National Institute for Health and Care Excellence

Draft for Consultation

Early and locally advanced breast cancer: diagnosis and management

[A] Evidence reviews for surgery to the breast

NICE guideline tbc

Evidence reviews

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Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Surgery to the breast

This evidence report contains information on 1 review relating to surgery to the breast.

- Review question 1.1 Do tumour-free tissue margins wider than 0 mm reduce local recurrence for people with invasive breast cancer and/or ductal carcinoma in situ (DCIS) treated with breast conserving surgery?

Review question 1.1 Do tumour-free tissue margins wider than 0 mm reduce local recurrence for people with invasive breast cancer and/or ductal carcinoma in situ (DCIS) treated with breast conserving surgery?

Introduction

Studies have demonstrated that for invasive breast cancer, breast conservation (surgical wide excision of tumour combined with radiotherapy to the breast) produces equivalent survival to mastectomy.

An important determinant of local recurrence is the surgical margin width (the distance from the breast cancer to the edge of the surgical excision). This is measured by the pathologist on examination of the excision specimen. If the surgical margin is considered 'involved' then where appropriate re-excision can take place as a further operation. Repeat surgery has implications for people and their further treatment, and so consensus on the optimum margin width is essential to ensure optimal oncological effectiveness whilst minimising morbidities from surgery and potential delays to any planned adjuvant therapies. Setting the threshold too high (wide margins required) will mean additional surgery, which may be unnecessary, whilst setting it too low (narrow surgical margins) may lead to an increased local recurrence rate.

Re-excision rates are variable across the country. The margin width threshold required to consider a margin 'clear' for invasive breast cancer was not previously specified in the previous guideline CG80 (NICE 2009) where it was stated that the 'optimum clear margin has yet to be defined and was not a topic identified for this guideline'. For ductal carcinoma in situ (DCIS) a radial margin width of 2 mm was previously recommended. As local recurrence rates have reduced, a review of the threshold for DCIS, and ascertainment of a recommended margin width for invasive breast cancer is now due.

PICO table

See Table 1 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults (18 or over) with invasive breast cancer (M0) and/or DCIS who have undergone, or are due to undergo, breast conserving surgery
Intervention	• >0-<1 mm • 1-2 mm • >2 mm
Comparison	• Tumour on ink (0 mm) • >0-<1 mm • 1-2 mm • >2 mm
Outcome	**Critical** • Re-operation rate • Local recurrence rate • Patient satisfaction **Important** • Overall survival

	• Disease-free survival • Treatment-related morbidity • HRQoL • Cosmetic result

HRQoL, health-related quality of life

For full details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 Conflicts of interest policy.

Clinical evidence

Included studies

The literature search did not identify any randomised controlled trials (RCTs) or controlled, non-randomised studies with at least 100 participants and 5 years of follow-up data; therefore, the protocol was amended to include any controlled, non-randomised studies and cohort studies with at least 100 participants and 5 years of follow-up data.

Eight articles (number of participants, N=7,998) were included in the review (Behm 2013; Dick 2011; Kreike 2008; MacDonald 2005; Shaikh 2016; Solin 2005; Tartter 2000; Zee 2015), which report data from 2 prospective cohort studies and 6 retrospective cohort studies.

Six studies compared margin widths >2 mm with 0 mm margins, 2 studies compared 1-2 mm margins with 0 mm margins, and 4 studies compared margins >0 - <1 mm with 0 mm margins. Additionally, 2 studies made the following comparisons: >2 mm vs. 1-2 mm, >2 mm vs. >0 - <1 mm, and 1-2 mm vs. >0 - <1 mm.

Six studies (Behm 2013; Kreike 2008; MacDonald 2005; Shaikh 2016; Solin 2005; Zee 2015) reported data for critical outcomes by subgroups of interest: invasive breast cancer ± DCIS (number of publications, k=2), DCIS without radiotherapy (k=2) and DCIS with radiotherapy (k=3).

The clinical studies included in this evidence review are summarised in Table 2 and evidence from these are summarised in the clinical GRADE evidence profiles below (Table 3 to Table 8). See also the study selection flow chart in appendix C, forest plots in appendix E, and study evidence tables in appendix D.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

1 Summary of clinical studies included in the evidence review

2 Table 2: Summary of included studies

Study	Additional inclusion/exclusion criteria	Interventions/comparison
Behm 2013	• Enrolled in the BCTQAP study • Exclusion: Paget's disease; phyllodes tumour; invasive breast cancer of special types; bilateral or metachronous breast cancer	• Intervention arm 1 (>0 - <1 mm): Closest surgical margin for invasive disease was 1 mm • Intervention arm 2 (1 – 2 mm): Closest surgical margin for invasive disease was 2 mm • Intervention arm 3 (>2 mm): Closest surgical margin for invasive disease was ≥3 mm (3 mm, 4 mm, 5 mm, and >5 mm groups combined) • Control arm (0 mm): Closest surgical margin for invasive disease was 0 mm • Margins considered: superficial, medial, lateral, inferior, deep, superior
Dick 2011	• Exclusion: history of cancer before the study; microinvasive disease; Paget's disease; lobular cancer; records could not be found or matched with census data	• Intervention arm: negative (>2 mm) margin • Control arm: positive (0 mm) margin
Kreike 2008	• Primary tumours were ≤5 cm in clinical diameter without signs of multifocal disease	• Intervention arm (>0 - <1 mm) • Control arm (0 mm) • Margin status scored irrespective of the involvement of the margin by an in situ component. One pathologist reviewed all available breast tumour specimens for the pathologic characteristics.
MacDonald 2005	• None reported	• Intervention arm 1 (>0 - <1 mm): The closest single distance between DCIS and an inked margin was between 0.1 mm and 0.9 mm • Intervention arm 2 (1 – 2 mm): The closest single distance between DCIS and an inked margin was between 1.0 mm and 1.9 mm • Intervention arm 3 (>2 mm): The closest single distance between DCIS and an inked margin was ≥2 mm (2.0-2.9, 3.0-5.9, 6.0-9.9, and ≥10 mm groups combined) • Control arm (0 mm): The tumour transected the inked margin • Margin width was determined by direct measurement or ocular micrometry.
Shaikh 2016	• Exclusion: invasive breast cancer; hypofractionated radiotherapy; male	• Intervention arm: >2 mm between tumour and inked margin • Control arm: DCIS present at inked margin
Solin 2005	• Unilateral, mammographically detected TisN0M0 DCIS; no physical examination finding, such as a breast mass or bloody nipple discharge; treatment with breast-conserving surgery followed by	• Intervention arm (>2 mm): Determined according to policy at participating institution. 8/10 participating institutions used 2 mm to differentiate between negative margins (>2 mm or ≥2 mm) and close margins (≤2 mm or <2 mm). One

Study	Additional inclusion/exclusion criteria	Interventions/comparison
	definitive whole-breast irradiation to a dose 4000 centigrays (cGy) • Exclusion: adjuvant chemotherapy or hormonal therapy; Paget's disease; prior or concurrent (micro)invasive ipsilateral or contralateral breast cancer; prior malignancy other than non-melanoma skin cancer	institution used 2–3 mm for this differentiation, and 1 institution used 3 mm. • Control arm (0 mm): tumour identified at inked margin
Tartter 200	• None reported	• Intervention arm (>0 - <1 mm): Tumour within 1 mm of the inked margin • Control arm (0 mm): Tumour present at the inked margin • Pathology reports were reviewed to establish the status of the resection margins
Zee 2015	• None reported	• Intervention arm: margin width >2 mm • Control arm: tumour on ink (0 mm)

BCTQAP, breast cancer treatment quality assurance project; cGY centigray; DCIS, ductal carcinoma in situ;TisN0M0, cancer cells are only growing in the most superficial layer of tissue with no lymph node involvement or distant metastases

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profile for this review question (surgical margins) is presented in Table 3 through to Table 8. All of the included evidence was very low quality because of the observational nature of the included studies, small number of events and risk of bias due to insufficient information regarding methods of cohort selection and comparability of groups at baseline.

