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ORIGINAL ARTICLE – BREAST ONCOLOGY

The Association of Surgical Margins and Local Recurrence in Women with Ductal Carcinoma In Situ Treated with Breast-Conserving Therapy: A Meta-Analysis

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ABSTRACT

Purpose. There is no consensus on adequate negative margins in breast-conserving surgery (BCS) for ductal carcinoma in situ (DCIS). We systematically reviewed the evidence on margins in BCS for DCIS.

Methods. A study-level meta-analysis of local recurrence (LR), microscopic margin status and threshold distance for negative margins. LR proportion was modeled using random-effects logistic meta-regression (frequentist) and network meta-analysis (Bayesian) that allows for multiple margin distances per study, adjusting for follow-up time.

Results. Based on 20 studies (LR: 865 of 7883), odds of LR were associated with margin status [logistic: odds ratio (OR) 0.53 for negative vs. positive/close ($p < 0.001$); network: OR 0.45 for negative vs. positive]. In logistic meta-regression, relative to >0 or 1 mm, ORs for 2 mm (0.51), 3 or 5 mm (0.42) and 10 mm (0.60) showed comparable significant reductions in the odds of LR. In the network analysis, ORs relative to positive margins for 2 (0.32), 3 (0.30) and 10 mm (0.32) showed similar reductions in the odds of LR that were greater than for >0 or 1 mm (0.45). There was weak evidence of lower odds at 2 mm compared with >0 or 1 mm [relative OR (ROR) 0.72, 95 % credible interval (CrI) 0.47–1.08], and no evidence of a difference between 2 and 10 mm (ROR 0.99, 95 % CrI 0.61–1.64). Adjustment for covariates, and analyses based only on studies using whole-breast radiotherapy, did not change the findings.

Conclusion. Negative margins in BCS for DCIS reduce the odds of LR; however, minimum margin distances above 2 mm are not significantly associated with further reduced odds of LR in women receiving radiation.

Breast cancer-specific mortality for women with ductal carcinoma in situ (DCIS) is low, regardless of whether breast-conserving surgery (BCS) or mastectomy is performed.[1] However, BCS is associated with higher rates of local recurrence (LR), and therefore has the potential to lead to additional treatment. Approximately half of all LRs are invasive, with an associated risk of breast cancer mortality;[2] therefore, it is critical that BCS is optimized to reduce the risk of LR, while maintaining its benefits to cosmesis and quality of life relative to more extensive surgery.[3]

Negative margins in BCS for DCIS have been shown to reduce the risk of LR;[4,5] however, the optimal margin distance (i.e. the threshold to declare a negative margin) remains a topic of debate.[6] Guidelines for BCS in invasive cancer, which recommend a minimum margin of no ink on tumor (>0 mm),[7] are not directly applicable to DCIS given the differences in the use of adjuvant whole-breast radiotherapy (WBRT) and systemic therapies. Furthermore, studies of the growth pattern of DCIS have found that multifocal lesions with intervening normal ductal segments are relatively common.[6] Therefore, while some guidelines have specified a minimum margin >0 mm,[8] wider thresholds of 1 mm[9] and 2 mm[10–12] have been adopted by others, and 10 mm has been recommended by a previous meta-analysis.[4]

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Given the lack of consensus on what constitutes an adequate negative margin, we undertook a systematic review of the association between margins and LR in DCIS to determine the optimal minimum negative margin width and support the development of consensus guidelines.[13] Using study-level meta-analysis, the evidence on surgical margins in women with DCIS treated with BCS was systematically examined to (i) estimate the effect of microscopic margin status on LR; (ii) investigate the effect of various thresholds to define negative margins; and (iii) define a minimum negative margin distance to maximize local control.

METHODS

Criteria for Study Eligibility

Inclusion and exclusion criteria are presented in Online Appendix A. Eligible studies enrolled women with DCIS undergoing BCS, and allowed calculation of the crude proportion of LR in relation to microscopic margin status and the threshold distance used to declare a negative margin. Only numerically defined margin thresholds (or negative margins defined as 'no ink on tumor'—interpreted as >0 mm) were included; studies that did not quantify negative margin distance or used unclear margin definitions were excluded. Studies were excluded if all patients had the same margin status.

Eligible studies were required to report mean or median age for the study population (based on the relationship between age and the risk of LR[14,15]); to present mean or median follow-up of at least 4 years to allow sufficient time for clinical endpoints to have occurred;[16,17] and to enrol a minimum of 50 women with DCIS undergoing BCS.

Studies that reported LR rates derived from Kaplan–Meier analysis, from which crude LR data could not be derived, were ineligible. Where studies fulfilled all other inclusion criteria but crude LR by margin status was not presented, study authors were contacted to obtain these data.

Literature Search

A systematic search of the biomedical literature was undertaken in October 2014. The MEDLINE and EMBASE databases were searched via EMBASE.com, and the PREMEDLINE and ALL EBM REVIEWS databases were searched via Ovid. Search terms were selected to link margins and DCIS. Keywords and medical subject headings included 'ductal carcinoma in situ', 'intraductal carcinoma', 'DCIS', and 'margin'. The full search strategy is available in Online Appendix B. Reference lists were searched and content experts consulted to identify additional studies.

Non-duplicate abstracts ($N = 1577$) were screened for eligibility by one author (MLM); a sample ($N = 135$) was assessed independently by another author (NH) to ensure consistent application of eligibility criteria; and the full text of potentially eligible studies ($N = 108$) was assessed by one author (MLM). Where two or more papers reported the same cohort, the most recent study providing margin-specific crude LR data was used to avoid duplication. Online Appendix C summarizes the screening and inclusion process. Comparison of eligible studies with those in a previous meta-analysis[4] is presented in Online Appendix D.

Data Extraction

Data were extracted independently by two authors (MLM, and either MM or LS) using predefined data extraction forms. Discrepancies were resolved through consensus with a third author (NH). Variables derived from each study were margin status (positive, close, negative); numeric margin distance(s) (mm); margin-specific LR; patient recruitment period (start/end years); number of patients included/excluded; age (mean/median); duration of follow-up (mean/median); proportion with invasive versus DCIS recurrence; proportion with WBRT; proportion with radiation therapy boost; WBRT, boost, and total doses (mean or median, Gy); proportion receiving endocrine therapy; proportion with screen-detected DCIS; proportion with comedonecrosis; nuclear grade (low, intermediate, high); proportion estrogen receptor positive; proportion hormone receptor positive; tumor size (mean/median, mm); and proportion with multifocal DCIS. Data on the proportion of patients receiving accelerated partial breast irradiation (APBI) were also collected; however, since only one study of APBI was eligible,[18] these data have not been analyzed separately.

