Margin status and survival outcomes after breast cancer conservation surgery: prospectively registered systematic review and meta-analysis

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ABSTRACT

OBJECTIVE

To determine if margin involvement is associated with distant recurrence and to determine the required margin to minimise both local recurrence and distant recurrence in early stage invasive breast cancer.

DESIGN

Prospectively registered systematic review and meta-analysis of literature.

DATA SOURCES

Medline (PubMed), Embase, and Proquest online databases. Unpublished data were sought from study authors.

ELIGIBILITY CRITERIA

Eligible studies reported on patients undergoing breast conserving surgery (for stages I-III breast cancer), allowed an estimation of outcomes in relation to margin status, and followed up patients for a minimum of 60 months. Patients with ductal carcinoma in situ only or treated with neoadjuvant chemotherapy or by mastectomy were excluded. Where applicable, margins were categorised as tumour on ink (involved), close margins (no tumour on ink but <2 mm), and negative margins (≥2 mm).

RESULTS

68 studies from 1 January 1980 to 31 December 2021, comprising 112 140 patients with breast cancer, were included. Across all studies, 9.4% (95% confidence interval 6.8% to 12.8%) of patients had involved (tumour on ink) margins and 17.8% (13.0% to 23.9%) had tumour on ink or a close margin. The rate of distant recurrence was 25.4% (14.5% to 40.6%) in patients with tumour on ink margins, 8.4% (4.4% to 15.5%) in patients with tumour on ink or close, and 7.4% (3.9% to 13.6%) in patients with negative margins. Compared with negative margins, tumour on ink margins were associated with increased distant recurrence (hazard ratio 2.10, 95% confidence interval 1.65 to 2.69, P<0.001) and local recurrence (1.98, 1.66 to 2.36, P<0.001). Close margins were associated with increased distant recurrence (1.38, 1.13 to 1.69, P<0.001) and local recurrence (2.09, 1.39 to 3.13, P<0.001) compared with negative margins, after adjusting for receipt of adjuvant chemotherapy and radiotherapy. In five studies published since 2010, tumour on ink margins were associated with increased distant recurrence (2.41, 1.81 to 3.21, P<0.001) as were tumour on ink and close margins (1.44, 1.22 to 1.71, P<0.001) compared with negative margins.

CONCLUSIONS

Involved or close pathological margins after breast conserving surgery for early stage, invasive breast cancer are associated with increased distant recurrence and local recurrence. Surgeons should aim to achieve a minimum clear margin of at least 1 mm. On the basis of current evidence, international guidelines should be revised.

SYSTEMATIC REVIEW REGISTRATION

CRD42021232115.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Oncology guidelines suggest that avoiding a tumour that touches ink margins after breast cancer surgery reduces local recurrence but no data exist for distant recurrence

Whether width of excision margin is associated with distant cancer recurrence after breast conserving surgery for early invasive breast cancer is unknown

WHAT THIS STUDY ADDS

Tumours at the inked margins (tumour on ink) or close margins (no tumour on ink, but tumour <2 mm) were associated with increased distant recurrence compared with wider margins, independent of the use of postoperative radiotherapy or adjuvant chemotherapy

Wider margins were also associated with a reduced risk of local recurrence

Margin width between tumour on ink and 2 mm is associated with increases in distant and local recurrence, and mortality after breast conserving surgery

Introduction

Pathological cancer specimens from breast conserving surgery are classified by a pathologist as involved if there is tumour at the edge of the specimen, implying that the specimen has been transected during surgery, or close if tumour is within a defined distance from the edge of the specimen or specimen margin, usually 1 mm or 2 mm.

Involved (tumour on ink or positive) or close (no tumour on ink to 2 mm) pathological margins after breast conserving surgery for early stage invasive breast cancer are associated with an increased risk of local recurrence.[1 2] Patients who develop local recurrence have an increased risk of developing distant recurrence and of death from breast cancer.[3] In 2014, American Society of Clinical Oncology[4] stated that tumour (invasive cancer or ductal carcinoma in situ) not touching the ink at the specimen edge is acceptable to prevent local recurrence.[4 5]

The effect of margin involvement on distant recurrence or mortality is relatively unknown. A UK study of young women, aged 40 or younger, with early stage invasive breast cancer reported that in those undergoing breast conserving surgery, 239

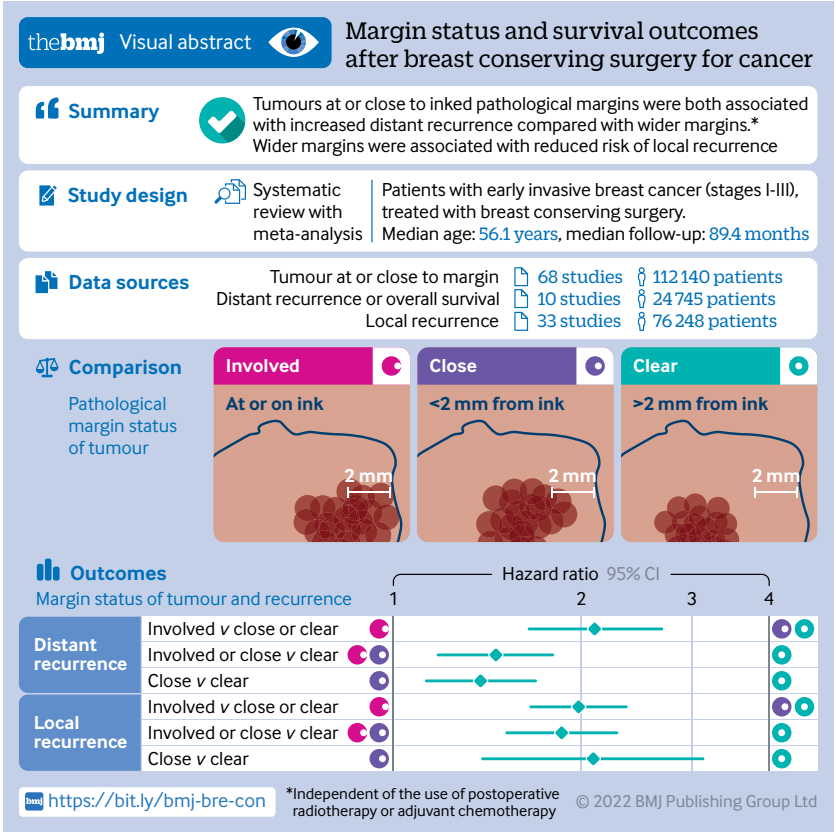
(21%) of 1135 had margins of 1 mm or less, and this was associated with a 13.4% higher rate of distant recurrence and an 11.1% decrease in overall survival at five years compared with women who had margins of more than 1 mm.[6] Positive margins worsen oncological outcomes, therefore avoiding these presents an achievable route to improve breast cancer outcomes.

