-level variables. For continuous measures, the median, range, and interquartile range (IQR) were calculated. The proportion of women who had a LR was modeled using random effects logistic meta-regression. Random study effects were included in all models to allow for anticipated heterogeneity between studies beyond what would arise from within study sampling error alone. Taking account of both within, and between study variability provides valid standard errors, confidence intervals, and P values. Statistical significance was set at $P < 0.05$ (two-sided); $P < 0.1$ was considered as weak evidence of association for analysis of covariates (see below).

Modeling was used to assess whether the odds of LR were associated with margin status and distance, adjusted for study-specific median follow-up time (given that risk of LR is known to increase with longer follow-up time and based on evidence of association in our prior and present meta-analysis). Margin status and distance were tested for interaction. Each covariate was fitted both univariately (in a model that did not include margins) and also jointly with margin status and distance, and study median follow-up time (adjusted models). Study-specific median age and median follow-up time were fitted as continuous variables. Covariates that showed *at least* a weak association ($P < 0.1$) with LR *either* univariately or in the adjusted models were further examined and reported in the models; LR type also was included in modeling based on clinical relevance. *Covariates reported in less than half of studies were not considered reliable for modeling*.

In Model 1, margin status was fitted as a dichotomous variable (positive/close vs negative) and distance was fitted as a categorical variable (>0 mm vs. 1 mm vs. 2 mm vs. 5 mm), using 1 mm as the referent category. Each model was refitted to test for trend across distance categories (coded as 1, 2, 3) by treating the categories as equally spaced on a continuous scale, after excluding the group >0 mm (because the order of this group on a continuous scale cannot be definitively determined). In Model 2, margin status was fitted as three categories: positive versus close versus negative (referent category); distance was fitted as a categorical variable (1 mm (referent) vs. 2 mm vs. 5 mm); and testing for trend across distance categories was as described for Model 1. For both adjusted models, we also examined pair-wise comparisons of the various distances used to declare a negative margin. Models were fitted using Proc NLmixed in SAS.

RESULTS

Thirty-three studies reporting on 32,363 subjects were eligible for inclusion in this review, and provided margins

data in 28,162 subjects (1,506 LRs) included in our models.[23–55] Study-specific characteristics are summarized in online-Appendix 2. Table 1 reports descriptive analyses; the median of the reported median follow-up times was 79.2 months (IQR 58.8–110.6), and the median prevalence of LR was 5.3 % (IQR 2.3–7.6 %) in 28,162 subjects with margins data. In 18 studies, all subjects had stage I–II BC, and 15 studies included subjects with stage I–II BC in >90 % of the cohort—overall >96 % of subjects in this meta-analysis had stage I–II invasive BC. Studies were retrospective, with the exception of Bellon et al.[36] (RCT of sequencing of therapy) and Voogd et al.[47] (which scored margins for BCS arms of two RCTs). The prevalence of LR in 3,391 subjects with unknown margins (not included in models) was 10 %.

For analytic purposes, one study using 1 high-power field for negative margins was included in the 1-mm group, and one study using 3 mm was included in the 5-mm group.[41,47] Neuschatz et al.[39] reported two thresholds for distance: 5 mm was used in our analysis to balance the distribution of studies across distance categories.

Effect of Margins on LR

Model 1 Based on 33 studies reporting LR in 1,506 of 28,162 subjects with data on positive and/or close and negative margins; study-specific and (unadjusted) pooled odds ratios (OR) are shown in Fig. 1.[23–55] The proportion of subjects with LR stratified by the distance for negative margins is shown in Fig. 2. Model estimates of effect are presented in Table 2 (model 1): in the *unadjusted* model (which does not factor differences in follow-up time between studies) the odds of LR were associated with margin status ($P < 0.001$) and weakly associated with margin distance ($P = 0.06$) with evidence that the odds of LR decreased as the distance for declaring negative margins increased ($P = 0.011$ for trend). Based on prior information and evidence of association between the odds of LR and study-specific median follow-up time ($P < 0.0001$) in this analysis, the *adjusted model* shows all estimates adjusted for median follow-up time (Table 2). In the adjusted model, the odds of LR were associated with margin status ($P < 0.001$) but *not* with margin distance ($P = 0.12$), and there was no statistical evidence that the odds of LR decreased as the distance for negative margins increased ($P = 0.21$ for trend). There was no evidence of interaction: effect of margin status did not vary by distance or vice versa ($P = 0.17$).