Table 3: Summary clinical evidence profile: Comparison 1: >2 mm surgical margins versus 0 mm surgical margins

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: 0 mm	Corresponding risk: >2 mm			
Re-operation rate (immediate re-excision)	585 per 1000	544 per 1000 (316 to 942)	RR 0.93 (0.54 to 1.61)	411 (1 study)	Low[1]
Local recurrence - Whole sample (5 to 10 year follow-up)	80% free from local recurrence at 5 years	89% free from local recurrence at 5 years (84% to 93%)	HR 0.51 (0.34 to 0.77)	3068 (2 studies)	Very low[2]
Local recurrence - Invasive +/- DCIS (5 year follow-up)	NR	Cannot be calculated	HR 0.52 (0.11 to 2.44)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: 0 mm	Corresponding risk: >2 mm			
Local recurrence - DCIS RT+ (8.5 to 10 year follow-up)	84% free from local recurrence at 8.5 years	90% free from local recurrence at 8.5 years (84% to 94%)	HR 0.59 (0.35 to 0.98)	1897 (2 studies)	Very low[2,3]
Local recurrence - DCIS RT- (5 to 2 year follow-up)	53% free from local recurrence at 5 years	85% free from local recurrence at 5 years (80% to 90%)	HR 0.25 (0.17 to 0.35)	1503 (2 studies)	Very low[2,4,5,6]

Rates of local recurrence in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)
CI: Confidence interval; DCIS: ductal carcinoma in situ; HR: Hazard ratio; NR: not reported; RR: Risk ratio; RT: radiotherapy
[1] <300 events and 95% CI crosses both boundaries for no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values
[2] <300 events
[3] Significant heterogeneity - I squared value 78% - heterogeneity not explored - not possible to further explore heterogeneity as no additional subgroups of interest were identified by the GC. Estimated effects for both studies in same direction
[4] Unclear whether method of selection was appropriate and whether different margin groups were comparable
[5] Significant heterogeneity - I squared value 85% - not possible to further explore heterogeneity as no additional subgroups of interest were identified by the GC. Estimated effects for both studies in same direction and exceed threshold for clinically meaningful difference
[6] Estimated HR <0.50

Table 4: Summary clinical evidence profile: Comparison 2: 1 – 2 mm surgical margins versus 0 mm surgical margins

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: 0 mm	Corresponding risk: 1-2 mm			
Local recurrence (5 year follow-up)	53% free from local recurrence at 5 years	61% free from local recurrence at 5 years (52% to 68%)	HR 0.78 (0.6 to 1.02)	52 (2 studies)	Very low[1,2,3]
Local recurrence - Invasive +/- DCIS (5 year follow-up)	NR	Cannot be calculated	HR 0.81 (0.61 to 1.07)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
Local recurrence - DCIS RT- (5 year follow-up)	53% free from local recurrence at 5 years	69% free from local recurrence at 5 years (40% to 86%)	HR 0.58 (0.23 to 1.44)	52 (1 study)	Very low[1,3]

Rates of local recurrence in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)
CI: Confidence interval; DCIS: ductal carcinoma in situ; HR: Hazard ratio; NR: not reported; RR: Risk ratio; RT: radiotherapy
[1] Unclear whether method of selection was appropriate or whether different margin groups were comparable
[2] Population: unclear what proportion of received radiotherapy for Behm 2013
[3] <300 events

Table 5: Summary clinical evidence profile: Comparison 3: >0 - <1 mm surgical margins versus 0 mm surgical margins

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: 0 mm	Corresponding risk: >0 - <1 mm			
Re-operation rate (immediate re-excision)	476 per 1000	95 per 1000 (24 to 371)	RR 0.2 (0.05 to 0.78)	63 (1 study)	Very low[1,2]
Local recurrence (5 to 13.3 year follow-up)	53% free from local recurrence at 5 years	52% free from local recurrence at 5 years (39% to 63%)	HR 1.03 (0.72 to 1.47)	341 (3 studies)	Very low[2,3,4]
Local recurrence - Invasive +/- DCIS (5 to 13.3 year follow-up)	82% free from local recurrence at 13.3 years	78% free from local recurrence at 13.3 years (68% to 85%)	HR 1.26 (0.83 to 1.92)	256 (2 studies)	Very low[2,5,6,7]
Local recurrence - DCIS RT- (5 year follow-up)	53% free from local recurrence at 5 years	67% free from local recurrence at 5 years (47% to 82%)	HR 0.61 (0.31 to 1.2)	85 (1 study)	Very low[2,8]

Rates of local recurrence in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)
CI: Confidence interval; DCIS: ductal carcinoma in situ; HR: Hazard ratio; RR: Risk ratio; RT: radiotherapy
[1] Unclear whether different margin groups were comparable
[2] <300 events
[3] Unclear whether different margin groups were comparable and unclear whether method of selection was appropriate for 2 of the 3 studies
[4] Significant heterogeneity - I squared value 83% - heterogeneity explored in subsequent subgroup analysis5based on cancer type and treatment
[5]Unclear whether different margin groups were comparable and unclear whether method of selection was appropriate for 1 of the 2 studies
[6] Significant heterogeneity - I squared value 88% - not possible to further explore heterogeneity as no additional subgroups of interest were identified by the GC
[7] Unclear what proportion received radiotherapy for 1 of the 2 studies
[8] Unclear whether different margin groups were comparable and unclear whether method of selection was appropriate

Table 6: Summary clinical evidence profile: Comparison 4: >2 mm surgical margins versus 1 – 2 mm surgical margins

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: 1-2 mm	Corresponding risk: >2 mm			
Local recurrence (5 year follow-up)	65% free from local recurrence at 5 years	84% free from local recurrence at 5 years (66% to 93%)	HR 0.41 (0.18 to 0.95)	433 (2 studies)	Very low[1,2,3,4]
Local recurrence - Invasive +/- DCIS (5 year follow-up)	NR	Cannot be calculated	HR 0.64 (0.18 to 2.29)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
Local recurrence - DCIS RT (5 year follow-up)-	65% free from local	88% free from local recurrence	HR 0.29 (0.1 to 0.89)	433 (1 study)	Very low[1,3,4]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: 1-2 mm	Corresponding risk: >2 mm			
	recurrence at 5 years	at 5 years (68% to 96%)			

Rates of local recurrence in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)
CI: Confidence interval; DCIS: ductal carcinoma in situ; HR: Hazard ratio; NR: not reported; RT: radiotherapy
[1] Unclear whether method of selection was appropriate and if different margin groups were comparable
[2] Unclear what proportion received radiotherapy from Behm 2013
[3] <100 events
[4] Estimated HR <.50

Table 7: Summary clinical evidence profile: Comparison 5: >2 mm surgical margins versus >0 - <1 mm surgical margins

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: >0 - <1 mm	Corresponding risk: >2 mm			
Local recurrence (5 year follow-up)	66% free from local recurrence at 5 years	90% free from local recurrence at 5 years (83% to 94%)	HR 0.26 (0.15 to 0.46)	466 (2 studies)	Very low[1,2,3]
Local recurrence - Invasive +/- DCIS (5 year follow-up)	NR	Cannot be calculated	HR 0.23 (0.09 to 0.6)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
Local recurrence - DCIS RT- (5 year follow-up)	66% free from local recurrence at 5 years	89% free from local recurrence at 5 years (80% to 94%)	HR 0.28 (0.14 to 0.55)	466 (1 study)	Very low[1,3]

Rates of local recurrence in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)
CI: Confidence interval; DCIS: ductal carcinoma in situ; HR: Hazard ratio; NR: not reported; RT: radiotherapy
[1] Unclear whether method of selection was appropriate and if groups were comparable
[2] Unclear what proportion received radiotherapy for Behm 2013
[3] <300 events

Table 8: Summary clinical evidence profile: Comparison 6: 1 – 2 mm surgical margins versus >0 - <1 mm surgical margins

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: >0 - <1 mm	Corresponding risk: >2 mm			
Local recurrence (5 year follow-up)	66% free from local recurrence at 5 years	85% free from local recurrence at 5 years (81% to 88%)	HR 0.39 (0.3 to 0.52)	73 (2 studies)	Very low[1,2,3,4]
Local recurrence - Invasive +/-	NR	Cannot be calculated	HR 0.36 (0.26 to 0.48)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: >0 - <1 mm	Corresponding risk: >2 mm			
DCIS (5 year follow-up)					therefore overall quality
Local recurrence - DCIS RT- (5 year follow-up)	66% free from local recurrence at 5 years	67% free from local recurrence at 5 years (39% to 85%)	HR 0.95 (0.39 to 2.29)	73 (1 study)	Very low[1,4]

Rates of local recurrence in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)
CI: Confidence interval; DCIS: ductal carcinoma in situ; HR: Hazard ratio; NR: not reported; RT: radiotherapy
[1] Unclear whether method of selection was appropriate and if groups were comparable
[2] Significant heterogeneity - I squared value 77% - heterogeneity not present in subsequent subgroup analysis based on cancer type and treatment
[3] Unclear what proportion received radiotherapy for Behm 2013
[4] <300 events

See appendix F for full GRADE tables.

Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

Evidence statements

Comparison 1: >2 mm surgical margins versus 0 mm surgical margins

Critical outcomes

Re-operation rate

- There is very low quality evidence from 1 prospective cohort study (N=411) that there is no clinically important effect of margin width on immediate re-operation rate for people with DCIS treated with breast-conserving surgery and radiotherapy.