Definition of Key Variables

Margins Study-specific information on the definition of final microscopic margins, from excision or re-excision, was extracted based on margin status (negative, close, positive) and margin distance (the threshold for declaring negative margins relative to positive or close). A standard definition of positive margins was considered to be the presence of DCIS at the transected or inked margin; however, alternative definitions of positive margins were also extracted. Such alternative definitions combined positive and close margins, where a close margin indicated the presence of tumor within a specified

distance of the resection margin. When margins were not positive (or not positive/close), margins were considered to be negative (i.e. no tumor at resection margin, or no tumor within the specified close distance). Where close margins were reported separately from positive margins, these data were extracted as multiple, distance-specific, negative margin categories. Data from multiple, discrete close categories were extracted when available.

Where reported, data from unknown margins were extracted. Because the unknown category cannot contribute data on the effect of margins, it has not been included in the models;[16,17] however, these data were included in descriptive analyses.

Local Recurrence Data were extracted using individual study definitions of LR (either a 'first' event or 'any' LR), but commonly the definition of LR was not specified. LR included both DCIS and invasive recurrences.

Statistical Analysis

Descriptive analyses examined the distribution of study characteristics. Categorical study-level variables were summarized as percentages; for continuous measures, the median, range, and interquartile range (IQR) were calculated.

Positive Margins Due to heterogeneity in margin definitions across studies, positive margins were recategorized as either 0 mm (ink on tumor, nine studies[19–27]) or <1 mm (seven studies[28–34]). In addition, margins <2 mm (three studies[18,35,36]) or <3 mm (one study[37]) were considered positive when 0 mm or <1 mm were not reported.

Negative Margins Negative margins of >0 or 1 mm were combined into one category due to variability in those definitions; negative distances of 3 or 5 mm were also combined due to a lack of data. Thus, negative margins were categorized as >0 or 1, 2, 3 (or 5), and 10 mm. Using that classification, nine studies[18,23,25,29,31,32,35,36] reported one cut-point for margin distance, and 11 studies[19–22,26–28,30,33,34,37] reported multiple cut-points within each study.

Two complementary meta-analytic approaches were used to investigate data from all 20 studies. Random effects logistic modeling dichotomized studies at one cut-point, creating a combined positive/close category and an 'open-ended' negative category (see Houssami et al.[16,17]). Bayesian network meta-analysis incorporated single and multiple cut-points per study following the approach used by Wang et al.[4] Multiple cut-points resulted in 'closed' negative categories with an upper bound. Therefore, for all but 10 mm (open-ended), these distance classifications included a combination of open-ended and closed categories (Online Appendix E).

Random Effects Logistic Meta-Regression (Frequentist Models) The proportion of women who had LR was modeled using random effects logistic meta-regression (Proc NLmixed in SAS). Random study effects, assumed to follow a normal distribution, were included in all models to allow for anticipated heterogeneity between studies beyond what would arise from within study sampling error alone, thereby taking account of both within- and between-study variability. Explanatory variables included in the models (margin status, distance, and covariates) were fitted as a fixed effect. Statistical significance was set at $p < 0.05$ (two-sided); $p < 0.10$ was considered weak evidence of association.

The association between LR and margin status and distance was estimated by including both as categorical variables in the model. One margin distance could be included for each study. When multiple distances were available, the largest was chosen (with the exception of the only study to apply a 5 mm distance,[19] and a large study defining 'close' margins as <2 mm[27]). The effect of alternative distance categorizations for potentially influential studies was investigated. Effect modification between margin status and distance was tested for statistical interaction between these variables.

In addition to margin status analyzed as negative versus positive/close, models of positive, close and negative margins as separate categories were attempted. However, these models failed to converge due to few studies reporting separate categories,[19–23,26,27] and are consequently not reported.

Network Meta-Analysis Network meta-analysis allows data for more than one margin distance per study to be utilized, and takes account of the correlations between multiple observations within studies. The approach used [mixed treatment comparison (MTC)[38]] considers margin thresholds as different 'treatments' tested in different studies, and compares them through a network structure informed by both direct (within study) and indirect comparisons (between studies using a common comparator, i.e. positive margins) (Online Appendix F).

To compare the probability of LR between margin status (negative vs. positive), a simplified version of the MTC for two 'treatments' was used. An extended version of the MTC for multiple 'treatments' was used to compare the probability of LR between all pairs of margin distances (positive; >0 or 1, 2, 3, 10 mm). The MTC is a Bayesian random-effects hierarchical model where the probability of LR within each margin distance was modeled using a