We performed a systematic review and meta-analysis to determine the incidence of tumour on ink and close margins after breast conserving surgery and any association between margin involvement with subsequent distant recurrence and overall survival in early stage invasive breast cancer. We also aimed to update the evidence on the association between margin width and local recurrence.

Methods

Design and search strategy

This prospectively registered meta-analysis on PROSPERO (CRD 42021232115)[7] identified literature published from 1 January 1980 to 31 December 2021 to determine the association between margin status and oncological outcomes (local recurrence, distant recurrence, and overall survival). We included studies of patients with early stage invasive breast cancer undergoing breast conserving surgery with involved or close surgical margins, or both, comparing patients with negative margins, and with margin distances used to define a close margin. Outcome data collected included local recurrence, distant recurrence, and overall survival. PRISMA guidelines[8] were used in reporting the findings (supplementary table 5).



We searched the literature across Medline (PubMed), Embase, and Proquest online databases, using MeSH terms and search terms as appropriate (supplementary table 4). All eligible studies were identified by two reviewers, who independently extracted data onto a prespecified data collection tool. Two researchers reviewed abstracts and full texts. Any disputes were resolved by a third reviewer. The bibliographies of relevant studies were examined for further publications. To be eligible, studies reported on patients undergoing curative breast conserving surgery for early stage invasive breast cancer (stage I-III), allowed an estimation of outcomes in relation to margin status, and followed up patients for a minimum of 60 months. Oestrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 status were recorded, as was the use of postoperative radiotherapy or chemotherapy, or local re-excision after primary surgery. We excluded patients with ductal carcinoma in situ only or those who were treated with neoadjuvant chemotherapy or had a mastectomy. Where multiple studies reported on the same group of patients, data were included in each analysis once only.

Data extraction and outcome definitions

We used the following criteria for categorisation of tumour distance from margin; where positive margins were defined as the presence of (invasive or in situ) cancer at the resection margin, we defined this category as a tumour at inked margin and the margin distance was considered 0 mm for subsequent analyses. Where studies dichotomised patients into two groups with respect to margin width and grouped patients (eg, <2 mm, <1 mm, etc), these patients were defined as positive or close margins, with the alternative group defined as wider. Where studies presented three or more groups, including patients with tumour on ink, close, or wider margins, these were collected and analysed both as separate groupings and additionally with outcomes from involved (tumour on ink) margin and close margin groups pooled to add to an analysis of involved or close versus wider margins. All margin distances stated were final surgical margins for any patients receiving re-excision.

Local recurrence was defined as recurrence within the ipsilateral breast or axilla, and distant recurrence as recurrence occurring in distant sites or supraclavicular nodes. Data were extracted as time-to-event data (hazard ratios for recurrence comparing margin width groups) and in binary form (numbers with recurrence in each group)

Methodological quality

We used study level observational data. Where data relevant to the analysis were incomplete, but evidently available to the study authors, these unpublished data were sought directly from authors. All study authors referencing, but not publishing, data for distant recurrence within their study were approached to provide those data for the review and any data that

were not reported in the studies, required for the meta-analyses, were sought directly from these authors.

All studies were graded for methodological and reporting quality using the Cochrane risk of bias tool appropriate to the included study type. For most studies, we used the ROBINS-E tool for non-randomised observational studies. Two reviewers independently scored each paper and disputes were resolved by a third reviewer (supplementary table 3). Overall, the quality of evidence was summarised according to GRADE (Grading of Recommendations, Assessment, Development and Evaluations).[9]

Statistical analysis

Estimate of prevalence of involved (tumour on ink) or close margins

An estimate of the incidence of tumour on ink and close margins was sought from published cohort studies. Any study that included all patients undergoing breast conserving surgery within a specific time period was included. Overall pooled prevalence of tumour on ink and tumour on ink and close margins was calculated using a random effects, random intercept, logistic regression model.

Impact of involved (tumour on ink) or close margins on oncological outcomes

As time to recurrence and survival outcomes necessitate both the number and timing of recurrences and deaths, the primary summary statistic extracted and pooled from studies was hazard ratios derived from Cox-proportional hazard models.[10] Adjusted and unadjusted hazard ratios were pooled using random effects modelling, using restricted maximum likelihood modelling. Hazard ratios from adjusted models were included preferentially, if both unadjusted and adjusted were reported; however, unadjusted hazard ratios were included where adjusted hazard ratios were not reported to avoid the introduction of bias by exclusion of negative studies.[10-12] To explore a required minimum margin distance and to present a summary of the full range of data in the published literature, three models were considered for each outcome: involved margins (tumour on ink) versus wider than tumour on ink margins, tumour on ink and close margins (tumour not at ink) versus negative margins, and close margins versus negative margins. Subsequently, to define more precisely a minimum clear margin required, model three was split into three subgroups: tumour 0.1-2.0 mm from ink versus >2.0 mm; tumour 0.1-1.0 mm from ink versus >2.0 mm; and tumour 1.1-2.0 mm from ink versus >2.0 mm.

Meta-analyses were summarised using forest plots and I^2 statistics were calculated as measures of heterogeneity. To investigate causes of heterogeneity, prespecified subgroups were analysed,[7] initially using data from papers that reported specifically on that subgroup, and additionally, using meta-regression techniques, as outlined here.[11 13]

Publication biases were examined using funnel plots (supplementary figures 2 and 3) and Egger linear regression tests. Statistical analyses were done using R Statistical Software (R version 4.0.1), package metafor.

Patient and public involvement

NJB and DD have regular meetings with patient representatives about ongoing scientific projects and activities. NJB and DD contacted patient representatives of Independent Cancer Patients' Voice and sought their opinion on the findings. JEG surveyed the patients from the Independent Cancer Patients' Voice and they suggested that we make the findings clear and avoid technical terms as far as possible, to enable wide dissemination of the results given the relevant implications for research and clinical practice, which we implemented. The importance of transparency and full disclosure in the patient-surgeon relationship, especially surrounding the potential impact of positive margins on outcomes, was a recurring theme.