Local recurrence rate

- There is very low quality evidence from 2 retrospective cohort studies (N=3,068) that surgical margins >2 mm produce clinically meaningful reductions in local recurrence at 5 to 10 year follow-up compared with surgical margins of 0 mm for people with invasive breast cancer and/or DCIS treated with breast-conserving surgery (± radiotherapy).
- There is evidence from 1 retrospective cohort study (N: NR) that there is no clinically important effect of margin width on local recurrence rate at 5 year follow-up for people with invasive breast cancer (± DCIS) treated with breast-conserving surgery (± radiotherapy). It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported
- There is very low quality evidence from 2 retrospective cohort studies (N=1,897) that surgical margins >2 mm produce clinically meaningful reductions in local recurrence at 8.5 to 10 year follow-up compared with surgical margins of 0 mm for people with DCIS treated with breast-conserving surgery and radiotherapy.
- There is very low quality evidence from 2 retrospective cohort studies (N=1,503) that surgical margins >2 mm produce clinically meaningful reductions in local recurrence at 5

to 10 year follow-up compared with surgical margins of 0 mm for people with DCIS treated with breast-conserving surgery alone.

Patient satisfaction

- No evidence was found for this outcome.

Important outcomes

Overall survival

- No evidence was found for this outcome.

Disease-free survival

- No evidence was found for this outcome.

Treatment-related morbidity

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Cosmetic results

- No evidence was found for this outcome.

Comparison 2: 1-2 mm surgical margins versus 0 mm surgical margins

Critical outcomes

Re-operation rate

- No evidence was found for this outcome.

Local recurrence rate

- There is evidence from 1 retrospective cohort study (N: NR) that there is no clinically important effect of margin width on local recurrence rate at 5 year follow-up for people with invasive breast cancer (± DCIS) treated with breast-conserving surgery (± radiotherapy). It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported
- There is low quality evidence from 1 retrospective cohort study (N: 52) that there is no clinically important effect of margin width on local recurrence rate at 5 year follow-up for people with DCIS treated with breast-conserving surgery alone.

Patient satisfaction

- No evidence was found for this outcome.

Overall survival

- No evidence was found for this outcome.

Disease-free survival

- No evidence was found for this outcome.

Treatment-related morbidity

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Cosmetic results

- No evidence was found for this outcome.

Comparison 3: >0 - <1 mm surgical margins versus 0 mm surgical margins

Critical outcomes

Re-operation rate

- There is low quality evidence from 1 prospective cohort study (N=63) that surgical margins >0 mm - <1 mm produce clinically meaningful reductions in immediate re-operation rate compared with surgical margins of 0 mm for people with invasive breast cancer and/or DCIS treated with breast-conserving surgery (± radiotherapy).

Local recurrence rate

- There is very low quality evidence from 2 retrospective cohort studies (N>256; NR for one study) that there is no clinically important effect of margin width on local recurrence rate at 5 to 13.3 year follow-up for people with invasive breast cancer (± DCIS) treated with breast-conserving surgery (± radiotherapy).
- There is very low quality evidence from 1 retrospective cohort study (N: 85) that there is no clinically important effect of margin width on local recurrence rate at 5 year follow-up for people with DCIS treated with breast-conserving surgery alone.

Patient satisfaction

- No evidence was found for this outcome.

Important outcomes

Overall survival

- No evidence was found for this outcome.

Disease-free survival

- No evidence was found for this outcome.

Treatment-related morbidity

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Cosmetic results

- No evidence was found for this outcome.

Comparison 4: >2 mm surgical margins versus 1-2 mm surgical margins

Critical outcomes

Re-operation rate

- No evidence was found for this outcome.

Local recurrence rate

- There is evidence from 1 retrospective cohort study (N: NR) that there is no clinically important effect of margin width on local recurrence rate at 5 year follow-up for people with invasive breast cancer (± DCIS) treated with breast-conserving surgery (± radiotherapy). It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported
- There is very low quality evidence from 1 retrospective cohort study (N=433) that surgical margins >2 mm produce clinically meaningful reductions in local recurrence at 5 year follow-up compared with surgical margins of 1 – 2 mm for people with DCIS treated with breast-conserving surgery alone.

Patient satisfaction

- No evidence was found for this outcome.

Important outcomes

Overall survival

- No evidence was found for this outcome.

Disease-free survival

- No evidence was found for this outcome.

Treatment-related morbidity

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Cosmetic results

- No evidence was found for this outcome.

Comparison 5: >2 mm surgical margins versus >0 - <1 mm surgical margins

Critical outcomes

Re-operation rate

- No evidence was found for this outcome.

Local recurrence rate

- There is evidence from 1 retrospective cohort study (N: NR) that surgical margins >2 mm produce clinically meaningful reductions in local recurrence at 5 year follow-up compared with surgical margins >0 mm - <1 mm for people with invasive breast cancer (± DCIS) treated with breast-conserving surgery (± radiotherapy). It was not possible to judge

imprecision, and therefore the quality of this evidence, as number of events were not reported

- There is very low quality evidence from 1 retrospective cohort study (N=466) that surgical margins >2 mm produce clinically meaningful reductions in local recurrence at 5 year follow-up compared with surgical margins >0 mm - <1 mm for people with DCIS treated with breast-conserving surgery alone.

Patient satisfaction

- No evidence was found for this outcome.

Important outcomes

Overall survival

- No evidence was found for this outcome.

Disease-free survival

- No evidence was found for this outcome.

Treatment-related morbidity

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Cosmetic results

- No evidence was found for this outcome.

Comparison 6. 1-2 mm surgical margins versus >0 - <1 mm surgical

Critical outcomes

Re-operation rate

- No evidence was found for this outcome.

Local recurrence rate

- There is evidence from 1 retrospective cohort study (N: NR) that surgical margins of 1 – 2 mm produce clinically meaningful reductions in local recurrence at 5 year follow-up compared with surgical margins >0 mm - <1 mm for people with invasive breast cancer (± DCIS) treated with breast-conserving surgery (± radiotherapy). It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported
- There is very low quality evidence from 1 retrospective cohort study (N=73) that there is no clinically important effect of margin width on local recurrence rate at 5 year follow-up for people with DCIS treated with breast-conserving surgery alone.

Patient satisfaction

- No evidence was found for this outcome.

Important outcomes

Overall survival

- No evidence was found for this outcome.

Disease-free survival

- No evidence was found for this outcome.

Treatment-related morbidity

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Cosmetic results

- No evidence was found for this outcome.

Recommendations

A1. Offer further surgery (re-excision or mastectomy, as appropriate) after breast-conserving surgery where invasive cancer and/or DCIS is present at the radial margins ('tumour on ink'; 0 mm).

A2. For women who have had breast-conserving surgery where invasive cancer and/or DCIS is present within 2 mm of, but not at, the radial margins (greater than 0 mm and less than 2 mm):

- discuss the benefits and risks of further surgery (re-excision or mastectomy) to minimise the risk of local recurrence
- take into account the woman's preferences, comorbidities, tumour characteristics and the potential use of radiotherapy (see also evidence report H).

Research recommendation

What is the optimum tumour-free margin width after breast-conserving surgery for women with ductal carcinoma in situ (DCIS) and invasive breast cancer?

Rationale and impact

Why the committee made the recommendations

There was some evidence that there was a reduced risk of ductal carcinoma in situ (DCIS) local recurrence if tissue margins were greater than 0 mm, so the committee recommended further surgery (re-excision or mastectomy) to extend the margins if needed. Although there was no consistent evidence about tissue margins for invasive breast cancer, the committee agreed that further surgery should be offered.

The committee agreed that complete excision of the tumour with clear margins was essential for the high-quality care of people with DCIS or invasive breast cancer.

Although there was evidence that aiming for wider margins reduced local recurrence, this did not improve overall survival. In addition, aiming for wider margins could lead to some people having unnecessary extra surgery. Given this uncertainty, the committee agreed the importance of personalised care and discussion to decide whether further surgery is needed.

Impact of the recommendations on practice

The rates of further surgery currently vary across the country. Although the committee noted that the recommendations will reinforce current best practice, there may be some centres that will need to amend their practice in order to follow these recommendations.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee prioritised re-operation rate, local recurrence rate and patient satisfaction as critical outcomes; re-operation rate and local recurrence rate were prioritised rather than overall and disease-free survival as they are more relevant to surgery and occur over a shorter-time frame. Overall survival, disease-free survival, treatment-related morbidity, HRQoL and cosmetic result were selected as important outcomes.

Evidence was only found for re-operation rate and local recurrence rate. Re-operation rate was only reported for the comparison of >2 mm surgical margins versus 0 mm surgical margins and >0 - <1 mm surgical margins versus 0 mm surgical margins.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE. For both re-operation rate and local recurrence rate the evidence was very low quality and was downgraded because of the observational nature of the studies, high rates of imprecision due to small number of events and insufficient information about methods of selection for cohorts and comparability of groups at baseline.