TABLE 1 Patient and study characteristics

Variable	No. of included		Median	IQR	Range
	Studies	Patients			
No. of patients (total)[a]	20	8651	226	108–439	50–2996
No. of patients with known margin status		7883	210	98–422	50–2788
Recruitment timeframe (year)	20	8651	–	–	–
Start		8651	1984	1977–1988	1968–2003
End		8651	2001	1995–2007	1990–2010
Mid-interval		8651	1991	1987–1996	1979–2006
Age, years (median or mean)	20	8651	53.7	53.0–56.7	43.0–62.1
Follow-up, months (median or mean)	20	8651	78.3	59.0–94.7	51.5–126.0
Prevalence of LR (patients with known margin status)	20	7883	8.3 %	5.0–11.9 %	2.2–24.0 %
Total no. of LRs		865	–	–	–
Type of LR	17	952	–	–	–
DCIS		479	50.0 %	42.9–57.1 %	0.0–75.0 %
Invasive		458	50.0 %	41.7–56.5 %	25.0–100.0 %
Unknown		15	0.0 %	0.0–0.0 %	0.0–7.1 %
WBRT	20	8920	–	–	–
Yes[b]		6353	100.0 %	50.3–100.0 %	0.0–100.0 %
No		2533	0.0 %	0.0–53.4 %	0.0–100.0 %
Unknown		34	0.0 %	0.0–0.0 %	0.0–1.1 %
WBRT dose, Gy (median)	11	3990	50.0	50.0–50.0	42.5–50.0
Radiation boost	19	5925	–	–	–
Yes		3207	70.9 %	28.4–95.5 %	0.0–100.0 %
No		2715	29.1 %	4.5–71.6 %	0.0–100.0 %
Unknown		3	0.0 %	0.0–0.0 %	0.0–0.6 %
Boost dose, Gy (median)	8	2734	10.0	10.0–10.0	10.0–10.8
Total dose, Gy (median)	12	3890	60.0	60.0–60.4	50.0–64.0
Endocrine therapy	19	8392	–	–	–
Yes[c]		1563	20.8 %	0.0–31.4 %	0.0–83.2 %
No		6722	79.2 %	68.6–100.0 %	16.8–100.0 %
Unknown		107	0.0 %	0.0–0.0 %	0.0–13.6 %
Screen detected	14	7661	–	–	–
Yes		6520	85.8 %	71.6–89.9 %	45.6–100.0 %
No		1106	14.2 %	10.1–27.2 %	0.0–54.4 %
Unknown		35	0.0 %	0.0–0.1 %	0.0–2.8 %
Comedonecrosis	14	6465	–	–	–
Present		3085	37.5 %	27.1–46.0 %	10.4–60.1 %
Absent		2713	55.5 %	34.3–61.5 %	2.0–81.6 %
Unknown		667	5.3 %	0.0–15.9 %	0.0–61.1 %
Grade	16	7225	–	–	–
I–II		4033	57.3 %	37.0–65.5 %	7.3–92.5 %
I[d]		901	17.5 %	9.1–25.2 %	1.8–64.5 %
II[d]		1163	28.0 %	23.6–34.9 %	5.5–45.0 %
III		2243	28.4 %	17.9–35.4 %	3.5–45.6 %
Unknown		949	9.2 %	0.0–37.3 %	0.0–87.3 %
Hormone receptor	5	1479	–	–	–
Positive		740	50.4 %	43.7–70.9 %	23.0–80.4 %
Negative		142	8.7 %	7.3–9.7 %	2.8–14.3 %
Unknown		597	40.9 %	16.8–46.6 %	14.8–69.8 %

TABLE 1 continued

Variable	No. of included		Median	IQR	Range
	Studies	Patients			
Estrogen receptor	3	1023	–	–	–
Positive		522	46.8 %	14.9–70.7 %	14.9–70.7 %
Negative		117	12.3 %	3.1–14.3 %	3.1–14.3 %
Unknown		384	40.9 %	15.0–82.0 %	15.0–82.0 %
Tumor size, mm	8	1880	10.9	8.0–14.9	8.0–20.5
Multifocality	2	286	–	–	–
Present		46	12.6 %	0.0–25.1 %	0.0–25.1 %
Absent		134	58.5 %	16.9–100.0 %	16.9–100.0 %
Unknown		106	29.0 %	0.0–58.0 %	0.0–58.0 %

APBI Accelerated partial breast irradiation, *DCIS* ductal carcinoma in situ, *Gy* gray, *IQR* interquartile range, *LR* local recurrence, *WBRT* whole-breast radiotherapy

[a] Total no. of patients included in margins analyses by eligible studies, including those with unknown margin status. Excludes 269 patients with unconfirmed DCIS from one study (Bijker et al.[31]); these patients did not contribute to the analysis of margins in that study, but were included in descriptive covariate information. Hence, patient numbers for covariates in this table may include those patients, and may sum to more than 8651

[b] Includes 194 patients with APBI from one study

[c] Of 11 studies using endocrine therapy, seven used tamoxifen, one used either tamoxifen or other, and three did not report the type of endocrine therapy

[d] From a subset of 13 studies reporting grade I and II separately

Binomial likelihood at the first level. A logit-normal random effects model was used to link the probability of LR with covariates of interest in a combined MTC and meta-regression framework. All models are adjusted for median follow-up time (centred to their mean), fitted as a fixed effect. Online Appendix G provides further technical details of this model, including explanation of estimates and 95 % credible intervals [CrIs; analogous to 95 % confidence intervals (CIs) in providing a range of likely values for a statistical estimate].

The rjags package implemented in the R package was used for all Bayesian analyses.

Assessment of Covariates All models were adjusted for study-specific follow-up time, based on prior evidence that LR increases with longer follow-up, and evidence of association in the random effects logistic meta-regression analysis (see the "Results" section). Other potential study-level confounders of the relationship between margins and LR [median age (years), median year of recruitment, radiotherapy (%) radiotherapy boost (%), total radiotherapy dose (Gy), DCIS recurrence (%), endocrine therapy (%), screen detection (%), comedonecrosis (%), and high grade (%)] were also fitted in univariate logistic meta-regression models (not including margins). Covariates that showed at least a weak association ($p < 0.10$) with LR were adjusted for in both the logistic and Bayesian network models to assess the effect on estimates for margin distance (i.e. age, median year of recruitment, endocrine therapy, and high grade) (see Online Appendix H). The effect of radiotherapy was also investigated on prior grounds. Variables that were extracted but reported in less than half of the studies were not considered reliable for modeling.

Two covariates had missing data (endocrine therapy and high grade). In the network model, a number of statistical techniques for dealing with missing data were investigated but the results were equivalent to models restricted to studies with non-missing covariate data.

RESULTS

Study Characteristics

Twenty studies were eligible for inclusion,[18–37] reporting data on 8651 patients with DCIS; 7883 had known margin status (865 LRs) and were included in our models. Two studies were prospectively designed,[18,31] and the remaining 18 studies were retrospective. Study characteristics are summarized in Table 1. Studies enrolled patients between 1968 and 2010 (median mid-point of recruitment, 1991). The median proportion of patients receiving WBRT across studies was 100 % (IQR 50.3–100.0 %); 71 % of all patients in eligible studies received WBRT. Median study-level proportion of patients receiving endocrine therapy was 20.8 % (IQR 0.0–31.4 %). Median follow-up time was 78.3 months (IQR 59.0–94.7), and the prevalence of LR was 8.3 % (IQR 5.0–11.9 %) in 7883 patients with margins data. In