Exclusion of two studies reporting data for locoregional recurrence from the model had little effect on model estimates.[30,45] The odds of LR were not associated with whether studies reported no losses or <5 % losses to follow-up or whether they did not provide any information on losses to follow-up ($P = 0.27$; adjusted model).[27,31,36,38,41,48,54] The odds of LR did not differ according to whether or not studies included some subjects treated with quadrantectomy ($P = 0.58$; adjusted model).

Effect of Study Time-Frame

Based on all 33 studies, the LR rates by median year of study recruitment declined over time (online-Fig. 3); median year of study recruitment was strongly associated with LR rates ($P < 0.0001$) in univariate analysis and also associated with LR in the adjusted model ($P = 0.0086$).

Effect of Covariates in Model 1

Only covariates meeting predefined criteria for potential association or relevance (see "Statistical Analysis" section) were further examined for effect on model estimates. Table 3 summarises results for these covariates, showing association with LR in univariate analysis, and the association once each of these covariates was entered into a model that included margins and median follow-up time; remaining associations were for age, median year of study recruitment, proportion receiving endocrine therapy, proportion ER-positive, proportion that had reexcision, and LR type.

Adjusting model 1 for covariates (Table 3) did not alter the effect of margin *status*: there was a significant association ($P < 0.001$) between margin status and the odds of LR in *all* adjusted analyses. In all (except one) of the adjusted models, there was no evidence of an association between the odds of LR and margin distance, nor evidence of a significant decrease in the odds of LR as the distance for negative margins increased (Table 3). In the model that adjusted for LR type, there was weak evidence that the odds of LR decreased as the threshold distance for negative margins increased ($P = 0.074$ for trend).

Pair-wise comparisons of negative distance—adjusted model 1

The odds of LR were significantly higher for the studies using >0 mm relative to 5 mm ($P = 0.021$): this finding persisted when adjusted for the covariates age ($P = 0.023$), median-year of study recruitment ($P = 0.012$), proportion with re-excision ($P = 0.048$), or LR type ($P = 0.02$). For all other pair-wise comparisons of negative distance, there were no statistically significant differences in the odds of LR in the adjusted model.

Model 2 Based on the subset of 19 studies reporting LR in 753 of 13,081 subjects with data on positive, close, and negative margins (from 14,952 subjects), estimates of effect are shown in Table 2.[24,25,28,29,31,33,35–37,39–42,47–52]

TABLE 1 Summary descriptive characteristics of studies in a meta-analysis of the effect of surgical margins on local recurrence in invasive breast cancer

Variable	Number of studies providing data[a]	Median estimate	Interquartile range
Study and cohort characteristics			
Recruitment timeframe (year)			
Start	33	1984	1979–1990
End	33	1996	1992–2001
Mid-interval	33	1990	1985–1995 (1980–2004)
Number of subjects in each study[b]	33	701	452–1024 (range 79–3899)
Underlying prevalence of local recurrence	33	5.3 %	2.3–7.6 %
Median (or mean) follow-up time (months)	33	79.2	58.8–110.6 (range 48.0–160)
Median time to local recurrence (months)	14	53.5	47.0–60.0
Proportion with systemic relapse/metastases as first (or first and only) event[c]	15	8.3 %	5.3–12.5 %
Age, years			
Median (or mean)	32	53.4	51.0–57.0 (range 45.0–60.6)
Minimum value in study-specific age range	26	24.0	22.0–25.0
Maximum value in study-specific age range	26	86.0	79.0–89.0
Tumour characteristics			
Stage distribution[e]			
0	11	0 %	0–1.4 %
I	11	55.0 %	52.5–56.9 %
II	11	44.4 %	39.4–45.9 %
III	11	0 %	0–0 % (maximum 0.9 %)
Node status			
Positive	30	25.8 %	17.9–28.8 %
Negative	30	70.5 %	65.5–74.2 %
Unknown or NR	30	0.9 %	0–7.7 %
Median tumour size (cm)	8	1.6	1.5–2.1
Tumour grade distribution			
Grade I	15	25.0 %	16.7–32.1 %
Grade II	15	35.5 %	31.8–41.0 %
Grade I–II combined	17	66.0 %	57.5–68.9 %
Grade III	17	28.3 %	20.6–30.6 %
Unknown or NR	17	2.9 %	0.8–21.5 %
Estrogen receptor (ER) status			
Positive	24	45.5 %	38.4–56.3 %
Negative	24	20.5 %	16.6–26.3 %
Unknown or NR	24	28.4 %	14.2–42.0 %
Progesterone receptor (PR) status			
Positive	10	40.6 %	33.5–47.0 %
Negative	10	22.0 %	19.4–28.0 %
Unknown or NR	10	38.4 %	23.8–44.7 %
Extensive intraductal component (EIC) (present)	16	9.6 %	7.5–15.7 %
Lymphovascular invasion (LVI) (present)	16	17.1 %	12.0–30.3 %
Treatment variables			
Reexcision rate	17	48.0 %	22.4–55.6 %
Received chemotherapy[d]	26	25.6 %	18.3–38.0 %
Received endocrine therapy	27	38.0 %	19.3–59.5 %