Benefits and harms

There was evidence of decreased local recurrence with a tumour free tissue margin of >0 mm in people with DCIS. The committee noted that there was no consistent evidence of benefit for people with invasive disease having a tumour free tissue margin of > 0 mm. However, based on their experience and knowledge of related evidence, particularly evidence from the Society of Surgical Oncology – American Society for Radiation Oncology (SSO-ASTRO) consensus guideline (Moran 2014; based on the Houssami 2014 meta-analysis) that tumour on ink is associated in at least a two-fold increase in risk of local recurrence that is not mitigated by additional endocrine therapy or radiotherapy, the committee agreed that a margin of > 0 mm would also be needed in people with invasive disease. The committee therefore agreed that further surgery would be needed for people where radial margins are involved (i.e. are 0 mm). Despite the low quality of the evidence, the committee made a strong recommendation as they agreed that complete excision of the tumour with clear margins was imperative to providing high-quality care.

There was limited evidence suggesting that a tumour free tissue margin wider than 2 mm for DCIS might be beneficial in terms of reduced local recurrence, particularly for people who have not had radiotherapy. However the committee noted that no survival benefit had been shown from having wider margins and there was the potential risk of over-diagnosis and over-treatment for people with lower grades of DCIS who may not receive radiotherapy. The committee also noted that for invasive disease there was no evidence of a clear and consistent benefit of having tumour free tissue margins between >0 mm and 2 mm. Given this uncertainty, the committee were unable to make recommendations about whether or not further surgery was warranted to achieve margins wider than 0 mm. Instead they agreed to recommend that the risks and benefits of further surgery be discussed with person where their radial margins are between >0 mm to 2 mm.

The committee discussed the balance of benefits and harms, noting that optimal surgical treatment should result in less local recurrence and a reduction in the number of second operations needed. In turn this would likely result in fewer delays in the treatment pathway and would hopefully improve cosmesis. However, they also noted that for people with a radial margin of >0 mm to 2 mm there was uncertainty about the effect on local recurrence and it was possible that this could increase in the group. They balanced this potential harm by recommending more personalised care.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The committee considered that there was unlikely to be a significant resource impact from the recommendations as they reflect standard practice and so there should be minimal changes to practice nationwide. However, it was agreed that there could potentially be cost savings as a result of optimal surgical treatment aiming for appropriate margins at initial surgery, meaning less need for second operations.

References

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Appendices

Appendix A – Review protocols

Review protocol for review question 1.1 Do tumour-free tissue margins wider than 0 mm reduce local recurrence for people with invasive breast cancer and/or ductal carcinoma in situ (DCIS) treated with breast conserving surgery?

Field (based on PRISMA-P)	Content
Review question	Do tumour-free tissue margins wider than 0 mm reduce local recurrence for people with invasive breast cancer and/or ductal carcinoma in situ (DCIS) treated with breast conserving surgery?
Type of review question	Intervention review
Objective of the review	The objective of this review is to determine the recommended margin width for DCIS and invasive breast. Recommendations will aim to cover thresholds below which re-excision may be required.
Eligibility criteria – population/disease/condition/issue/domain	Adults (18 or over) with invasive breast cancer (M0) and/or DCIS who have undergone, or are due to undergo, breast conserving surgery
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• >0-<1 mm • 1-2 mm • >2 mm
Eligibility criteria – comparator(s)/control or reference (gold) standard	• Tumour on ink (0 mm) • >0-<1 mm • 1-2 mm • >2 mm
Outcomes and prioritisation	Critical (up to 3 outcomes) • Re-operation rate (MID: GRADE default values) • Local recurrence rate (MID: any statistically significant difference) • Patient satisfaction (MID: GRADE default values) Important but not critical

Field (based on PRISMA-P)	Content
	• Overall survival (MID: any statistically significant difference) • Disease-free survival (MID: any statistically significant difference) • Treatment-related morbidity (MID: GRADE default values) • Health-related quality of life (MID: values from the literature where available; GRADE default value for FACT-B endocrine scale) • Cosmetic result (MID: GRADE default values) Immediate to 1 year follow-up periods will be prioritised for patient satisfaction. 5 year follow-ups will be prioritised for all remaining outcomes if multiple time points are reported. MID values from the literature: • HRQoL: • FACT-G total: 3-7 points • FACT-B total: 7-8 points • TOI (trial outcome index) of FACT-B: 5-6 points • BCS of FACT-B: 2-3 points • WHOQOL-100: 1 point
Eligibility criteria – study design	• Systematic reviews/meta-analyses of RCTs • RCTs • Controlled, non-randomised study (minimum no. of participants 100 with 5 years of follow up data) No RCTs, or controlled non-randomised studies were found so the protocol was amended to include: • Any controlled, non-randomised studies • Cohort studies (N≥100; minimum 5 year follow-up)
Other inclusion exclusion criteria	Foreign language studies, conference abstracts, and narrative reviews will not routinely be included.

Field (based on PRISMA-P)	Content
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroups (for critical outcomes only – excluding treatment-related morbidity): • Invasive cancer with or without DCIS with post-operative radiotherapy • DCIS without invasive cancer with post-operative radiotherapy • DCIS without invasive cancer without post-operative radiotherapy
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the reviewing team. Quality control will be performed by the senior systematic reviewer. Dual sifting will not be performed for this question.
Data management (software)	Study sifting and data extraction will be undertaken in STAR. Pairwise meta-analyses will be performed using Cochrane Reviewer Manager (RevMan 5). GRADEpro will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	The following key databases will be searched: Cochrane Library (CDSR, DARE, CENTRAL, HTA) through Wiley, Medline & Medline in Process and Embase through OVID. Additionally Web of Science may be searched and consideration will be given to subject-specific databases and used as appropriate. The focus of this review question has changed since the previous guideline. Therefore the search will be undertaken from 1977 when the first paper regarding breast-conserving surgery was published by Veronesi et al.
Identify if an update	Previous question: What is the optimal tumour-free tissue margin to achieve in patients who undergo breast conserving surgery for ductal carcinoma in situ? Date of search: 06/02/2008 Relevant recommendation(s) from previous guideline: 1) For all patients treated with breast conserving surgery for DCIS a minimum of 2 mm radial margin of excision is recommended with pathological examination to NHS Breast Screening Programme reporting standards. 2) Re-excision should be considered if the margin is less than 2 mm after discussion of the risks and benefits with the patient.
Author contacts	For details please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual

Field (based on PRISMA-P)	Content
Search strategy	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see Section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods chapter
Meta-bias assessment – publication bias, selective reporting bias	For details please see Section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see Sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Alliance (NGA) and chaired by Dr Jane Barrett in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.

Field (based on PRISMA-P)	Content
Roles of sponsor	NICE funds NGA to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	N/A

BCS, breast cancer subscale; DCIS, ductal carcinoma in situ; FACT-B, Functional assessment of cancer therapy – Breast cancer; FACT-G, Functional assessment of cancer therapy – General; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HRQoL, health-related quality of life; M0, no distant metastases; MID, minimally important difference; N/A, not applicable; NHS, National Health Service, NICE, National Institute of Health and Care Excellence; NGA, National Guideline Alliance; RCT, randomised controlled trial; TOI, Trial outcome index; WHOQOL, World Health Organization quality of life

Appendix B – Literature search strategies

Review question: Do tumour-free tissue margins wider than 0 mm reduce local recurrence for people with invasive breast cancer and/or ductal carcinoma in situ (DCIS) treated with breast conserving surgery?

Database: Medline & Embase (Multifile)

Last searched on Embase 1974 to 2017 January 29, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present.Date of last search: 30 January 2017.

#	Searches
1	exp breast cancer/ use oemezd
2	exp breast carcinoma/ use oemezd
3	exp medullary carcinoma/ use oemezd
4	exp intraductal carcinoma/ use oemezd
5	exp breast tumor/ use oemezd
6	exp Breast Neoplasms/ use prmz
7	exp "Neoplasms, Ductal, Lobular, and Medullary"/ use prmz
8	Carcinoma, Intraductal, Noninfiltrating/ use prmz
9	Carcinoma, Lobular/ use prmz
10	Carcinoma, Medullary/ use prmz
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp breast/ use oemezd
13	exp Breast/ use prmz
14	breast.tw.
15	12 or 13 or 14
16	(breast adj milk).tw.
17	(breast adj tender$).tw.
18	16 or 17
19	15 not 18
20	exp neoplasm/ use oemezd
21	exp Neoplasms/ use prmz
22	20 or 21
23	19 and 22
24	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
25	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
26	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz

#	Searches
27	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz
28	exp Paget nipple disease/ use oemezd
29	Paget's Disease, Mammary/ use prmz
30	(paget$ and (breast$ or mammary or nipple$)).tw.
31	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	11 or 31
33	(duct$ carcinoma$-in-situ or duct$ carcinoma$ in-situ or duct$ carcinoma$ in situ or DCIS).tw.
34	32 or 33
35	Mastectomy, Segmental/ use prmz
36	partial mastectomy/ use oemezd
37	(segmentectom$ or post?segmentectom$).tw.
38	(lumpectom$ or post?lumpectom$).tw.
39	(quadrectom$ or post?quadrectom$).tw.
40	((local or limited or sector or segment$ or partial) adj2 (excision or resection)).tw.
41	((partial or segment$) adj2 (mammectom$ or mastectomy$)).tw.
42	(breast adj conserv$).mp.
43	breast?conserv$.mp.
44	(conserv$ adj2 (surgery or therapy)).tw.
45	excision alone.tw.
46	35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47	Reoperation/ use prmz
48	reoperation/ use oemezd
49	(re-operat$ or reoperat$ or re-excis$ or reexcis$).tw.
50	Neoplasm Recurrence, Local/ use prmz
51	tumor recurrence/ use oemezd
52	(local adj (failure or relaps$ or recurrence$)).tw.
53	ipsilateral breast tumo?r recurren$.tw.
54	ipsilateral breast tumo?r relaps$.tw.
55	IBTR.tw.
56	(recurrence free survival or RFS).tw.
57	exp Patient Satisfaction/ use prmz
58	exp patient satisfaction/ use oemezd
59	(patient adj3 (satisf$ or attitude$ or preference$)).tw.
60	47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59
61	margin$.tw.
62	34 and 46 and 60 and 61
63	margin$.m_titl.
64	34 and 46 and 63
65	62 or 64
66	remove duplicates from 65

Database: Cochrane Library via Wiley Online

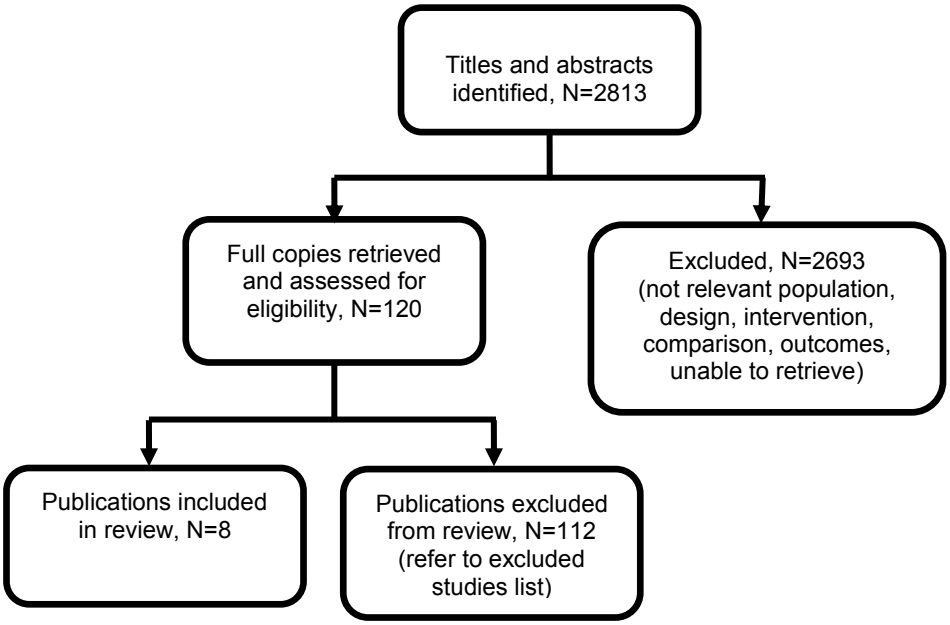
Date of last search: 30 January 2017

#	Searches
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#3	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] explode all trees
#4	MeSH descriptor: [Carcinoma, Lobular] this term only
#5	MeSH descriptor: [Carcinoma, Medullary] this term only
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Breast] explode all trees
#8	breast:ti,ab,kw (Word variations have been searched)
#9	#7 or #8
#10	(breast next milk):ti,ab,kw (Word variations have been searched)
#11	(breast next tender*):ti,ab,kw (Word variations have been searched)
#12	#10 or #11
#13	#9 not #12
#14	MeSH descriptor: [Neoplasms] explode all trees
#15	#13 and #14
#16	(breast* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#17	(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#18	MeSH descriptor: [Paget's Disease, Mammary] this term only
#19	(paget* and (breast* or mammary or nipple*)):ti,ab,kw (Word variations have been searched)
#20	#15 or #16 or #17 or #18 or #19
#21	#6 or #20
#22	MeSH descriptor: [Mastectomy, Segmental] this term only
#23	(segmentectom* or post segmentectom* or post-segmentectom* or postsegmentectom*):ti,ab,kw (Word variations have been searched)
#24	(lumpectom* or post lumpectom* or post-lumpectom* or postlumpectom*):ti,ab,kw (Word variations have been searched)
#25	(quadrectom* or post quadrectom* or post-quadrectom* or postquadrectom*):ti,ab,kw (Word variations have been searched)
#26	((local or limited or sector or partial or segment$) near/2 (excision or resection)):ti,ab,kw (Word variations have been searched)
#27	((partial or segment*) near/2 (mammectom* or mastectomy*)):ti,ab,kw (Word variations have been searched)
#28	(breast next conserv*):ti,ab,kw (Word variations have been searched)
#29	(conserv* near/2 (surgery or therapy)):ti,ab,kw (Word variations have been searched)
#30	excision alone:ti,ab,kw (Word variations have been searched)
#31	#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#32	MeSH descriptor: [Reoperation] explode all trees

#	Searches
#33	(re-operat* or reoperat* or re-excis* or reexcis*):ti,ab,kw (Word variations have been searched)
#34	MeSH descriptor: [Neoplasm Recurrence, Local] explode all trees
#35	(local next (failure or relaps* or recurrence*)):ti,ab,kw (Word variations have been searched)
#36	(ipsilateral near/3 (relaps* or recurren*)):ti,ab,kw (Word variations have been searched)
#37	IBTR:ti,ab,kw (Word variations have been searched)
#38	(recurrence free survival or RFS):ti,ab,kw (Word variations have been searched)
#39	MeSH descriptor: [Patient Satisfaction] explode all trees
#40	(patient near/3 (satisf* or attitude* or preference*)):ti,ab,kw (Word variations have been searched)
#41	#32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40
#42	margin*:ti,ab,kw (Word variations have been searched)
#43	#21 and #31 and #41 and #42
#44	margin*:ti (Word variations have been searched)
#45	#21 and #31 and #44
#46	#43 or #45

Appendix C – Clinical evidence study selection

Figure 1: Flow diagram of clinical article selection for surgical margins



Appendix D – Clinical evidence tables

Table 9: Studies included in the evidence review for surgical margins

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Behm, E. C., Beckmann, K. R., Dahlstrom, J. E., Zhang, Y., Cho, C., Stuart-Harris, R., Craft, P., Rezo, A., Buckingham, J. M., Surgical margins and risk of locoregional recurrence in invasive breast cancer: An analysis of 10-year data from the breast cancer treatment quality assurance project, Breast, 22, 839-844, 2013 **Ref Id** 578522 **Country/ies where the study was carried out** Australia **Study type** Retrospective cohort study **Aim of the study**	**Sample size** 2300 - only interested in those that had breast-conserving surgery as opposed to mastectomy (N=1123) **Characteristics** Gender: 100% women Age: Median/Range NR Ethnicity: NR **Inclusion criteria** Patients enrolled in the BCTQAP study from July 1997 to June 2007 treated by either breast-conserving surgery or mastectomy for invasive breast cancer and for whom at least 3 years follow-up data were available **Exclusion criteria** Paget's disease of the breast, phyllodes tumour, invasive breast cancer of special types, bilateral or metachronous breast	**Interventions** **Intervention arm 1:** 1 mm margin **Intervention arm 2:** 2 mm margin **Intervention arm 3:** ≥3 mm margin **Control arm:** 0 mm margin	**Details** **Intervention arm 1 (>0 - <1 mm):** Closest surgical margin for invasive disease was 1 mm (margins considered: superficial, medial, lateral, inferior, deep, superior) **Intervention arm 2 (1 - 2 mm):** Closest surgical margin for invasive disease was 2 mm (margins considered: superficial, medial, lateral, inferior, deep, superior) **Intervention arm 3 (>2 mm):** Closest surgical margin for invasive disease was ≥3 mm (3 mm, 4 mm, 5 mm, and >5 mm groups combined - margins considered: superficial, medial, lateral, inferior, deep, superior)	**Results** **Intervention arm 1 (>0 - <1 mm) vs. Control arm (0 mm)** **Locoregional recurrence (mean follow-up 7.9 years):** O-E: 9.41; V: 11.50 **Intervention arm 2 (1 - 2 mm) vs. Intervention arm 1 (>0 - <1 mm)** **Locoregional recurrence (mean follow-up 7.9 years):**	**Selection** Admission criteria to BCTQAP unclear - hard to judge whether sample was representative or how selected. Critical outcome (recurrence) not present at start **Comparability** Unclear - not reported whether different margin groups had equivalent characteristics **Outcome** Assessment of outcomes and follow-up were adequate **Indirectness** Population: Unclear what proportion received radiotherapy: serious. Intervention: arm 1 margin is 1 mm rather than <1 mm: unclear. Outcome: locoregional recurrence