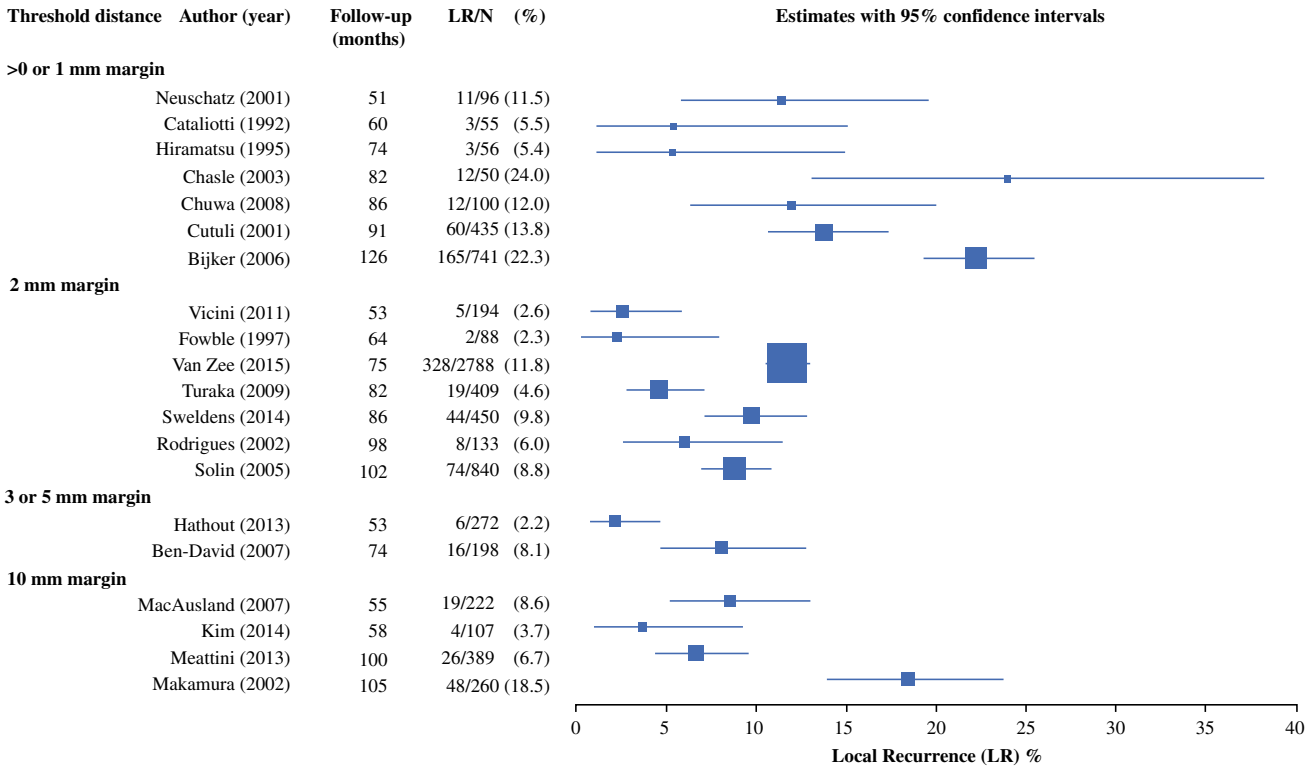

FIG. 1 Forest plot of study-specific prevalence of LR

768 patients with unknown margins (not included in our models), the prevalence of LR was 12.4 % (95 LRs).

Random-Effects Logistic Meta-Regression Modeling

Figure 1 presents study-specific prevalence of LR, stratified by margin threshold used in the models and ordered by follow-up time. Heterogeneity was evident within margin categories; however, prevalence was generally higher at >0 or 1 mm relative to wider thresholds.

Models were adjusted for median follow-up time, given strong evidence that LR increased with follow-up [odds ratio (OR) for every additional year of follow-up = 1.29, 95 % CI 1.11–1.51; $p = 0.002$]. In multivariable models, there was no evidence that the effect of margin status was modified by distance (p for interaction = 0.26). Table 2 presents ORs from a model of the main effects of margin status and distance. The OR for negative versus positive/close margin status was 0.53 (95 % CI 0.45–0.62; $p < 0.001$). The odds of LR were also associated with margin distance [p for association = 0.046; degrees of freedom [df] = 3]. Relative to >0 or 1 mm, ORs for 2 mm (0.51, 95 % CI 0.31–0.85; $p = 0.01$), 3 or 5 mm (0.42, 95 % CI 0.18–0.97; $p = 0.04$) and 10 mm (0.60, 95 % CI 0.33–1.08; $p = 0.09$) showed comparable, statistically significant reductions in the odds of LR. Pairwise comparisons found no evidence of differences in ORs between the 2, 3 or 5, and 10 mm thresholds (all $p > 0.40$). There was no evidence for a trend in ORs across distance thresholds ($p = 0.11$; df = 1). Predicted probabilities of LR at 10 years derived from this model are presented in Table 3.

Table 2 presents results for models adjusted for covariates. The proportion of patients with high-grade DCIS was the only statistically significant covariate in multivariable models ($p < 0.03$). For all analyses, adjustment for covariates did not substantially change model estimates.

Network Meta-Analysis

For direct comparisons between positive and negative margins (adjusted for median follow-up), patients with negative margins were significantly less likely to experience LR than patients with positive margins (OR 0.45, 95 % CrI 0.30–0.62).

Table 4 shows estimated relative margin threshold effect parameters on the OR scale compared with the reference category (positive margin group) provided by Bayesian analysis of the network. ORs for 2 mm (0.32, 95 % CrI 0.21–0.48), 3 mm (0.30, 95 % CrI 0.12–0.76), and 10 mm (0.32, 95 % CrI 0.19–0.49) all showed similar reductions in the odds of LR that were greater than for >0 or 1 mm (0.45, 95 % CrI 0.32–0.61). Probabilities for each

TABLE 2 Main effects of margin status and distance on LR (random-effects logistic meta-regression)