TABLE 1 continued

Variable	Number of studies providing data[a]	Median estimate	Interquartile range
Received any systemic therapy	19	40.0 %	24.0–77.0 %
Radiation therapy (doses in Gy)			
Whole breast radiotherapy (WBR)[f]			
Median (or mean) WBR dose	26	47.2 Gy	45.0–50.0 Gy
Minimum dose in study-specific WBR range	17	44.0 Gy	40.0–46.0 Gy
Maximum dose in study-specific WBR range	17	50.4 Gy	50.0–54.0 Gy
Radiotherapy boost			
Received boost	30	96.0 %	73.1–100 %
Median boost dose	12	10.0 Gy	10.0–13.1 Gy
Minimum dose in study-specific boost range	19	10.0 Gy	9.0–14.8 Gy
Maximum dose in study-specific boost range	19	18.0 Gy	16.0–20.0 Gy
Total dose to tumour bed (TDT)			
Median TDT	13	61.0 Gy	60.0–62.0 Gy
Received radiation to regional nodes[g]	11	10.5 %	4.3–26.0 %

[a] Variables reported in fewer than half of the included studies were not considered in our models

[b] Three studies reported data per affected/treated breast resulting in 42 additional breasts included as subjects in the total 32,363 subjects

[c] Reported in 17 studies; however, we excluded 2 studies [30,49] (reporting systemic relapse combined with other cancers and/or contralateral breast cancer) from descriptive analysis of this variable

[d] Type of chemotherapy varied across studies as well as within individual studies, or was not specified in some studies (details available from authors)

[e] Stage distribution (where specified)—18 studies included only subjects with stage I–II invasive breast cancer (only some of these studies reported exact distribution) and 15 studies included stage I–II in the vast majority of subjects (see "Methods" section); overall >96 % of subjects had stage I–II invasive breast cancer

[f] Whole breast radiotherapy (WBR) is an inclusion criterion in this review (all subjects had WBR)

[g] Use of nodal irradiation was reported in 16 studies, however specific data were provided in 11 studies

In the *unadjusted* model, the odds of LR were significantly associated with margin status ($P < 0.001$) but not with negative distance ($P = 0.32$); however, there was weak evidence that LR odds decreased as the distance for negative margins increased ($P = 0.074$ for trend). In the *adjusted* model 2, the odds of LR were associated with margin status ($P < 0.001$) but not with margin distance ($P = 0.9$) and there was no statistical evidence that the odds of LR decreased as the distance for declaring negative margins increased ($P = 0.58$ for trend). There was no evidence of interaction between margin status and distance ($P = 0.53$).

Effect of Covariates in model 2

Table 4 shows the covariates associated with LR ($P < 0.1$) in a univariate analysis, and associations after entering each covariate into a model that also included margins and follow-up time. Adjusting model 2 for each covariate did not alter the effect of margin *status*; there was significant association ($P < 0.001$) between margin status and the odds of LR in *all* adjusted models (Table 4). In all adjusted models, there was no evidence of association between margin distance and the odds of LR (P value range 0.32–0.95) nor evidence that the odds of LR decreased as the threshold distance for negative margins increased (P for trend range 0.14–0.75).

Pair-Wise Comparisons of Negative Distance—Adjusted Model 2

For all pairwise comparisons of negative distance (1 vs. 2 mm, 1 vs. 5 mm, or 2 vs. 5 mm), there were no significant differences in the odds of LR in the adjusted model. There was no evidence of an association between the stage-group categories (defined in Methods, "Covariates" section) and LR in the margins-adjusted models ($P = 0.25$, $P = 0.65$ for models 1 and 2 respectively).