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Investigate the relationship between surgical margin distance and locoregional recurrence for women with invasive breast cancer **Study dates** July 1997 to June 2007 **Source of funding** None reported	cancer and those with evidence of distance metastasis **Reported subgroups** All patients invasive cancer with or without DCIS		**Control arm (0 mm):** Closest surgical margin for invasive disease was 0 mm (margins considered: superficial, medial, lateral, inferior, deep, superior)	O-E: -43.85; V: 42.45 **Intervention arm 2 (1 – 2 mm) vs. Control arm (0 mm)** **Locoregional recurrence (mean follow-up 7.9 years):** O-E: -10.64; V: 49.60 **Intervention arm 3 (>2 mm) vs. Intervention arm 2 (1 - 2 mm)** **Locoregional recurrence (mean follow-up 7.9 years):** O-E: -1.05; V: 2.39	rather than local recurrence: unclear **Limitations** Central histopathology was not performed and data were extracted from reports prepared by multiple histopathologists from several different laboratories. This meant our study lacked standardised histopathology reporting, and consequently precise measurements for each margin distance were not always available for every patient. Therefore, some margin distances were determined based on size of the tumour, distance of the specified margins and macroscopic dimensions of the specimen **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Intervention arm 3 (>2 mm) vs. Intervention arm 1 (>0 - <1 mm) **Locoregional recurrence (mean follow-up 7.9 years):** O-E: -6.05; V: 4.11 **Intervention arm 3 (>2 mm) vs. Control arm (0 mm)** **Locoregional recurrence (mean follow-up 7.9 years):** O-E: -1.05; V: 1.61	
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Selection**
Dick, A. W., Sorbero, M. S., Ahrendt, G. M., Hayman, J.	994 - only interested in those that had breast-conserving		**Intervention arm (>2 mm):** no further details	**Local recurrence**	Method of selection appropriate and likely to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
A., Gold, H. T., Schiffhauer, L., Stark, A., Griggs, J. J., Comparative effectiveness of ductal carcinoma in situ management and the roles of margins and surgeons, Journal of the National Cancer Institute, 103, 92-104, 2011 **Ref Id** 578868 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To investigate the following: 1) the comparative effectiveness of the treatment strategies in the management of DCIS; 2) the factors associated with unfavourable outcomes; 3) the role of margin status as an intermediate outcome; and 4) the role of the treating surgeon in treatment, margin status, and outcomes.	surgery as opposed to mastectomy (N=611) **Characteristics** Gender: 100% women Age: Mean/Range NR; 58% aged between 40 and 64 Ethnicity: 79% Caucasian; 15% Black; 1% Asian **Inclusion criteria** Women diagnosed with DCIS between the years 1985 and 2000 **Exclusion criteria** Patients with a history of cancer before the study period were excluded, as were those with microinvasive disease, Padget's disease or lobular cancer; also excluded patients for whom records could not be found or matched with census data **Reported subgroups**	**Intervention arm:** negative (>2 mm) margin **Control arm:** positive (0 mm) margin	**Control arm (0 mm):** no further details	**(median follow-up 5 years):** O-E: -3.44; V: 2.18	produce representative cohort. Local recurrence not present at start of study **Comparability** Unclear - not reported whether different margin groups had equivalent characteristics **Outcome** Follow-up was adequate but unclear how outcome was assessed **Indirectness** None **Limitations** Data did not include detailed pathological characteristics of margins (i.e., extent of margin involvement or location of involved margins) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Diagnosed between 1985 and 2000 **Source of funding** National Cancer Institute at the National Institutes of Health (R01 CA922444-01A1)	All patients DCIS - not reported separately based on radiotherapy				
Full citation Kreike, B., Hart, A. A., van de Velde, T., Borger, J., Peterse, H., Rutgers, E., Bartelink, H., van de Vijver, M. J., Continuing risk of ipsilateral breast relapse after breast-conserving therapy at long-term follow-up, International Journal of Radiation Oncology, Biology, Physics, 71, 1014-21, 2008 **Ref Id** 579518 **Country/ies where the study was carried out** Netherlands **Study type**	**Sample size** 1026 (2 excluded due to missing unique patient identity) **Characteristics** Gender: NR Age: Mean 50; Range 22-85 Etnicity: NR **Inclusion criteria** Received radiotherapy between 1979 and 1988 at The Netherlands Cancer Institute as a part of breast-conserving therapy for early invasive breast cancer. All primary tumours were ≤5 cm in clinical diameter without clinical or radiologic signs of multifocal disease.	**Interventions** **Intervention arm:** doubtful tumour-free margin - <1 mm **Control arm:** involved margin - primary tumour lesion extended into the surgical margin	**Details** **Intervention arm (>0 - <1 mm):** The margin status was scored irrespective of the involvement of the margin by an in situ component. **Control arm (0 mm):** The margin status was scored irrespective of the involvement of the margin by an in situ component. One pathologist reviewed all available breast tumour specimens for the pathologic characteristics	**Results** **Local recurrence (median follow-up 13.3 years):** O-E: -4.34; V: 10.27	**Selection** Method of selection appropriate and likely to produce representative cohort. Local recurrence not present at start of study **Comparability** Unclear - not reported whether different margin groups had equivalent characteristics **Outcome** Assessment of outcomes and follow-up were adequate **Indirectness** None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Retrospective cohort study **Aim of the study** Not clearly stated - to determine risk factors for ipsilateral breast cancer relapse **Study dates** Received radiotherapy as part of breast-conserving therapy between 1979 and 1988 **Source of funding** Dutch Cancer Society (Grant NKB2002-2575)	Treatment consisted of local excision and axillary lymph node dissection followed by whole breast radiotherapy **Exclusion criteria** No additional criteria reported **Reported subgroups** All patients invasive breast cancer with post-operative radiotherapy				**Limitations** **Other information**
Full citation MacDonald, H. R., Silverstein, M. J., Mabry, H., Moorthy, B., Ye, W., Epstein, M. S., Holmes, D., Silberman, H., Lagios, M., Local control in ductal carcinoma in situ treated by excision alone: Incremental benefit of larger margins, American journal of surgery, 190, 521-525, 2005 **Ref Id**	**Sample size** 445 **Characteristics** Gender: NR Age: NR Ethnicity: NR **Inclusion criteria**	**Interventions** **Intervention arm 1:** 0.1 - 0.9 mm margin **Intervention arm 2:** 1.0 - 1.9 mm margin	**Details** **Intervention arm 1 (>0 - <1 mm):** Margin width was determined by direct measurement or ocular micrometry. The closest single distance between DCIS and an inked margin was between 0.1 mm and 0.9 mm	**Results** **Intervention arm 1 (>0 - <1 mm) vs. Control arm (0 mm)** **Locoregional recurrence (5 year follow-up):** O-E: 4.15; V: 8.39	**Selection** Insufficient information about method of selection so unclear if cohort is representative. Local recurrence not present at start of study. **Comparability** Unclear if groups were comparable or any attempt was made to control for differences.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
579690 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To determine the effect of increasing margin width on local treatment failure **Study dates** Treated with excision between 1972 and 2004 **Source of funding** Not reported	Minimal reporting of criteria: pure DCIS treated with excision alone **Exclusion criteria** No additional criteria reported **Reported subgroups** All patients DCIS without radiotherapy	**Intervention arm 3:** ≥2 mm margin **Control arm:** 0 mm (transected) margin	**Intervention arm 2 (1 - 2 mm):** Margin width was determined by direct measurement or ocular micrometry. The closest single distance between DCIS and an inked margin was between 1.0 mm and 1.9 mm **Intervention arm 3 (>2 mm):** Margin width was determined by direct measurement or ocular micrometry. The closest single distance between DCIS and an inked margin was ≥2 mm (2.0-2.9, 3.0-5.9, 6.0-9.9, and ≥10 mm groups combined) **Control arm (0 mm):** Margin width was determined by direct measurement or ocular micrometry. The tumour transected the inked margin	**Intervention arm 2 (1 - 2 mm) vs. Intervention arm 1 (>0 - <1 mm)** **Locoregional recurrence (5 year follow-up):** O-E: -0.25; V: 4.97 **Intervention arm 2 (1 - 2 mm) vs. Control arm (0 mm)** **Locoregional recurrence (5 year follow-up):** O-E: -2.53; V: 4.64 **Intervention arm 3 (>2 mm) vs.**	**Outcome** Follow-up adequate. Outcome assessment unclear. **Indirectness** None **Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Intervention arm 2 (1 - 2 mm) **Locoregional recurrence (5 year follow-up):** O-E: -3.84; V: 3.13 **Intervention arm 3 (>2 mm) vs. Intervention arm 1 (>0 - <1 mm)** **Locoregional recurrence (5 year follow-up):** O-E: -10.55; V: 8.27 **Intervention arm 3 (>2 mm) vs. Control arm (0 mm)**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Locoregional recurrence (5 year follow-up): O-E: -33.77; V: 19.06	
Full citation Shaikh, T., Li, T., Murphy, C. T., Zaorsky, N. G., Bleicher, R. J., Sigurdson, E. R., Carlson, R., Hayes, S. B., Anderson, P., Importance of Surgical Margin Status in Ductal Carcinoma In Situ, Clinical breast cancer, 16, 312-318, 2016 **Ref Id** 580534 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** To identify the effect of margin status and re-excision on local control in a cohort of	**Sample size** 498 **Characteristics** Gender: 100% women Age: Median 58 years; range 30-91 Ethnicity: NR **Inclusion criteria** Women with DCIS treated at a National Cancer Institute-designated comprehensive cancer center between 1989 and 2014 **Exclusion criteria** Patients were excluded if they had invasive breast cancer, underwent mastectomy, received hypofractionated radiotherapy, had metastatic disease, or were male.	**Interventions** **Intervention arm:** >2 mm between tumour and inked margin **Control arm:** DCIS present at inked margin	**Details** **Intervention arm (>2 mm):** no further details **Control arm (0 mm):** no further details	**Results** **Re-operation rate:** >2 mm 6/11; 0 mm 234/400	**Selection** Method of selection appropriate and likely to produce representative cohort **Comparability** Groups comparable at baseline with exception of radiotherapy dose received (higher proportion received stronger dose in positive margin group) **Outcome** Follow-up and outcome assessment adequate **Indirectness** None **Limitations** Insufficient presentation of results to include local recurrence outcome in