	Negative margin relative to positive/close: [OR (95 % CI)][a]	Threshold distance for negative margins relative to >0 or 1 mm [no. of patients and OR (95 % CI) adjusted for follow-up]				*p* Value (*p* value for trend)
		>0 or 1 mm	2 mm	3 or 5 mm	10 mm	
Main model	7883	1533	4902	470	978	0.046 (0.11)
	0.53 (0.45–0.62)	Referent	0.51 (0.31–0.85)[b]	0.42 (0.18–0.97)[b]	0.60 (0.33–1.08)	
Sensitivity analysis						
WBRT cohorts only	6042	1503	3420	470	649	
	0.52 (0.43–0.63)	Referent	0.50 (0.32–0.79)[b]	0.43 (0.20–0.92)[b]	0.54 (0.30–0.97)[b]	0.02 (0.03)
Van Zee et al.[27] excluded	5115	1553	2114	470	978	
	0.45 (0.37–0.56)	Referent	0.44 (0.30–0.65)[b]	0.43 (0.22–0.83)[b]	0.59 (0.39–0.89)[b]	0.004 (0.11)
Adding studies with no summary age data[c]	9220	1853	4902	1042	1423	
	0.53 (0.46–0.62)	Referent	0.49 (0.26–0.93)[b]	0.81 (0.36–1.82)	0.76 (0.38–1.52)	0.16 (0.65)
Adjustment for covariates (based on main model)						
Age	0.53 (0.45–0.63)	Referent	0.51 (0.31–0.85)[b]	0.42 (0.18–0.97)[b]	0.60 (0.33–1.08)	0.046 (0.11)
Median recruitment year	0.53 (0.45–0.62)	Referent	0.56 (0.31–0.99)[b]	0.45 (0.19–1.06)	0.63 (0.34–1.15)	0.15 (0.19)
Proportion with radiotherapy	0.53 (0.45–0.62)	Referent	0.54 (0.32–0.89)[b]	0.49 (0.20–1.19)	0.58 (0.33–1.03)	0.07 (0.08)]
Proportion with endocrine therapy[d]	0.55 (0.46–0.65)	Referent	0.52 (0.31–0.86)[b]	0.46 (0.19–1.13)	0.65 (0.34–1.23)	0.07 (0.24)
Proportion with high-grade DCIS[d]	0.55 (0.45–0.66)	Referent	0.55 (0.32–0.96)[b]	0.47 (0.19–1.17)	0.61 (0.27–1.38)	0.16 (0.25)

CI Confidence interval, *DCIS* ductal carcinoma in situ, *LR* local recurrence, *OR* odds ratio, *WBRT* whole-breast radiotherapy

[a] All statistically significant at $p < 0.001$

[b] Statistically significantly different from >0 or 1 mm at $p < 0.05$

[c] These studies (from the meta-analysis by Wang et al.[4]) were ineligible for inclusion in our meta-analysis because of a lack of summary age data (see eligibility criteria); hence, sensitivity analysis reports estimates if these were included in the models

[d] Due to missing covariate information, these analyses were undertaken in a reduced number of studies (19 for endocrine therapy; 16 for high-grade DCIS), therefore numbers analyzed in these models will be less than those shown in the main models

TABLE 3 Predicted probabilities of LR at 10 years from random-effects logistic meta-regression model (adjusted for follow-up)

Threshold distance for negative margins, mm	Overall probability (%) of 10 year LR as the endpoint (95 % CI)			
	Margin status (all studies)		Margin status (cohorts with WBRT)	
	Positive/close	Negative	Positive/close	Negative
>0 or 1	29.4 (20.0–41.0)	18.1 (11.7–26.7)	30.1 (21.3–40.6)	18.3 (12.5–26.0)
2	17.6 (11.1–26.7)	10.1 (6.3–16.0)	17.8 (11.6–26.4)	10.1 (6.5–15.5)
3 or 5	14.9 (6.5–30.6)	8.5 (3.6–18.9)	15.6 (7.1–31.1)	8.8 (3.8–18.9)
10	20.0 (12.1–31.2)	11.7 (6.7–19.4)	18.9 (12.1–28.2)	10.8 (6.7–17.1)

CI Confidence interval, *LR* local recurrence, *WBRT* whole-breast radiotherapy

threshold being the 'best' option were inconclusive because the model was not able to reliably rank them during the iterative process, for the reasons outlined by Jansen et al.[39]

Comparisons between 10 and 2 mm showed no meaningful difference in the odds of LR [relative OR (ROR) 0.99, 95 % CrI 0.61–1.64]. Comparing >0 or1 mm and 2 mm showed weak evidence of lower odds of LR for 2 mm (ROR 0.72, 95 % CrI 0.47–1.08). A similar ROR was observed for 10 mm compared with >0 or 1 mm (ROR 0.71, 95 % CrI 0.44–1.11). Comparisons involving 3 mm were not informative as just three studies contributed to that threshold.

Adjustment for covariates (age, mid-point of recruitment period, endocrine therapy, and high grade) using different techniques to deal with missing data found that, in

TABLE 4 Estimated treatment (margin threshold) effects on LR from the Bayesian network meta-analysis

	Threshold distance for negative margins relative to positive: (no. of patients and mean OR (95 % CrI) adjusted for follow-up)			
	>0 or 1 mm	2 mm	3 mm	10 mm
Main model	2230	2412	289	1963
	0.45 (0.32–0.61)	0.32 (0.21–0.48)	0.30 (0.12–0.76)	0.32 (0.19–0.49)
Sensitivity analysis				
WBRT cohorts only	1957	1851	272	1079
	0.45 (0.34–0.61)	0.33 (0.23–0.47)	0.22 (0.08–0.53)	0.37 (0.24–0.57)
Van Zee et al.[27] excluded	1781	1524	289	616
	0.43 (0.31–0.57)	0.29 (0.19–0.45)	0.32 (0.14–0.75)	0.27 (0.16–0.47)
Adding studies with no summary age data[a]	2692	2555	322[c]	2160
	0.44 (0.30–0.63)	0.31 (0.19–0.51)	0.32 (0.14–0.73)	0.20 (0.11–0.35)[d]
Adjustment for covariates (based on main model)				
Age	0.46 (0.33–0.63)	0.34 (0.22–0.51)	0.33 (0.13–0.83)	0.33 (0.20–0.51)
Median recruitment year	0.45 (0.31–0.62)	0.31 (0.19–0.46)	0.29 (0.12–0.68)	0.32 (0.20–0.49)
Proportion with radiotherapy	0.46 (0.33–0.63)	0.33 (0.22–0.49)	0.29 (0.12–0.74)	0.32 (0.20–0.50)
Proportion with endocrine therapy[b]	0.45(0.29–0.70)	0.33 (0.18–0.57)	0.29(0.10–0.79)	0.31(0.17–0.57)
Proportion with high-grade DCIS[b]	0.45 (0.32–0.62)	0.33 (0.21–0.48)	0.31(0.12–0.74)	0.39 (0.25–0.59)