DISCUSSION

It is remarkable that more than 25 years after the demonstration that survival after BCS and whole breast irradiation is equivalent to survival after mastectomy, there

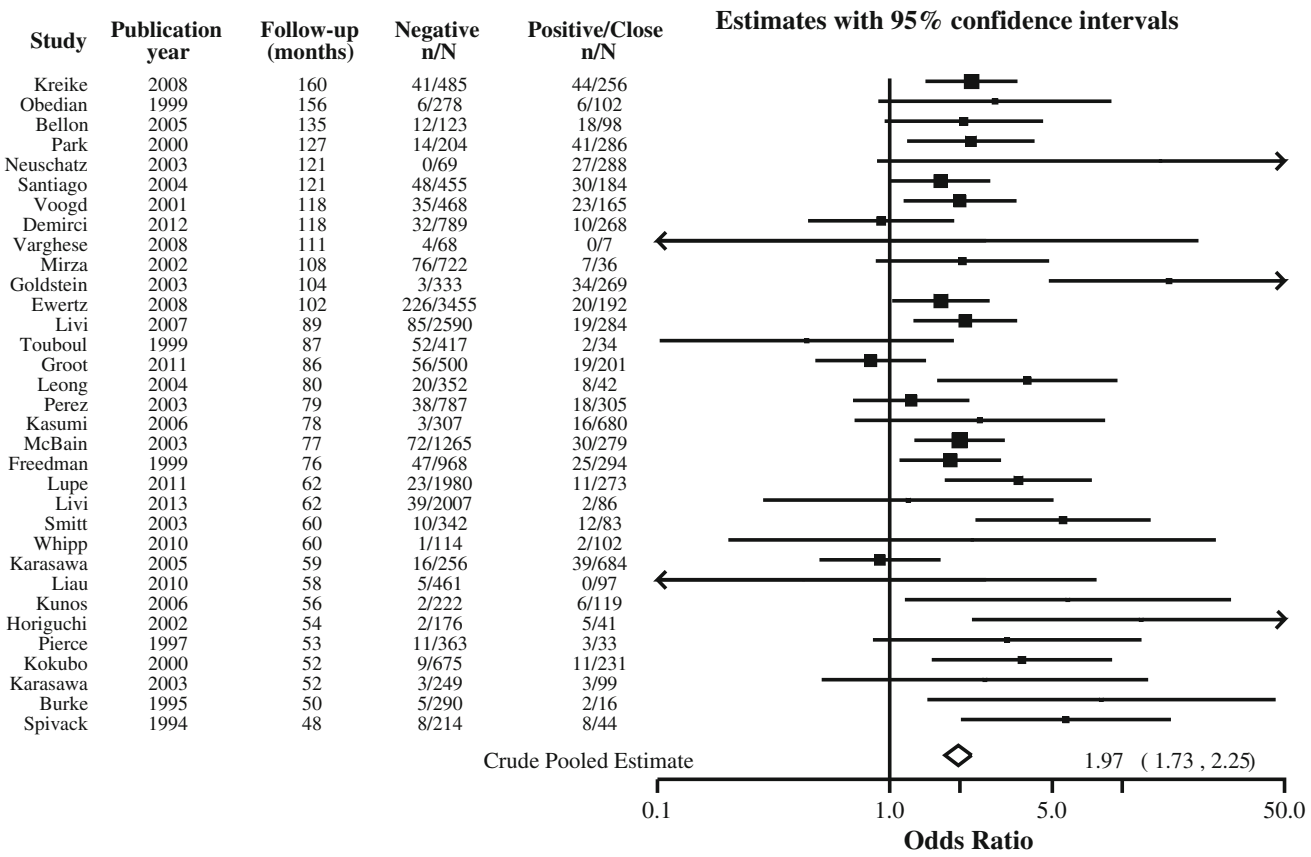

FIG. 1 The effect of margin status (positive/close relative to negative) on local recurrence: study-specific OR, ordered by median follow-up time. A crude pooled odds ratio of 1.97 (CI 1.73–2.25) is shown [modeled pooled odds ratio, *adjusted* for negative distance was 1.98 (CI 1.73–2.25) and also adjusted for median follow-up time was 1.96 (CI 1.72–2.24)]. Data for Mirza[45] and Ewertz[30] are for locoregional recurrence