Results

Study characteristics

We identified 1451 references, of which 68 studies containing 112 140 patients were included (fig 1, supplementary table 1). Included studies contained participants with an average median age of 56.1 (interquartile range 53.1-57.7) years and a median follow-up of 89.4 (interquartile range 65.0-118.0) months. Further characteristics of the included studies are described in detail in the supplementary text.

Criteria for defining margin status varied considerably across the included studies and multiple studies defined margins using two or more definitions. Thirty one studies reported a positive margin as tumour on ink. Eleven studies used a definition of close or positive margins as tumour less than 1 mm from ink. Thirty five studies used a definition of positive or close margins as tumour less than 2 mm from ink and 11 defined close or positive margins as a tumour less than 5 mm from ink (supplementary table 2).

From the 68 included studies, all provided data towards estimates of prevalence of margin status definitions. Twenty studies provided data of pooled estimates of distant recurrence rates with close or positive margins, eight of which provided Cox regression estimates of distant recurrence by margin definition. Fifty six studies provided data towards estimates of local recurrence rates with close or positive margins, with 32 providing Cox regression estimates for local recurrence by margin definition. Five studies provided data towards pooled estimates of overall survival with close or positive margins, all providing Cox regression estimates of overall survival by margin definition.

Meta-analysis of prevalence of positive and close margins

Thirty one studies, of 37 754 patients, reported numbers with tumour at inked margin, with a pooled estimate for the prevalence of tumour on ink margin of 9.4% (95% confidence interval 6.8% to 12.8%). Eleven studies, including 10 504 patients reported

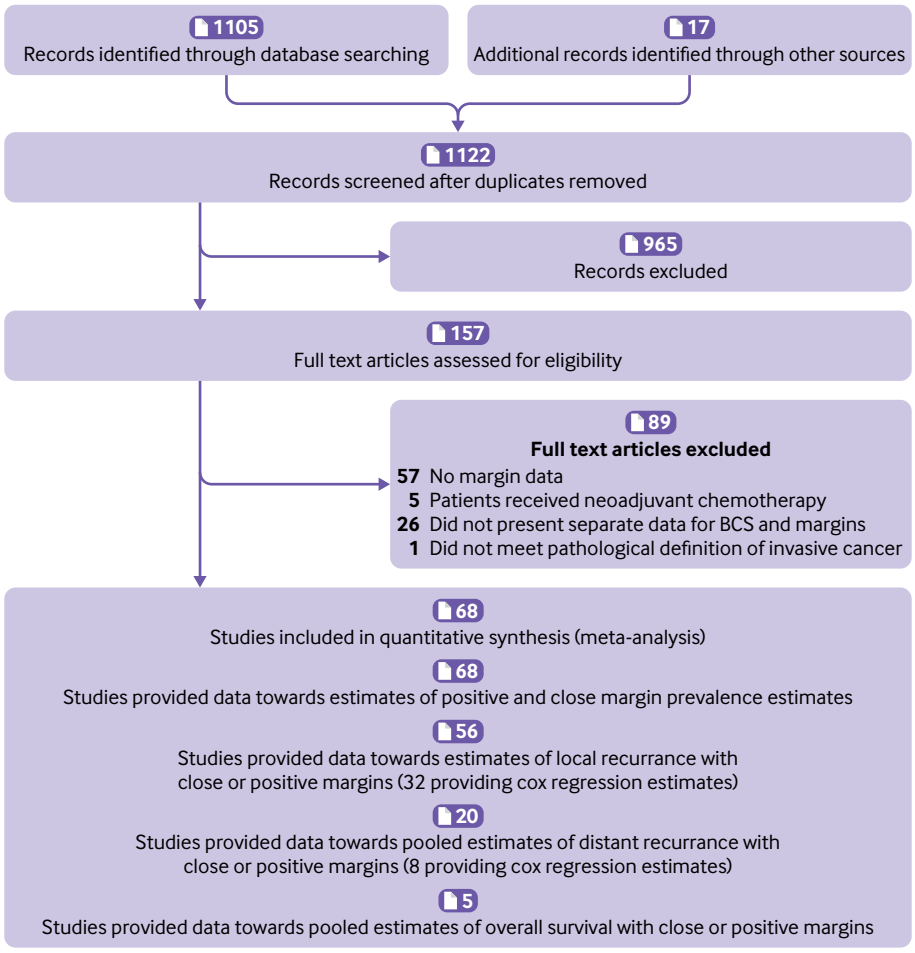


Fig 1 | PRISMA flowchart showing selection of abstracts and studies from searching through to inclusion in the meta-analysis and studies excluded with reasons. BCS=breast conserving surgery

on tumours within 1 mm of the inked margin, with a pooled estimate for the prevalence of a tumour within 1 mm of the inked margin of 14.7% (6.7% to 29.2%). Thirty three studies, of 71 185 patients, reported on tumours within 2 mm of the inked margin, with a pooled estimate for the prevalence of a tumour within 2 mm of the inked margin of 17.8% (13.0% to 23.9%). Ten studies, including 12 014 patients reported on tumour within 5 mm of the inked margin, with a pooled estimate for the prevalence of tumour within 5 mm of the inked margin of 24.4% (15.9% to 35.5%).

Distant recurrence and local recurrence by margin distance

Of 68 studies with a minimum follow up of 60 months, patients with tumour on ink margins had a pooled overall distant recurrence risk of 25.4% (95% confidence interval 14.5% to 40.6%) and a local recurrence risk of 15.9% (10.5% to 23.2%); whereas patients with a tumour at or close to inked margins had a distant recurrence risk of 8.4% (4.4% to 15.5%) and a local recurrence risk of 8.8% (6.3% to 12.4%). Patients with negative margins had a distant recurrence of 7.4% (3.9% to 13.6%) and a local recurrence risk of 3.9% (3.0% to 4.9%).

Distant recurrence

For tumour at ink versus tumour not at inked margin, five studies[6 14 15 17 21] presented multivariate hazard ratios for relative risk of distant recurrence according to tumour at inked margin (tumour on ink) versus negative margins. Tumour on ink was associated with increased risk of distant recurrence (hazard ratio 2.10 (95% confidence interval 1.65 to 2.69), P<0.001, I^2=38%, Egger's P value=0.43; fig 2; table 1,table 2).