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
patients with DCIS who received adjuvant radiation therapy **Study dates** Treated between 1989 and 2014 **Source of funding** National Cancer Institute, National Institutes of Health (P30 CA006927)	**Reported subgroups** All patients DCIS treated with radiotherapy				meta-analysis. Multiple treating physicians who might have had different techniques and biases, which cannot be controlled for. Furthermore, pathologist interpretation of surgical margins is subjective and interobserver and intraobserver variability is common. **Other information**
Full citation Solin, L. J., Fourquet, A., Vicini, F. A., Taylor, M., Olivotto, I. A., Haffty, B., Strom, E. A., Pierce, L. J., Marks, L. B., Bartelink, H., McNeese, M. D., Jhingran, A., Wai, E., Bijker, N., Campana, F., Hwang, W. T., Long-term outcome after breast-conservation treatment with radiation for mammographically detected ductal carcinoma in situ of the breast, Cancer, 103, 1137-1146, 2005 **Ref Id** 580828	**Sample size** 1003 **Characteristics** Gender: 100% women Age: Median 53 years; range 26-86 Ethnicity: NR **Inclusion criteria** 1) unilateral, mammographically detected TisN0M0 DCIS, 2) no physical examination finding, such as a breast mass or bloody nipple discharge, 3) treatment with breast-conserving surgery followed by definitive whole-	**Interventions** **Intervention arm:** negative (>2 mm or >3 mm) **Control arm:** positive (0 mm) margins	**Details** **Intervention arm (>2 mm):** Determined according to policy at participating institution. 8/10 participating institutions used 2 mm to differentiate between negative margins (>2 mm or ≥2 mm) and close margins (≤2 mm or <2 mm). One institution used 2–3 mm for this differentiation, and 1 institution used 3 mm. **Control arm (0 mm):** tumour identified at inked margin	**Results** **Local recurrence (median follow-up 8.5 years):** O-E: -7.10; V: 5.88	**Selection** Method of selection appropriate and likely to produce representative cohort. Outcomes not present at start of study **Comparability** Differences between groups controlled for in the analysis **Outcome** Follow-up and outcome assessment adequate **Indirectness** None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out USA, Canada, France, Netherlands **Study type** Retrospective cohort study **Aim of the study** To evaluate the long-term outcome for women with mammographically detected DCIS of the breast who underwent breast-conserving surgery followed by definitive breast irradiation **Study dates** Treated between 1973 and 1995 **Source of funding** Breast Cancer Research Foundation	breast irradiation to a dose 4000 centigrays (cGy) **Exclusion criteria** 1) adjuvant systemic chemotherapy or hormonal treatment, 2) Paget disease of the nipple, 3) prior or concurrent invasive or microinvasive carcinoma of the ipsilateral or contralateral breast, 4) prior or concurrent malignancy other than DCIS, except for nonmelanoma skin cancer. **Reported subgroups** All patients DCIS treated with radiotherapy				**Limitations** Lack of a standard definition for margin evaluation and the lack of a central pathology review **Other information**
Full citation Tartter, P. I., Kaplan, J., Bleiweiss, I., Gajdos, C., Kong, A., Ahmed, S., Zapetti,	**Sample size** 296 **Characteristics**	**Interventions** **Intervention arm:** close (<1 mm) margins	**Details** **Intervention arm (>0 - <1 mm):** The pathology reports were reviewed to establish	**Results** **Re-operation rate:** >0 - <1	**Selection** Method of selection appropriate and likely to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
D., Lumpectomy margins, reexcision, and local recurrence of breast cancer, American journal of surgery, 179, 81-85, 2000 **Ref Id** 581138 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** To investigate the relationship between local control and margin status in a group of patients treated with breast conservation **Study dates** Referred 1985 to 1993 **Source of funding** None reported	Gender: NR Age: Mean 56; range 27-95 Ethnicity: NR **Inclusion criteria** Patients treated with surgery and radiation therapy without mastectomy **Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest (93% invasive cancer with radiotherapy)	**Control arm:** positive (0 mm) margins	the status of the resection margins. Close margins represent tumour within 1 mm of the inked margin **Control arm (0 mm):** The pathology reports were reviewed to establish the status of the resection margins. Invasive or noninvasive ductal carcinoma or invasive lobular carcinoma was present at the inked margin	mm 2/21; 0 mm 20/42	produce representative cohort **Comparability** Unclear whether groups were comparable **Outcome** Follow-up and outcome assessment adequate **Indirectness** None **Limitations** **Other information**
Full citation	**Sample size** 2996	**Interventions**	**Details**	**Results** **Whole sample**	**Selection**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Zee, K. J., 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, Annals of surgery, 262, 623-31, 2015 **Ref Id** 581302 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To investigate the relationship between margin width and recurrence **Study dates** Underwent breast-conserving surgery from 1978 to 2010 **Source of funding**	**Characteristics** Gender: 100% women Age: Median 57 years; range 20-92 Ethnicity: NR **Inclusion criteria** Patients undergoing definitive breast-conserving surgery for DCIS **Exclusion criteria** No additional criteria reported **Reported subgroups** DCIS with radiotherapy; DCIS without radiotherapy	**Intervention arm:** margin width >2 mm **Control arm:** tumour on ink (0 mm)	**Intervention arm (>2 mm):** no further details reported (combined >2 -10 mm and >10 mm groups) **Control arm (0 mm):** no further details reported	**Locoregional recurrence (10 year follow-up):** O-E: -11.75; V: 20.26 **DCIS with RT** **Locoregional recurrence (10 year follow-up):** O-E: -0.62; V: 8.58 **DCIS without RT** **Locoregional recurrence (10 year follow-up):** O-E: -9.97; V: 12.14	Method of selection appropriate and likely to produce representative cohort. Local recurrence not present at start of study **Comparability** Potential confounding variables were controlled for in the analysis **Outcome** Follow-up and outcome assessment adequate **Indirectness** Outcome: outcome was any recurrence, however this was ipsilateral in all but one case (distant metastases without local recurrence): not serious **Limitations** Very few women had positive margins - most positive margins were at the dermis or the pectoralis fascia, rather than at a radial margin and cases with positive or close margins generally had very

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
NIH/NCI Cancer Center Support Grant P30 CA008748					limited, focal disease at or near the inked margin. Suggests that these patients with close or positive margins likely had a lower residual disease burden than some other series. This limitation may cause reported recurrence rates for close and positive margins to underestimate recurrence rates for women with a greater volume of disease at or near the margin, as it is known that volume of disease is related to recurrence **Other information**

BCTQAP, breast cancer treatment quality assurance project; cGy, centigray; DCI, ductal carcinoma in situ; NR, not reported; TisN0M0 cancer cells are only growing in the most superficial layer of tissue with no lymph node involvement or distant metastases

Appendix E – Forest plots

Comparison 1. >2 mm surgical margins versus 0 mm surgical margins

Figure 2: Re-operation rate (immediate re-excision)