is still no consensus on what constitutes an adequate negative margin for BCT.[1,2] Ink on tumour cells, a universally accepted definition of a positive margin, is associated with an increased risk of LR, but the amount of normal breast tissue which constitutes the optimal negative margin remains controversial. We therefore have systematically examined the evidence on the association of surgical margins with LR in early-stage invasive BC, providing estimates of effect that factor *both* margin status and the threshold distance for declaring negative margins across studies. We confirm that positive and close margins (combined) significantly increase the odds of LR (OR 1.96; $P < 0.001$) relative to negative margins. However, the distance used to declare negative margins across studies was either weakly associated or not associated with the odds of LR in our two models respectively, and once adjusted for study-specific median follow-up time there was no statistical evidence that the distance used to define a negative margin significantly contributed to the risk of LR ($P = 0.12$ and $P = 0.9$ in models 1 and 2). In addition, in the adjusted models, there was no evidence that the odds of LR significantly decreased as the distance for defining negative margins increased ($P = 0.21$ and $P = 0.58$ *for trend* in models 1 and 2 respectively).

A survey of surgeons selected from a population-based sample, who were asked what negative margin width precluded the need for reexcision, and offered the choices of tumour not touching ink, >1–2, >5, and >10 mm, found that no choice was endorsed by more than 50 % of the respondents, and only 11 % selected tumour not touching ink.[90] Similar findings were reported by Taghian et al.[15] in a survey of 1,133 radiation oncologists in North America and Europe. Again, no margin width was endorsed by more than 50 % with European radiation oncologists tending to favor larger margins than their North American counterparts. The net result of this confusion is wide variation in the use of reexcision with reported rates ranging from 6 to 49 % of cases, with the majority noting re-excision in 15–30 % of patients.[18,20,91–93] McCahill et al.[18] reported that of 2,200 BCS patients, 509 had reexcision, and 48 % of these reexcisions were performed in patients with negative margins to obtain a more widely clear margin. Thus, failure