Three[6 17 23] studies presented multivariable hazard ratio for tumours within 1 mm of margins compared with wider than 1 mm. Tumours within 1 mm were associated with an increased risk of distant recurrence, compared with tumours wider than 1 mm from the margin (hazard ratio 1.53 (95% confidence interval 1.17 to 1.99), P=0.001, I^2=0%; fig 2). Tumours less than 2 mm from the inked margin versus tumours further than 2 mm were associated with distant recurrence (1.46 (1.18 to 1.80), P<0.001, I^2=0%; fig 2).[16 20]

For tumours close to, but not at, inked margins versus wider margins, three studies[6 17 23] reported on patients with close margins and distant recurrence. Tumours between 0.1 mm and 2.0 mm from inked margins compared with tumours further than 2 mm from margins were associated with an increased risk

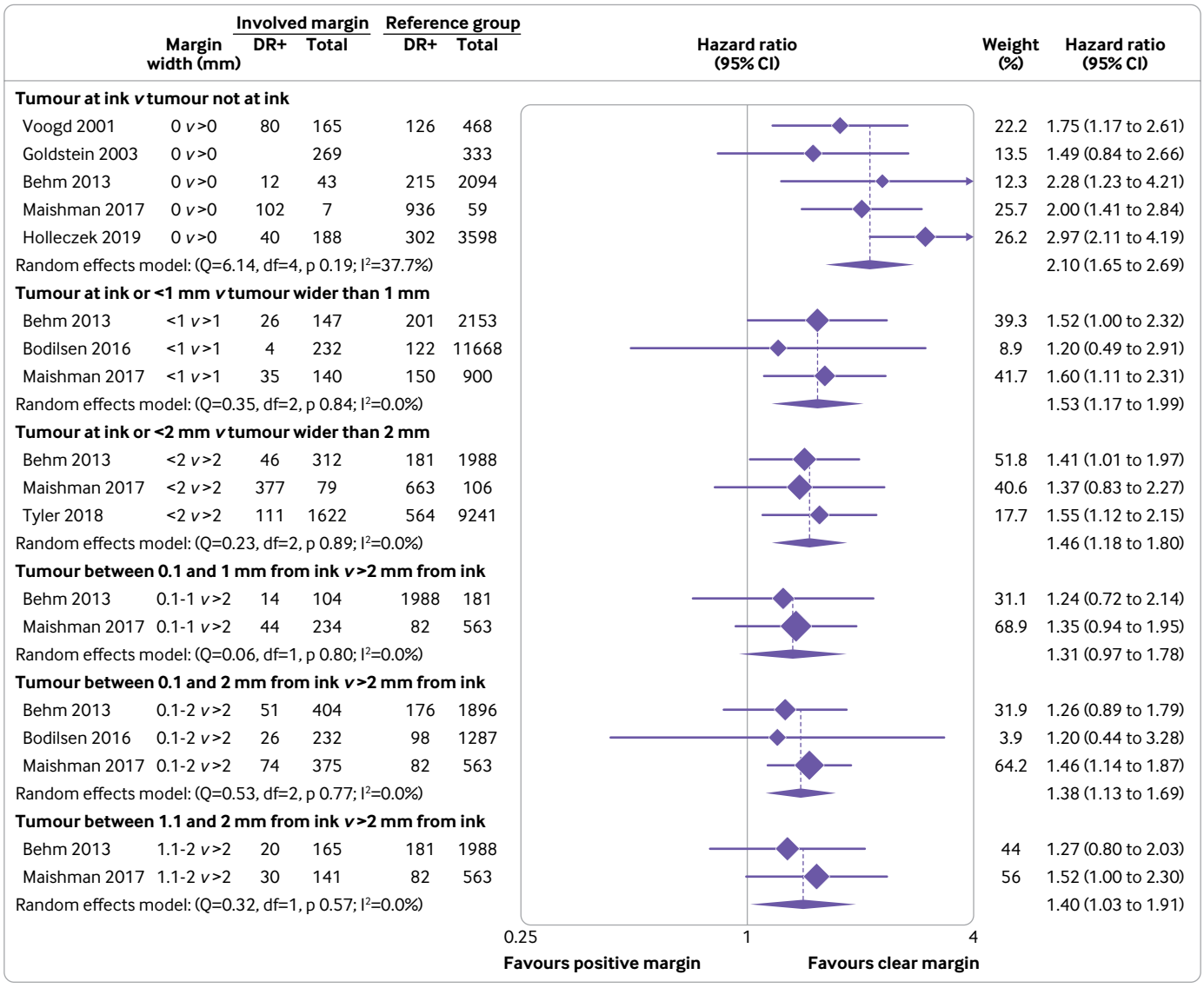


Fig 2 | Forest plots of margin involvement and distant recurrence, showing tumour on ink versus tumour not at ink; tumour on ink or tumour at ‹1 mm defined versus wide margins ›1 mm; tumour on ink and ‹2 mm margin versus wide margin ›2 mm; tumour between 0.1 and 1 mm from ink versus wide margins ›2 mm; tumour 0.1-2 mm from ink versus wider margins ›2 mm; tumour 1.1-2 mm from ink margin versus margins ›2 mm from ink. DR=distant recurrence; RE=random effects; df=degrees of freedom; NS=not stated

of distant recurrence (1.38 (1.13 to 1.69), P=0.001, I^2=0%; fig 2). Tumours between 0.1 mm and 1 mm from inked margins compared with tumours further than 2 mm from margin were associated with an increased risk of distant recurrence (1.31 (0.97 to 1.78), P=0.08, I^2=0%; fig 2). Tumours between 1.1 mm and 2.0 mm from the margin compared with tumours further than 2 mm from margin were associated with an increased risk of distant recurrence (1.40 (1.03 to 1.91), P=0.03, I^2=0%; fig 2). The overall quality of evidence contributing to all distant recurrence analyses was assessed as moderate in each instance (table 2, supplementary table 3).

Local recurrence

Hazard ratios for the impact of a tumour on inked margin on local recurrence were available for 12 studies (10 studies from adjusted models).[6 14 15 17 21 24-29] Tumour on ink was associated with increased rates of local recurrence (hazard ratio 1.98 (95% confidence interval 1.66 to 2.36), P<0.001; fig 3).