CrI Credible interval, *DCIS* ductal carcinoma in situ, *LR* local recurrence, *OR* odds ratio, *ROR* relative odds ratio, *WBRT* whole-breast radiotherapy

[a] These studies (from the meta-analysis by Wang et al.[4]) were ineligible for inclusion in our meta-analysis because of a lack of summary age data (see eligibility criteria); hence, sensitivity analysis reports estimates if these were included in the models

[b] Due to missing covariate information, these analyses were undertaken in a reduced number of studies (19 for endocrine therapy; 16 for high-grade DCIS), therefore numbers analyzed in these models will be less than those shown in the main models. Alternative methods to deal with missing data produced similar results

[c] Two studies using a 5 mm threshold were included with the 3 mm threshold group

[d] 95 % CrI for ROR of 10 mm versus >0 or 1 mm did not cross 1

all cases, the model with no covariates gave the best fit. Estimates from adjusted and unadjusted models were similar (Table 4).

Sensitivity Analyses

Sensitivity analyses were conducted that included only study cohorts with adjuvant WBRT. The pattern of results was not altered in either logistic meta-regression (Tables 2, 3) or network models (Table 4). Models in patients without WBRT failed to converge due to the small number of studies. Sensitivity analyses excluding the potentially influential study by Van Zee et al.[27] resulted in similar ORs to those in the main analyses. Logistic meta-regression investigating the effect of reclassifying Van Zee et al.[27] at 10 mm resulted in a complex model (Online Appendix I), highlighting the limitations of modeling a single threshold per study.

Additional sensitivity analysis explored the effect of introducing four studies from the meta-analysis by Wang et al. not included in our analysis because they did not report summary age data.[40–43] Similar results to the main analysis were found for the network model for all but the 10 mm threshold group, for which a lower OR was observed (Table 4). There was evidence of a lower OR for 10 mm relative to >0 or 1 mm (ROR 0.46, 95 % CrI 0.26–0.77), attributable to the inclusion of one non-WBRT study[43] at 10 mm. There was no evidence of a difference in the OR for 10 mm relative to 2 mm (ROR 0.66, 95 % CrI 0.35–1.23), or in the OR for 2 mm relative to >0 or 1 mm (ROR 0.70, 95 % CrI 0.42–1.16). In logistic models (Table 2), ORs for the 3 or 5 mm (0.81, 95 % CI 0.36–1.82) and 10 mm (0.76, 95 % CI 0.38–1.52) thresholds were larger than for the main analysis and not significantly different from >0 or 1 mm ($p > 0.42$), reflecting the inclusion of non-WBRT studies at 3 or 5 mm[28] and 10 mm[43] with a relatively high prevalence of LR (31.0 % and 17.8 %, respectively). Pairwise comparisons found no evidence that 2, 3 or 5 mm, and 10 mm were different from one another ($p > 0.20$ for all).

Network models were not sensitive to assumptions on the prior distributions and the parameters of these distributions, or to the assumed correlation structure for multiple thresholds within studies.

DISCUSSION

We sourced data on 8651 patients with DCIS from 20 studies, and meta-analyzed these for 7883 patients with known margins with a median follow-up of 78 months. Most study cohorts received WBRT but not endocrine therapy. Two analytic approaches explored how best these heterogeneous data could be modeled: the Bayesian network approach supported more robust and efficient meta-analysis that could utilize data at all margin thresholds compared with conventional random-effects logistic meta-regression. The network analysis showed that the odds of LR are reduced in negative margins relative to positive margins (OR 0.45, 95 % CrI 0.30–0.62), and also showed that, relative to positive margins, the 2 mm (OR 0.32, 95 % CrI 0.21–0.48), 3 mm (OR 0.30, 95 % CrI 0.12–0.76), and 10 mm thresholds (OR 0.32, 95 % CrI 0.19–0.49) all had a similar reduction in the odds of LR that was lower than for >0 or 1 mm (OR 0.45, 95 % CrI 0.32–0.61). These findings were largely consistent with the logistic meta-regression analyses when we classified a large study[27] at 2 mm.

Our results differ to those of Wang et al.[4], who found decreasing ORs as the threshold distance increased up to 10 mm, and hence recommended a 10 mm margin for DCIS. In contrast, the odds of LR in our analysis did not decrease beyond a distance of 2 mm. Compared with our network analysis, Wang et al.[4] included fewer studies, patients, and events at 10 mm. Our sensitivity analyses incorporating studies included by Wang et al.[4] that did not meet our eligibility criteria suggested that a single no-WBRT study[43] (the only study in Wang et al. directly comparing 2 and 10 mm, and the only study to contribute additional data at 10 mm in our sensitivity analysis), was influential in lowering the odds of LR at 10 mm.

When we restricted analyses to only those cohorts receiving WBRT, the pattern of results was unchanged, highlighting the applicability of our findings to patients who received adjuvant WBRT. Models in patients without WBRT failed to converge due to the small number of studies; therefore, our analysis is unable to investigate whether the effect of margins is modified by receipt or non-receipt of WBRT. However, a recent, large study comparing WBRT and no-WBRT cohorts provides evidence that the effect of margins on LR is modified by adjuvant WBRT; larger margin distances were significantly associated with lower rates of LR in those without WBRT but not those with WBRT.[27]

There are limitations to the analysis of study-level covariates in this meta-analysis, particularly where aggregate data are similar across studies (e.g. age), or where a specific therapy is (or is not) received in the majority (e.g. WBRT and APBI).[16,17] An individual patient data meta-analysis of four randomized controlled trials found BCS and adjuvant WBRT to be significantly associated with a reduction in any LR compared with BCS alone (15.2 % absolute reduction in 10 year risk).[44] However, the study-level proportion of patients receiving WBRT was found not to be univariately associated with LR in our analysis, and therefore did not meet the criterion for inclusion in multivariable models. This is likely to be due to WBRT being used in a majority of patients (71 %). Nevertheless, we investigated the effect of WBRT on prior grounds, and both modeling approaches found no substantial differences between models with or without adjustment for WBRT. In addition, given the fact that only one study using APBI was included in the analysis, we were unable to draw conclusions about the effect of margins in patients treated with APBI.