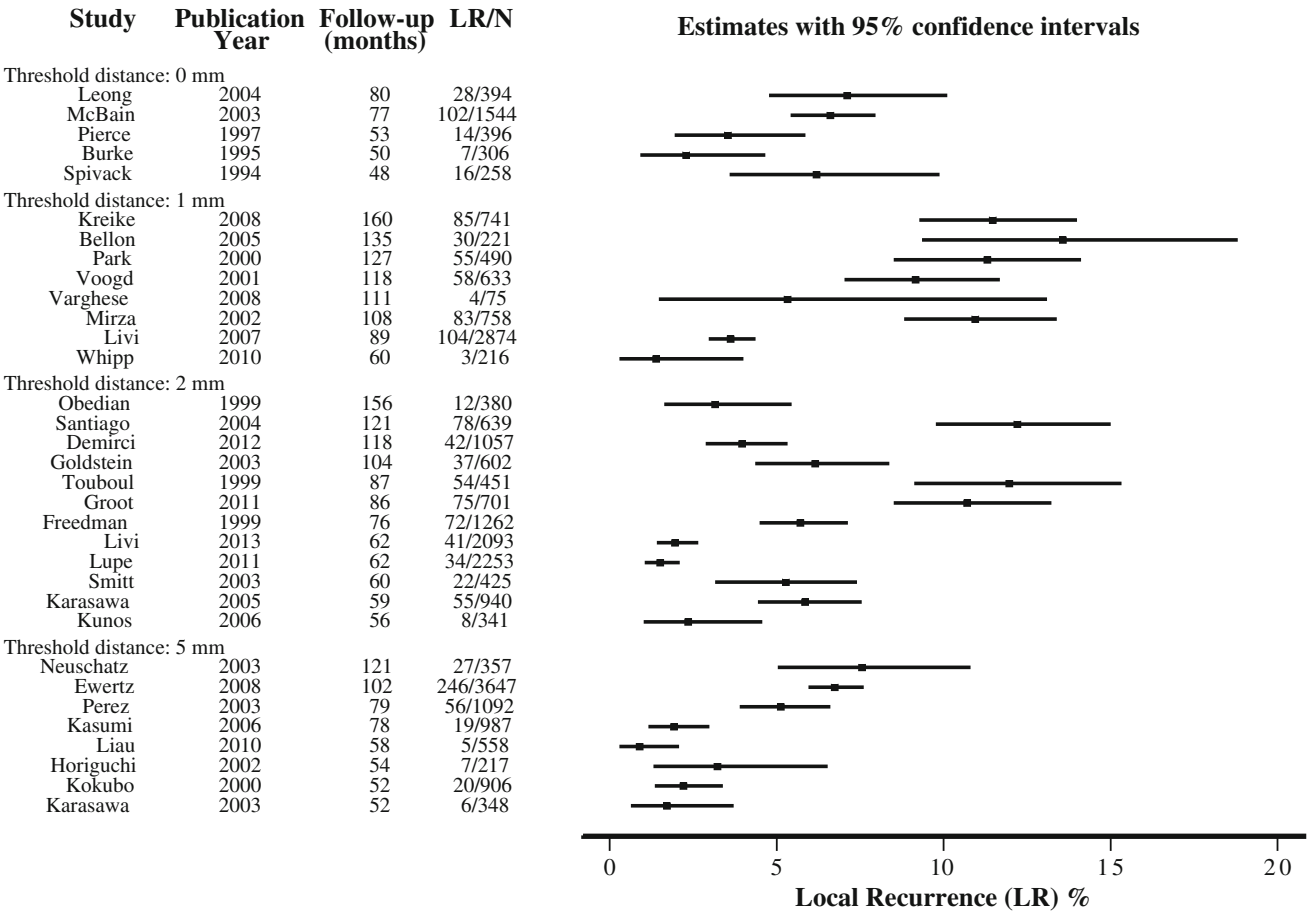

FIG. 2 Study-specific proportion with LR stratified by threshold distance for negative margins, ordered by median follow-up time. Data for Neuschatz[39] were based on 5-mm distance; data for Perez[41] were based on 3-mm distance (this was included in the 5-mm group in our analysis); data for Mirza[45] and Ewertz[30] were for locoregional recurrence

to achieve consensus on margin width is a potential cause of unnecessary surgery, leading to worse cosmetic outcome, and increased health care costs. The findings of our analysis should therefore guide evidence-based practice through highlighting that more widely clear margins are unlikely to confer patient benefit.

Examination of covariates in our meta-analysis showed that the association between margin *status* and the odds of LR was significant in all adjusted models. The microscopic status of surgical margins, although not an exact test, because it relies on sampling of representative tissue sections, is a robust prognostic factor for LR. In contrast, the distance used to define negative margins was not significantly associated with LR even after adjustment for potential confounders. We found little to no evidence of association between margin distance and the odds of LR, and there was little to no evidence that the odds of LR decreased as the distance for declaring negative margins across studies increased (Tables 3, 4). It may be noted that the OR for the studies with the widest threshold distance (5 mm) to define negative margins have relatively lower point estimates than the other categories; however, aside from the lack of statistical association, the estimates should be interpreted with consideration of the effect of adjustment for important covariates. For example, in Table 4, it is clear that adjustment for receipt of endocrine therapy or a radiation boost almost nullify differences in the estimated ORs for wide (5 mm) relative to narrow (1 mm) negative margins.

Pairwise comparison between distance categories for negative margins (in the adjusted models) showed that there were no significant differences in the odds of LR, except that the odds of LR were higher for studies using >0 mm relative to 5 mm ($P = 0.021$) in the adjusted model 1. For all other pairwise comparisons of negative distance, there were no statistically significant differences in the odds of LR in either of the adjusted models. The number of studies reporting negative margins as >0 mm

TABLE 2 Models of the effect of surgical margins on LR in early-stage invasive breast cancer

	Number in model		Model estimates adjusted for study-specific median follow-up time		
	Subjects	LR	Odds of LR (odds ratio)	95 % CI	*P* value[a] [*P* for trend]
Model 1 (median study-specific median follow-up time 6.6 years)	28,162	1,506	–	–	
Margin status					<0.001
Negative	21,984	1,005	1.0	–	
Positive/close	6,178	501	1.96	1.72–2.24	
Threshold distance for negative margins[b]					0.12 [0.21[c]]
>0 mm	2,898	167	1.47	0.67–3.20	
1 mm	6,008	422	1.0	–	
2 mm	11,144	530	0.95	0.54–1.67	
5 mm	8,112	386	0.65	0.34–1.26	
Model 2 (median study-specific median follow-up time 8.7 years)	13,081	753	–	–	–
Margin status					<0.001
Negative	9,033	393	1.0	–	
Close	2,407	176	1.74	1.42–2.15	
Positive	1,641	184	2.44	1.97–3.03	
Threshold distance for negative margins[b]					0.90 [0.58]
1 mm	2,376	235	1.0	–	
2 mm	8,350	414	0.91	0.46–1.80	
5 mm	2,355	103	0.77	0.32–1.87	