For a tumour at inked margin or within 1 mm or 2 mm versus tumour wider from the inked margins, 20 studies presented hazard ratios for the impact of a positive or close margin on local recurrence from either adjusted or unadjusted models (16 from adjusted models).[6 17 18 20 27 30-39] Tumours within 1 mm were associated with an increased risk of local recurrence, compared with tumours wider than 1 mm from the margin (hazard ratio 1.86 (95% confidence interval 1.14 to 3.04), P=0.01, I^2=41%; fig 3). Tumours within 2 mm were associated with an increased risk of local recurrence, compared with tumour wider than 2 mm from the margin (1.86 (1.52 to 2.28), P<0.001, I^2=35%; fig 3).

Table 1 | Specific characteristics of studies reporting on margin status and distant recurrence or overall survival outcomes. Data are number (%), unless otherwise specified

Study	P/C	TOI	Total	%P/C	Radiotherapy	Adjuvant chemotherapy	Hormone therapy	Re-excision	Grade 3	N0	Factors adjusted*; adequate adjustment†
Voogd 2001[14]	165	165	633	26.0	633 (100)	272 (43)	NS	NS	311 (49.1)	543 (85.8)	Age, T stage, N stage, histology, grade, vascular invasion; N
Goldstein 2003[15]	269	269	602	44.7	602 (100)	95 (15.8)	224 (37.2)	441 (73.2)	174 (39.9)	441 (73.3)	Age, T stage; N
Ewertz 2008[16]	192	—	3647	5.3	3506 (96.1)	1250 (34.2)	2232 (61.2)	NS	NS	2649 (72.6)	Age, T stage, N stage, radiotherapy; N
Behm 2013[17]	206	43	2300	9.0	1457 (63.3)	1112 (48.3)	1747 (75.9)	1452 (63.1)	717 (31.2)	1325 (57.6)	Age, radiotherapy, grade, nodal involvement, ER/PR status, hormone therapy, chemotherapy; Y
Bodilsen 2016[18]	39	—	1519	2.6	1519 (100)	616 (40.6)	912 (60)	178 (11.7)	332 (21.9)	934 (61.5)	Age, histology, N stage, vascular invasion, re-excision, chemotherapy, boost radiotherapy; N
Bosma 2016[19]	1155	621	8485	13.6	8485 (100)	1858 (22)	2567 (30)	761 (8.9)	2061 (29)	4964 (66)	Age, T stage, N stage, histology, grade, chemotherapy, radiotherapy; Y
Maishman 2017[6]	239	102	1055	17.1	1055 (96)	1055 (100)	839 (60.1)	290 (20.7)	848 (60.8)	837 (60)	Age, T stage, N stage, histology, boost dose radiotherapy, focality; Y
Tyler 2018[20]	1622	—	10 863	14.9	10 863 (100)	3950 (36.3)	8073 (74.3)	1622 (14.9)	3260 (30)	7720 (71.1)	Age, grade, vascular invasion, N stage, radiotherapy, histology, systemic adjuvant therapy; Y
Holleczek 2019[21]	188	188	3786	4.9	3786 (100)	70% of node positive	7955 (85)	NS	1060 (28)	3435 (90.7)	Age, T stage, N stage, grade, molecular phenotype; Y
Livi 2007[22]	303	303	3834	7.9	3834 (100)	920 (24)	1796 (47)	NS	NS	2701 (70.4)	Age, T stage, N stage, chemotherapy; N
Totals	2920	—	24 745	11.8	23 705 (95.8)	8078 (39.7)	14 027 (69.0)	3983 (23.8)	6528 (31.9)	17 884 (72.2)	—

ER=oestrogen receptor; PR=progesterone receptor; TOI=number of patients with tumour at ink; P/C=Number of patients with tumour at ink or close (within a defined margin distance); %P/C=The percentage of the total cohort with patients with tumour at ink or within a defined margin distance; RT=Radiotherapy; HT+=Hormone therapy; N0=lymph node negative patients; NS=not stated in paper.
*Other than margin status.
†To be adequately adjusted a study must adjust for age, tumour stage (T/N), grade, chemotherapy, radiotherapy OR must contain exclusively patients (>95%) receiving chemotherapy/radiotherapy if not adjusting for these covariates.

Six studies presented hazard ratios for the impact of a tumour close to (within 1 mm or 2 mm, not including tumour on ink) margins versus tumour further from margins.[6 17 18 37 38 40] Tumours between 0.1 mm and 2 mm from the margin compared with tumours further than 2 mm from margin were associated with an increased risk of local recurrence (hazard ratio 2.09 (95% confidence interval 1.39 to 3.13), P<0.001, I^2=55%; fig 3) in six studies.[6 17 18 37 38 40] Tumours between 0.1 and 1 mm from margin compared with tumours further than 2 mm from margin were associated with an increased risk of local recurrence (1.60 (1.13 to 2.25), P=0.007, I^2=0%; fig 2). Tumours between 1.1 mm and 2 mm from margin compared with tumours further than 2 mm from margin were associated with an increased risk of local recurrence (1.81 (0.95 to 3.45), P=0.07; fig 2). The overall quality of evidence contributing to all the local recurrence analyses outlined above was assessed as low (supplementary tables 1 and 2).

Overall survival

Two studies reported on overall survival,[6 22] comparing patients with tumour on ink versus not on inked margins. Tumours on ink margins were associated with an increased rate of mortality (1.61 (1.19 to 2.17), P<0.001, I^2=41%; supplementary fig 1A).

Positive or close margins (tumour on ink or <2 mm) versus wider (tumour ≥2 mm) margins were associated with increased rates of mortality (1.32 (1.01 to 1.73), P=0.05, I^2=23%; supplementary fig 1B). The quality of evidence contributing to both of these overall survival analyses was assessed as moderate.