A strength of the Bayesian network model is its capacity to include multiple distance thresholds per study, maximizing comparisons to inform conclusions about appropriate negative margin thresholds in DCIS. A possible limitation of that approach is that multiple thresholds result in 'closed' distance categories for smaller thresholds, potentially attenuating their effect on LR. In our analysis, this applied particularly to the >0 or 1 mm threshold, for which 10 of 16 data points are 'closed' categories (four with an upper bound of 2 mm). In contrast, of seven data points at 2 mm, there was just one closed category (10 mm upper bound). Therefore, the network analysis may have exaggerated differences between the 2 mm and >0 or 1 mm thresholds. However, a similar pattern of results was observed in our logistic meta-regression models, where the limitation of closed margin categories did not apply. These complementary analyses therefore suggest that our results showing lower odds of LR at 2 mm compared with >0 or 1 mm are likely to be robust.

Heterogeneity in margin definitions among included studies lead to thresholds of >0 mm and 1 mm being combined in our analysis. This ameliorated the effect of 'closed' categories associated with a distance of >0 mm, thereby minimizing heterogeneity between thresholds. This approach also maximized direct comparisons in the network models; a network structure including separate >0 mm and 1 mm categories would result in models driven by indirect comparisons, which are potentially unreliable. However, as a result, this analysis has the limitation of being unable to compare margins of >0 and 1 mm.

Notwithstanding the limitations inherent in study-level analyses, the two alternative but complementary meta-analytic approaches reported in our work were consistent in finding reductions in LR at a threshold distance of 2 mm relative to smaller thresholds in BCS for DCIS. There was no evidence that minimum margins wider than 2 mm were

associated with additional reductions in LR in women receiving adjuvant WBRT. Therefore, our meta-analysis indicates that a negative margin threshold of 2 mm is an appropriate recommendation for surgical management of DCIS in women receiving BCS with WBRT.

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REFERENCES

1. Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. *J Natl Cancer Inst.* 2010;102:170–8.
2. Wapnir IL, Dignam JJ, Fisher B, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. *J Natl Cancer Inst.* 2011;103:478–88.
3. Irwig L, Bennetts A. Quality of life after breast conservation or mastectomy: a systematic review. *Aust N J Surg.* 1997;67:750–54.
4. Wang S-Y, Chu H, Shamliyan T, et al. Network meta-analysis of margin threshold for women with ductal carcinoma in situ. *J Natl Cancer Inst.* 2012;104:507–16.
5. Dunne C, Burke JP, Morrow M, Kell MR. Effect of margin status on local recurrence after breast conservation and radiation therapy for ductal carcinoma in situ. *J Clin Oncol.* 2009;27:1615–20.
6. Pilewskie M, Morrow M. Extent and role of margin control for DCIS managed by breast-conserving surgery. In: Newman LA, Bensenhaver JM, editors. Ductal carcinoma in situ and microinvasive/borderline breast cancer. New York: Springer; 2015. pp. 67–83.
7. Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *J Clin Oncol.* 2014;32:1507–15.
8. American Society of Breast Surgeons. The American Society of Breast Surgeons position statement on breast cancer lumpectomy margins. 2013. https://www.breastsurgeons.org/new_layout/about/statements/PDF_Statements/Lumpectomy_Margins.pdf. Accessed 28 Jul 2016.
9. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology, breast cancer version 1. 2016. http://www.nccn.org. Accessed 14 Dec 2015.
10. National Institute for Health and Care Excellence (NICE). Early and locally advanced breast cancer: diagnosis and treatment: NICE guidelines [CG80]. 2009. https://www.nice.org.uk/guidance/cg80/chapter/guidance#surgery-to-the-breast. Accessed 14 Dec 2015.
11. New Zealand Guidelines Group (NZGG). Ductal carcinoma in situ. Management of early breast cancer: evidence-based best practice guideline. Wellington: New Zealand Guidelines Group; 2015. pp. 133–41.
12. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2015;26:v8–30.
13. Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology—American Society for Radiation Oncology—American Society of Clinical Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. *Ann Surg Oncol.* 2016. doi:10.1245/s10434-016-5449-z.
14. Vicini FA, Recht A. Age at diagnosis and outcome for women with ductal carcinoma-in situ of the breast: a critical review of the literature. *J Clin Oncol.* 2002;20:2736–44.
15. Kong I, Narod SA, Taylor C, et al. Age at diagnosis predicts local recurrence in women treated with breast-conserving surgery and postoperative radiation therapy for ductal carcinoma in situ: a population-based outcomes analysis. *Curr Oncol.* 2014;21:e96–104.
16. Houssami N, Macaskill P, Marinovich ML, Morrow M. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. *Ann Surg Oncol.* 2014;21:717–30.
17. Houssami N, Macaskill P, Marinovich ML, et al. Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy. *Eur J Cancer.* 2010;46:3219–32.
18. Vicini F, Beitsch P, Quiet C, et al. Five-year analysis of treatment efficacy and cosmesis by the American Society of Breast Surgeons mammosite breast brachytherapy registry trial in patients treated with accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys.* 2011;79:808–17.
19. Hathout L, Hijal T, Theberge V, et al. Hypofractionated radiation therapy for breast ductal carcinoma in situ. *Int J Radiat Oncol Biol Phys.* 2013;87:1058–63.
20. Ben-David MA, Sturtz DE, Griffith KA, et al. Long-term results of conservative surgery and radiotherapy for ductal carcinoma in situ using lung density correction: The University of Michigan experience. *Breast J.* 2007;13:392–400.
21. Solin LJ, Fourquet A, Vicini FA, et al. Long-term outcome after breast-conservation treatment with radiation for mammographically detected ductal carcinoma in situ of the breast. *Cancer.* 2005;103:1137–46.
22. Rodrigues N, Carter D, Dillon D, Parisot N, Choi DH, Haffty BG. Correlation of clinical and pathologic features with outcome in patients with ductal carcinoma in situ of the breast treated with breast-conserving surgery and radiotherapy. *Int J Radiat Oncol Biol Phys.* 2002;54:1331–5.
23. Cutuli B, Cohen-Solal-Le NC, De LB, et al. Ductal carcinoma in situ of the breast results of conservative and radical treatments in 716 patients. *Eur J Cancer.* 2001;37:2365–72.
24. Hiramatsu H, Bornstein BA, Recht A, et al. Local recurrence after conservative surgery and radiation therapy for ductal carcinoma in situ: possible importance of family history. *Cancer J Sci Am.* 1995;1:55–61.
25. Cataliotti L, Distante V, Ciatto S, et al. Intraductal breast cancer: review of 183 consecutive cases. *Eur J Cancer.* 1992;28:917–20.
26. Turaka A, Freedman GM, Li T, et al. Young age is not associated with increased local recurrence for DCIS treated by breast-conserving surgery and radiation. *J Surg Oncol.* 2009;100:25–31.
27. Van Zee KJ, Subhedar P, Olcese C, Patil S, Morrow M. Relationship between margin width and recurrence of ductal carcinoma in situ: analysis of 2996 women treated with breast-conserving surgery for 30 years. *Ann Surg.* 2015;262:623–31.
28. Meattini I, Livi L, Franceschini D, et al. Role of radiotherapy boost in women with ductal carcinoma in situ: a single-center experience in a series of 389 patients. *Eur J Surg Oncol.* 2013;39:613–8.
29. Chuwa EWL, Tan VHS, Tan P-H, Yong W-S, Ho G-H, Wong C-Y. Treatment for ductal carcinoma in situ in an Asian population: outcome and prognostic factors. *ANZ J Surg.* 2008;78:42–8.
30. MacAusland SG, Hepel JT, Chong FK, et al. An attempt to independently verify the utility of the Van Nuys prognostic index for ductal carcinoma in situ. *Cancer.* 2007;110:2648–53.