[a] *P* reports *P* value for association; *P* in square brackets gives *P* for trend and reflects whether there was statistical evidence of a decrease in the odds of LR as the threshold distance for declaring negative margins increased

[b] Threshold distance for negative margins based on >0 mm (5 studies), 1 mm (referent; 8 studies), 2 mm (12 studies), and 5 mm (8 studies) in model 1; and based on 1 mm (referent; 6 studies), 2 mm (10 studies), and 5 mm (3 studies) in model 2

[c] Trend tested excluding studies using >0 mm (test based on 28 studies) for model 1—see "Methods" section

was small, and given the lack of significant differences among the other pairwise comparisons of margin distance and the lack of overall significance of increasing margin width in decreasing LR in the models, this is unlikely to be clinically significant.

Relative to our previous meta-analysis on margins in BCT, the updated OR estimates for the effect of margin status have remained largely unchanged, except for improved precision from the larger dataset in the present analysis.[10] We previously reported weak evidence of a trend showing that the odds of LR decreased as the threshold distance for declaring negative margins increased; however, this trend was not significant after adjustment for covariates.[10] In the present meta-analysis that included several relatively more recent publications, there was even less evidence of an effect of negative distance (relative to our prior analysis), and after adjustment for study-specific median follow-up time, there was no evidence that the distance used to define negative margins significantly contributed to the odds of LR. Overall, data synthesis in 28,162 subjects indicates that the risk of LR is not driven by the distance defining negative margins.

It is noteworthy that the overall median prevalence of LR in our analysis was only 5.3 %, despite the fact that many of the included studies antedated the routine use of systemic therapy for small, node-negative BCs. The observed temporal decline in LR can likely be attributed to the increasing use of systemic therapy, particularly in studies after 1990. Our work does not capture the full effect of improvements in systemic therapy, such as the use of aromatase inhibitors or HER2-directed therapy, such as trastuzumab, on local control, because the cohorts in this meta-analysis generally predated the routine use of these agents as adjuvant therapy (and given that our analysis required a minimum study median follow-up of 4 years to ensure a sufficient number of events). However, it is increasingly evident that therapies that improve distant disease-free survival result in a parallel decrease in LR, a concept most clearly illustrated by the decrease in LR observed in patients with HER2-overexpressing cancers

TABLE 3 Model 1—estimating the effect of surgical margins on LR in invasive breast cancer adjusted for covariates (covariates examined in model 1 were selected using criteria described in "Statistical Analysis" section)

Covariate (covariate definition and categories described in "Methods" section)	No. of studies	*P* for association of covariate with LR		Margin status (adjusted OR)		Threshold distance for negative margins (adjusted OR)				*P* for association [*P* for trend] for margin distance
		Unadjusted	Adjusted for margins & follow-up time	Negative	Positive/ close	>0 mm	1 mm	2 mm	5 mm	Adjusted for covariate
Effect of margins (adjusted for follow-up time)	33			1.0	1.96**	1.47	1.0	0.95	0.65	0.12 [0.21]
Age	32	0.11	0.089	1.0	1.91**	1.56	1.0	1.13	0.72	0.12 [0.29]
Median-year of study recruitment	33	<0.0001	0.0086	1.0	1.96**	1.47	1.0	0.95	0.65	0.26 [0.14]
Proportion had endocrine therapy	27	<0.0001	0.0011	1.0	2.07**	1.11	1.0	0.91	0.77	0.19 [0.32]
Proportion ER-positive	24	0.012	0.023	1.0	2.26**	0.87	1.0	0.98	0.56	0.44 [0.25]
Proportion had reexcision[a]	17	0.032	0.088	1.0	2.06**	1.41	1.0	0.82	0.52	0.22 [0.13]
LR type (first vs. any)[b]	33	0.12	0.058	1.0	1.96**	1.11	1.0	0.83	0.51	0.063 [0.074]

** Indicates OR significantly different to referent at $P < 0.001$

[a] Odds of LR increased as proportion receiving reexcision increased

[b] LR type (see "Definition of Variables" section in Methods): odds of LR were lower for 'first' than 'any'