Planned subgroup analysis and meta-regression

We carried out planned subgroup analyses of studies with adjusted effect estimates only, studies with effect estimates adjusted for a predefined optimal set of factors (T stage, N stage, tumour grade, chemotherapy, and radiotherapy), studies where more than 95% of patients received radiotherapy, with study publication year after 2010, studies of patients with negative lymph nodes, and in patients receiving chemotherapy (supplementary text). In particular, adjuvant chemotherapy use varied from 15% to 75% in the included studies reporting on distant recurrence. Meta-regression techniques provided evidence that the variation in adjuvant chemotherapy rates did not contribute to meta-analysis heterogeneity for both positive versus negative margins (P=0.47) and positive and close versus negative margin analyses, with respect to distant recurrence (P=0.32). Analysis of adequately adjusted studies only provided results consistent with the main analysis, supporting the persistence of these associations despite adjustment for T stage, N stage, pathological grade, adjuvant chemotherapy, and radiotherapy.

Table 2 | Tabulation of results by different outcomes and margin distance models, along with outcomes from assessment of evidence quality and risk of bias summaries

Outcomes and subgroup	No	HR (95% CI)	P value	I^2	Egger's P value	Risk of bias	Quality of evidence
Distant recurrence							
Model one, TOI *v* not TOI:							
Overall	5	2.10 (1.65 to 2.69)	<0.001	38	0.43	Low	Moderate ⊕⊕⊕◯
Adjusted only	5	2.10 (1.65 to 2.69)	<0.001	38	0.43		
Adequately adjusted*	3	2.41 (1.81 to 3.21)	<0.001	31	NA		
Published after 2010	5	2.10 (1.65 to 2.69)	<0.001	38	0.43		
Model two, TOI or close *v* wide margins (<1 mm *v* >1 mm):							
Overall	3	1.53 (1.17 to 1.99)	0.001	0	NA	Low	Moderate ⊕⊕⊕◯
Adjusted only	2	1.56 (1.19 to 2.06)	0.002	0	NA		
Adequately adjusted*	2	1.56 (1.19 to 2.06)	0.002	0	NA		
Published after 2010	3	1.53 (1.17 to 1.99)	0.001	0	NA		
Model two, TOI or close *v* wide margins (<2 mm *v* >2 mm):							
Overall	3	1.46 (1.18 to 1.80)	<0.001	0	NA	Low	Moderate ⊕⊕⊕◯
Adjusted only	3	1.46 (1.18 to 1.80)	<0.001	0	NA		
Adequately adjusted*	3	1.46 (1.18 to 1.80)	<0.001	0	NA		
Published after 2010	3	1.46 (1.18 to 1.80)	<0.001	0	NA		
Model three, close *v* negative margins (excluding TOI; 0.1 mm-2 mm *v* >2 mm):							
Overall	3	1.38 (1.13 to 1.69)	0.001	0	NA	Low	Moderate ⊕⊕⊕◯
Adjusted only	2	1.39 (1.14 to 1.7)	0.001	0	NA		
Adequately adjusted*	2	1.39 (1.14 to 1.7)	0.001	0	NA		
Published after 2010	3	1.38 (1.13 to 1.69)	0.001	0	NA		
Model three, close *v* negative margins (excluding TOI; 0.1 mm-1 mm *v* >2 mm):							
Overall	2	1.31 (0.97 to 1.78)	0.08	0	NA	Low	Moderate ⊕⊕⊕◯
Model three, close *v* negative margins (excluding TOI; 1.1 mm-2 mm *v* >2 mm):							
Overall	2	1.40 (1.03 to 1.91)	0.03	0	NA	Low	Moderate ⊕⊕⊕◯
Overall survival							
Model one, TOI *v* not TOI:							
Overall	2	1.61 (1.19 to 2.17)	<0.001	41	NA	Low	Moderate ⊕⊕⊕◯
Adjusted only	1	1.92 (1.34 to 2.76)	<0.001	NA	NA		
Adequately adjusted*	1	1.92 (1.34 to 2.76)	<0.001	NA	NA		
Published after 2010	1	1.92 (1.34 to 2.76)	<0.001	NA	NA		
Model two, TOI or close *v* wide margins:							
Overall	3	1.32 (1.01 to 1.73)	0.05	69	NA	Low	Moderate ⊕⊕⊕◯
Adjusted only	3	1.32 (1.01 to 1.73)	0.05	69	NA		
Adequately adjusted*	3	1.32 (1.01 to 1.73)	0.05	69	NA		
Published after 2010	3	1.32 (1.01 to 1.73)	0.05	69	NA		
Local recurrence							
Model one, TOI *v* not TOI:							
Overall	12	1.98 (1.66 to 2.36)	<0.001	0	0.33	Moderate	Low ⊕⊕◯◯
Adjusted only	10	1.92 (1.59 to 2.32)	<0.001	0	0.48		
Adequately adjusted*	4	1.98 (1.19 to 3.3)	0.008	56	0.86		
Published after 2010	8	2.11 (1.62 to 2.73)	<0.001	22	0.39		
Model two, TOI or close *v* wide margins (<1 mm *v* >1 mm):							
Overall	4	1.86 (1.14 to 3.04)	0.01	41	0.55	Moderate	Low ⊕⊕◯◯
Adjusted only	2	2.22 (0.59 to 8.33)	0.24	74	NA		
Adequately adjusted*	1	1.23 (0.63 to 2.39)	0.54	NA	NA		
Published after 2010	4	1.86 (1.14 to 3.04)	0.01	41	0.55		
Model two, TOI or close *v* wide margins (<2 mm *v* >2 mm):							
Overall	13	1.86 (1.52 to 2.28)	<0.001	35	0.03	Moderate	Low ⊕⊕◯◯
Adjusted only	10	1.95 (1.46 to 2.59)	<0.001	46	0.01		
Adequately adjusted*	6	1.66 (1.27 to 2.17)	<0.001	39	0.84		
Published after 2010	13	1.86 (1.52 to 2.28)	<0.001	35	0.03		
Model three, close *v* negative margins (excluding TOI; 0.1 mm-2 mm *v* >2 mm):							
Overall	6	2.09 (1.39 to 3.13)	<0.001	55	0.56	Moderate	Low ⊕⊕◯◯
Adjusted only	4	2.14 (1.33 to 3.47)	0.001	57	0.78		
Adequately adjusted*	2	2.10 (0.92 to 4.77)	0.08	81	NA		
Published after 2010	5	1.93 (1.28 to 2.91)	0.001	56	0.86		
Model three, close *v* negative margins (excluding TOI; 0.1 mm-1 mm *v* >2 mm);							
Overall	3	1.60 (1.13 to 2.25)	0.007	0	0.27	Moderate	Low ⊕⊕◯◯
Adjusted only	3	1.60 (1.13 to 2.25)	0.007	0	0.27		
Adequately adjusted*	1	1.42 (0.78 to 2.58)	0.25	0	NA		
Published after 2010	2	1.31 (0.79 to 2.17)	0.29	0	NA		
Model three, close *v* negative margins (excluding TOI; 1.1 mm-2 mm *v* >2 mm):							
Overall	1	1.81 (0.95 to 3.45)	0.07	NA	NA	Moderate	Low ⊕⊕◯◯