31. Bijker N, Meijnen P, Peterse JL, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853. A study by the EORTC breast cancer cooperative group and EORTC radiotherapy group. *J Clin Oncol.* 2006;24:3381–7.
32. Chasle J, Delozier T, Denoux Y, Marnay J, Michels J-J. Immunohistochemical study of cell cycle regulatory proteins in intraductal breast carcinomas: a preliminary study. *Eur J Cancer.* 2003;39:1363–9.
33. Nakamura S, Woo C, Silberman H, Streeter J, Lewinsky BS, Silverstein MJ. Breast-conserving therapy for ductal carcinoma in situ: A 20 year experience with excision plus radiation therapy. *Am J Surg.* 2002;184:403–9.
34. Neuschatz AC, DiPetrillo T, Safaii H, Lowther D, Landa M, Wazer DE. Margin width as a determinant of local control with and without radiation therapy for ductal carcinoma in situ (DCIS) of the breast. *Int J Cancer.* 2001;96:97–104.
35. Fowble B, Hanlon AL, Fein DA, et al. Results of conservative surgery and radiation for mammographically detected ductal carcinoma in situ (DCIS). *Int J Radiat Oncol Biol Phys.* 1997;38:949–57.
36. Sweldens C, Peeters S, Van LE, et al. Local relapse after breast-conserving therapy for ductal carcinoma in situ: a European single-center experience and external validation of the memorial Sloan-Kettering Cancer Center DCIS nomogram. *Cancer J.* 2014;20:1–7.
37. Kim H, Noh JM, Choi DH, et al. Excision alone for small size ductal carcinoma in situ of the breast. *Breast.* 2014;23:586–90.
38. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med.* 2004;23:3105–24.
39. Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC good practice task force report. *Value Health.* 2014;17:157–73.
40. Fisher ER, Dignam J, Tan-Chiu E, et al. Pathologic findings from the national surgical adjuvant breast project (NSABP) eight-year update of protocol b-17: intraductal carcinoma. *Cancer.* 1999;86:429–38.
41. Fish EB, Chapman J-A, Miller NA, et al. Assessment of treatment for patients with primary ductal carcinoma in situ in the breast. *Ann Surg Oncol.* 1998;5:724–32.
42. Sahoo S, Recant WM, Jaskowiak N, Tong L, Heimann R. Defining negative margins in DCIS patients treated with breast conservation therapy: The University of Chicago experience. *Breast J.* 2005;11:242–7.
43. Macdonald HR, Silverstein MJ, Mabry H, et al. Local control in ductal carcinoma in situ treated by excision alone: incremental benefit of larger margins. *Am J Surg.* 2005;190:521–5.
44. Correa C, McGale P, Taylor C, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. *J Natl Cancer Inst Monogr.* 2010;162–77.
45. Cutuli B, Cohen-Solal-Le NC, De LB, et al. Breast-conserving therapy for ductal carcinoma in situ of the breast: the French Cancer Centers' experience. *Int J Radiat Oncol Biol Phys.* 2002;53:868–79.
46. Tunon-De-Lara C, De-Mascarel I, Mac-Grogan G, et al. Analysis of 676 cases of ductal carcinoma in situ of the breast from 1971 to 1995: diagnosis and treatment. The experience of one institute. *Am J Clin Oncol Cancer Clin Trials.* 2001;24:531–36.
47. Fisher B, Land S, Mamounas E, Dignam J, Fisher ER, Wolmark N. Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the National Surgical Adjuvant Breast and Bowel Project experience. *Semin Oncol.* 2001;28: 400–18.
48. Chan KC, Fiona KW, Sinha G, et al. Extent of excision margin width required in breast conserving surgery for ductal carcinoma in situ. *Cancer.* 2001;91:9–16.
49. Warneke J, Grossklaus D, Davis J, et al. Influence of local treatment on the recurrence rate of ductal carcinoma in situ. *J Am Coll Surg.* 1995;180:683–8.
50. Kestin LL, Goldstein NS, Martinez AA, et al. Mammographically detected ductal carcinoma in situ treated with conservative surgery with or without radiation therapy. Patterns of failure and 10 year results. *Ann Surg.* 2000;231:235–45.
51. Ringberg A, Idvall I, Ferno M, et al. Ipsilateral local recurrence in relation to therapy and morphological characteristics in patients with ductal carcinoma in situ of the breast. *Eur J Surg Oncol.* 2000;26:444–51.
52. Rudloff U, Brogi E, Reiner AS, et al. The influence of margin width and volume of disease near margin on benefit of radiation therapy for women with DCIS treated with breast-conserving therapy. *Ann Surg.* 2010;251:583–91.
53. Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences (with discussion). *Stat Sci.* 1992;7:457–511.
54. Spiegelhalter DJ, Best NG, Carlin BP, Van Der Linde A. Bayesian measures of model complexity and fit. *J R Stat Soc Series B.* 2002;64:583–639.