TABLE 4 Model 2—estimating the effect of surgical margins on LR in invasive breast cancer adjusted for covariates (covariates examined in model 2 were selected using criteria described in "Statistical Analysis" section)

Covariate (covariate definition and categories described in "Methods" section)	No. of studies	*P* for association of covariate with LR		Margin status (adjusted OR)			Threshold distance for negative margins (adjusted OR)			*P* for association [*P* for trend] for margin distance
		Unadjusted	Adjusted for margins and follow-up time	Negative	Close	Positive	1 mm	2 mm	5 mm	Adjusted for covariate
Effect of margins (adjusted for follow-up time)	19	–	–	1.0	1.74**	2.44**	1.0	0.91	0.77	0.53 [0.58]
Age	18	0.089	0.11	1.0	1.68**	2.35**	1.0	1.12	0.94	0.86 [0.58]
Median-year of study recruitment	19	0.0013	0.0055	1.0	1.76**	2.45**	1.0	0.83	0.57	0.32 [0.14]
Proportion had endocrine therapy	16	0.0003	0.012	1.0	1.77**	2.53**	1.0	0.98	0.90	0.95 [0.75]
Proportion had radiation boost	18	0.015	0.34	1.0	1.75**	2.45**	1.0	0.82	0.92	0.86 [0.75]
Proportion ER-positive	15	0.036	0.078	1.0	1.92**	2.66**	1.0	1.08	0.63	0.67 [0.34]
Proportion had re-excision[a]	11	0.0017	0.0029	1.0	1.97**	2.84**	1.0	0.85	0.69	0.64 [0.34]
LR type (first vs. any)	19	0.46	0.19	1.0	1.74**	2.44**	1.0	0.85	0.65	0.67 [0.34]

** Indicates OR significantly different to referent at $P < 0.001$

[a] Odds of LR increased as proportion receiving reexcision increased

with the use of adjuvant trastuzumab.[94–96] The failure of more widely clear margins to decrease LR significantly in the setting of relatively less use or less effective adjuvant therapy than is in use today makes it exceedingly unlikely that the inclusion of even more recently treated cohorts of BC patients would change our results, but if it did this would be expected to lead to even less effect from wider margins. Although the underlying (crude) LR rates for studies included in this review have indeed declined with time, adjusting for this covariate did not alter the estimated ORs for margin status, which remained strongly associated with odds of LR. Therefore, we conclude that the

prognostic value of the status of surgical margins (positive vs. negative) in BCT is not diminished by temporal declines in LR rates, and obtaining negative margins remains relevant to current oncologic practice.

This work focuses on the relative effect of surgical margins; the absence of a significant effect in our models for some variables may be due (at least in part) to the use of *study-level* information, or the infrequent reporting of data for some variables, such as LVI or EIC. These limitations are inherent in study-level meta-analysis and could be overcome by using individual patient data. Furthermore, the relatively homogeneous distribution of some covariates across studies (such as median age, aggregate dose of WBR) also accounts for a lack of association (or of strong association) for some factors. This does not mean that these factors are unrelated to LR risk; it means that these variables (at an aggregate level) were similar across studies and did not account for differences in the odds of LR in modeling the effect of margins. Additionally, it is increasingly clear that the risk of LR varies with the molecular subtype of BC as approximated by ER, PR, and HER2 status.[97,98] We were unable to evaluate the interaction between BC subtype and margin width due to the lack of information on subtype or on HER2 status in a majority of studies. However, the finding that differences in rates of LR by subtype are similar after both BCT and mastectomy suggests that larger surgical excisions, whether in the form of more widely clear margins or mastectomy, are unlikely to alter aggressive biology.[99] Negative surgical margins do not guarantee the absence of residual cancer within the breast; histological studies using serial sub-gross sectioning of the breast have shown that additional cancer can be found in the breast in a substantial proportion of women despite adequate surgical resection.[100,101] A negative margin predicts that residual tumour burden is minimal and is likely to be controlled with adjuvant therapies.

This meta-analysis has investigated the association between surgical margins and LR, including the various distances used to define negative margins across a large number of studies. The implications for practice are that the association between margins and the risk of LR is largely driven by margin status, and ensuring negative margins in BCT contributes to reducing the risk of LR; however, the threshold distance for defining negative margins does not significantly contribute to the odds of LR. The adoption of wider margins for declaring negative margins in BCT is unlikely to have a substantial additional benefit for long-term local control over a minimally defined negative margin width in patients undergoing BCT for invasive BC.

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