Adjusted only subgroup contains only papers with adjusted summary estimates (hazard ratios) for the outcome (distant recurrence, local recurrence, or overall survival). CI=confidence interval; Egger's P value=P value from Egger's regression analyses of publication biases; HR=hazard ratio; NA=not available. TOI=tumour on ink.
*To be adequately adjusted a study must adjust for age, tumour stage (T/N), grade, chemotherapy, radiotherapy, or must contain exclusively patients (>95%) receiving chemotherapy or radiotherapy if not adjusting for these covariates.

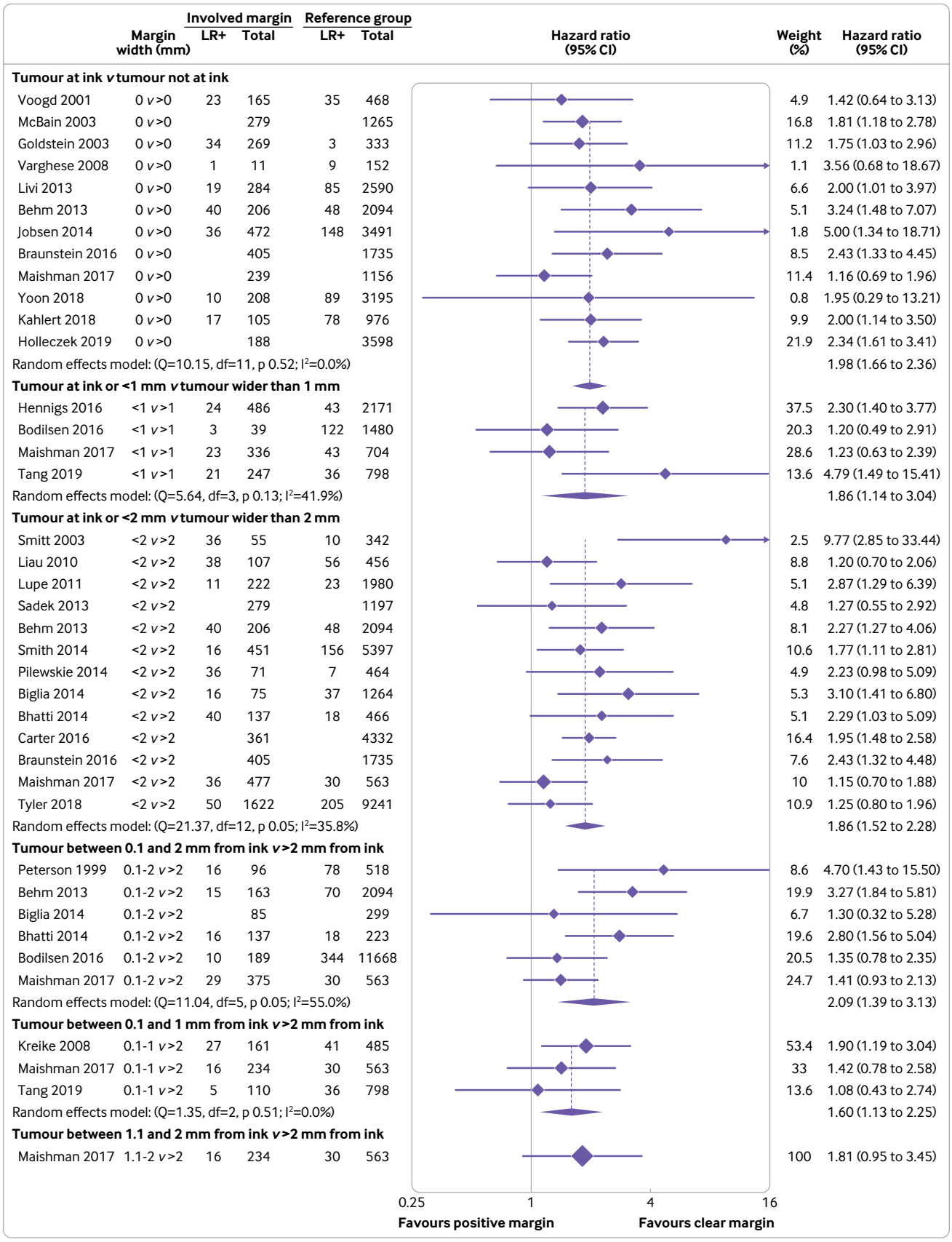


Fig 3 | Forest plots of margin involvement and local recurrence: tumour on ink versus tumour not at ink; tumour on ink or tumour at ‹1 mm defined versus wide margins ›1 mm; tumour on ink and ‹2 mm margin versus wide margin ›2 mm; tumour 0.1-1 mm from ink versus margins ›2 mm; tumour 0.1-2 mm from ink compared with wider margins ›2 mm; tumour 1.1-2 mm from ink margin compared with margins ›2 mm from ink. LR=local recurrence; df=degrees of freedom

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Evaluation of the strength of evidence

We present a summary of assessment of quality and strength of evidence based on the GRADE assessment in supplementary table 3. Studies contributing data to distant recurrence and overall survival outcomes were of low risk of bias (supplementary table 1), and moderate quality evidence, despite the use of observational studies. Studies contributing data to analysis of local recurrence were at greater overall risk of bias and were considered to contribute low quality evidence (supplementary table 3).[9]

Discussion

Principal findings

This meta-analysis identified 68 studies comprising 112 140 women and provided evidence, for the first time to our knowledge, of associations between pathological margins and the risk of distant recurrence and mortality after breast conserving surgery. This association was present despite adjustment for the use of postoperative radiotherapy and chemotherapy. Positive or close margins were associated with increased distant recurrence, local recurrence, and lower overall survival compared with negative or wide margins and, importantly, close margins without tumour at ink were also associated with increased distant and local recurrence.

Strengths and weaknesses

This paper collates data from about four times the number of patients included in the 2014 meta-analysis, which addressed local recurrence and margins.[1] This study is also the first to consider the association between distant recurrence and overall survival with margins. Where tumours were at, or close to, the margin, risk of distant recurrence (and local recurrence) was increased, even in patients treated with adjuvant chemotherapy; a finding consistent across all the margin width comparisons. Our analysis combined multivariable hazard ratios, the accepted standard for reporting time-to-event data, in preference to binary outcome data, avoiding bias introduced by the varying follow-up lengths of included studies. Missing distant recurrence data not presented in studies were obtained in some cases by writing to authors directly. Additionally, we conducted rigorous quality scoring of papers. Due to the study level nature of this analysis, we cannot fully exclude that differences in prognostic characteristics by margin group introduce confounding into our analyses; however, where possible, summary statistics meta-analysed were adjusted for commonly known potentially confounding factors. Therefore, this association is probably independent of these factors. Additionally, subgrouping of only adequately adjusted studies provided results consistent with the overall results of the analysis. Further studies could assess the impact of possible confounding factors, such as re-excision rates or boost radiotherapy, although boost radiotherapy has not been shown to affect distant recurrence or overall survival outcomes.

With the current practise of adjuvant systemic therapy for most patients with breast cancer, distant recurrence is the most frequent site of first relapse (rather than local recurrence). Thus, most distant recurrence is not due to previous local recurrence. Systemic therapy was associated with reduced distant recurrence rates in our meta-analysis but did not reduce the increased distant recurrence seen with involved margins (<1 mm).

Policy implications for breast cancer care

The American Society of Clinical Oncology guidelines in 2014 suggested that tumour margins (invasive cancer or ductal carcinoma in situ) not touching ink at the specimen edge are acceptable, but the relatively weak evidence available to address this issue was recognised.[4] Our study does not support the overall conclusion expressed in these guidelines.

Most international guidelines[5 41 42] advise a threshold margin to reduce local recurrence. Our study shows that margin proximity is associated with increased distant recurrence (as well as local recurrence), so the chosen margin width is important and should minimise distant recurrence.[4] Some distant recurrences probably result from involved margins, and in the future, multidisciplinary team decisions about margin clearance width should ensure maximal prevention of distant recurrence.[6 21 43] A minimum margin of at least more than 1 mm was the margin required to minimise both distant recurrence and local recurrence in this analysis, taking into account the wider confidence intervals in our analyses of close versus negative margins. The interplay between positive margins and chemotherapy on distant recurrence was analysed both as a metaregression and as a subgroup of studies, which had adjusted for use of chemotherapy. Within both of these analyses, the association between positive or close margins and adverse oncological outcomes was not attenuated by chemotherapy. Clear margins were associated with reduced distant recurrence by an absolute value of 5%[5] across all studies, a level of benefit for which chemotherapy is commonly offered to patients as an adjuvant therapy.[44 45] The American Society of Clinical Oncology meta-analysis highlighted the importance of reducing re-excision rates after breast conserving surgery but its focus was on local not distant recurrence.[4]

Differing rates of margin clearance between different continents and countries might relate to uncertainty over optimal width of clearance in guidelines or to an overemphasis on cosmetic outcomes. Since the widespread use of systemic therapy, four of the six studies (19 000 patients) considering margin status reported an increased distant recurrence with tumours close to or at inked margins. A Dutch study from 1980-2008[19] included in our meta-analysis but with contrasting results to the other studies, had 15.7% missing margin status. Additionally, less than 50% of included patients received systemic therapy and up to 20% received re-excision rates for positive or close margins, probably accounting for

the reduced association between margin status and distant recurrence within this study.[43 46] A national audit of margin involvement and re-excision rates completed in the Netherlands, was associated with a margin involvement reduction to 2.1%, and reduced distant recurrence and local recurrence.[43 46] Similar prospective audits might be helpful in other countries where involved margin rates remain high.

Further study of the nature of margin involvement (invasive cancer or ductal carcinoma in situ) and which margins lead to increased distant recurrence is required but previous studies have suggested that neither type nor site of involvement mattered in the development of local recurrence.[15 17]

Patient advocates stated a preference to minimise the risk of local and distant recurrence of breast cancer risk by ensuring a wider margin. Recognising that wider margins require further surgery, decisions about re-excision should be the product of an informed discussion between clinicians and patients[47] with full disclosure of the risks of increased distant recurrence associated with close margins.

Conclusions

We have conducted the largest meta-analysis of the association between margins after breast conserving surgery and outcomes, and show a relation between margin involvement, the development of metastatic disease, and poorer cancer survival. If, as is likely, the association between margin involvement and higher distant recurrence and mortality is causal, a re-appraisal of existing international guidelines is needed. These comprehensive data indicate the likelihood that inadequate margin widths result in higher risks of distant recurrence and breast cancer mortality, as well as increased local recurrence. A margin of no tumour on ink is inadequate and we recommend a minimum tumour free distance of 1 mm from the margin for either invasive disease or ductal carcinoma in situ to ensure optimum oncological outcomes.

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Contributors: JB searched the literature, extracted data, performed data analysis and co-wrote the manuscript. BS and KB contributed and checked data analysis and reviewed the manuscript, BH and JED contributed data and reviewed the manuscript. JG surveyed the patient group and represented and interpreted their opinions of the study and reviewed the manuscript. SM, RIC, DD, and NJB extracted data and co-wrote the manuscript. NJB is the guarantor of the paper. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: Approval was not required for this meta-analysis as all individual included studies had satisfied local ethics boards requirements for publication.

Data sharing: Data are available on reasonable request from the corresponding author (Bundredn@manchester.ac.uk).

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Dissemination will be to the Association of Breast Surgeons, British Association of Surgical Oncology (BASO), British Breast Group, and Royal College of Radiologists as well as to patients and public via Independent Cancer Patients' Voice and other bodies. We will issue a press release from the University of Manchester, put a commentary piece on the ABS monthly email and arrange a commentary piece written with a patient about the implication of the results. We will tweet the results through Independent Cancer Patients' Voice and ABS, as well as through our private twitter accounts. Distribution via ICPV will ensure wide circulation to surgeons, researchers, minority groups, and the public. We plan to use social media to create greater awareness.

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Web appendix: Supplementary materials