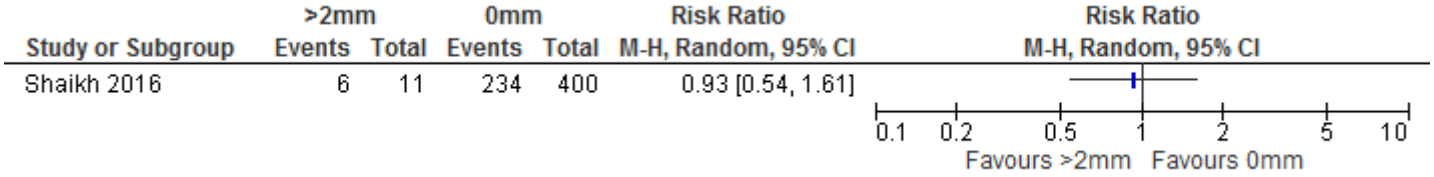
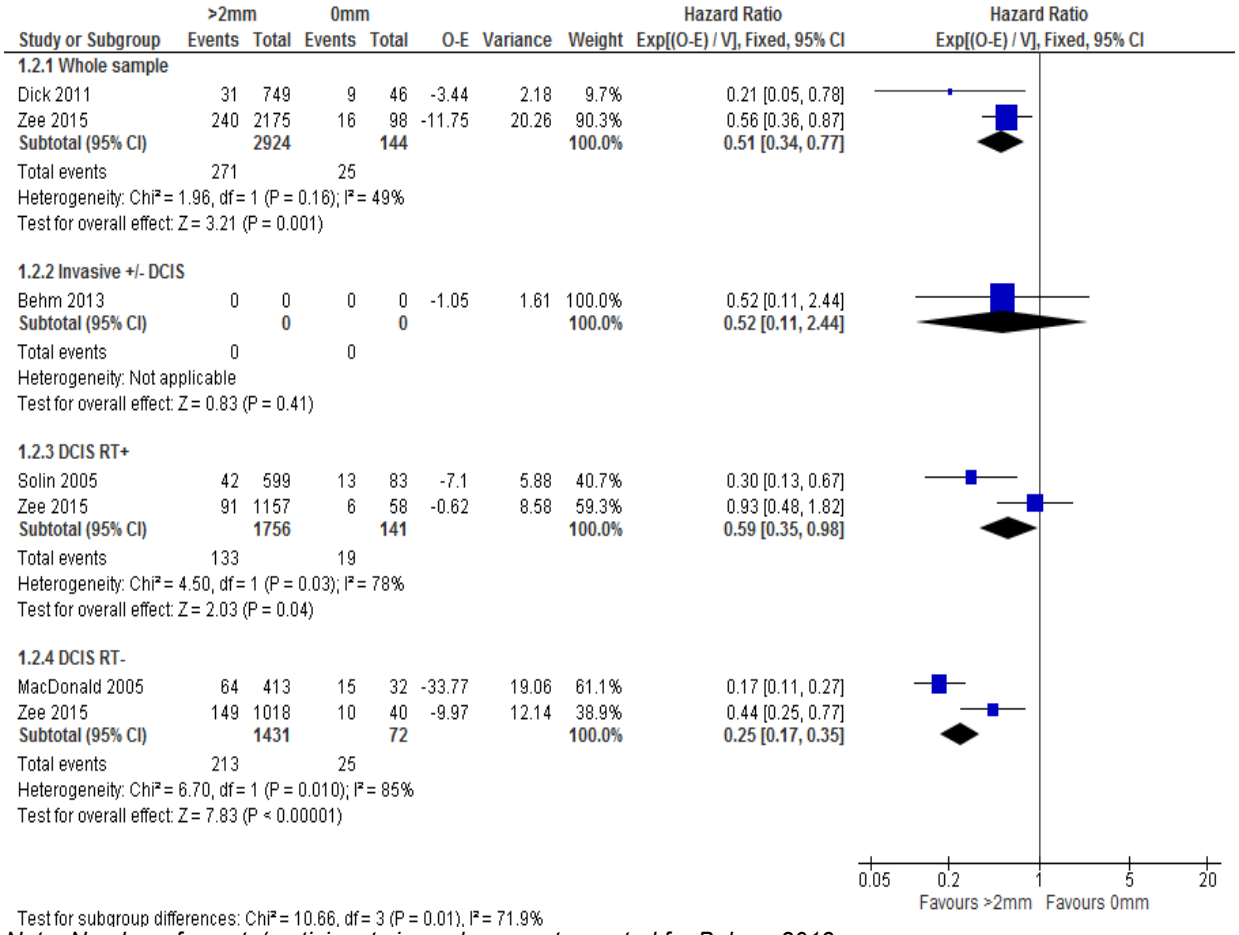


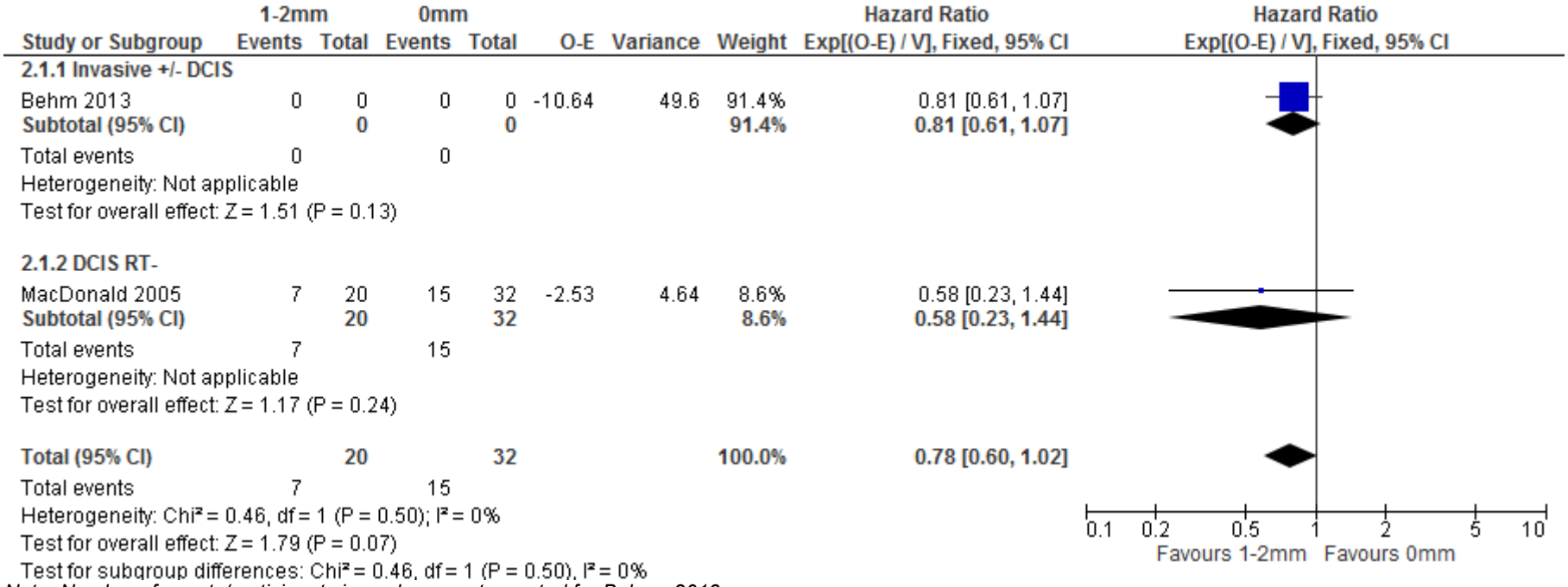
Figure 3: Local recurrence rate at 5 to 10 year follow-up



Note: Number of events/participants in each arm not reported for Behm, 2013

Comparison 2. 1-2 mm surgical margins versus 0 mm surgical margins

Figure 4: Local recurrence rate at 5 year follow-up



Note. Number of events/participants in each arm not reported for Behm, 2013

Comparison 3. >0 to <1 mm surgical margins versus 0 mm surgical margins

Figure 5: Re-operation rate (immediate re-excision)

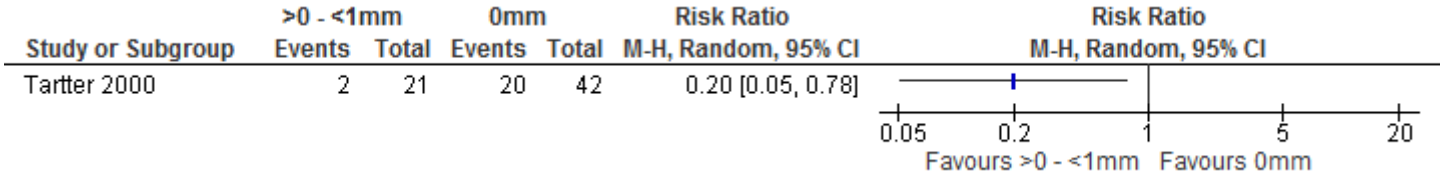
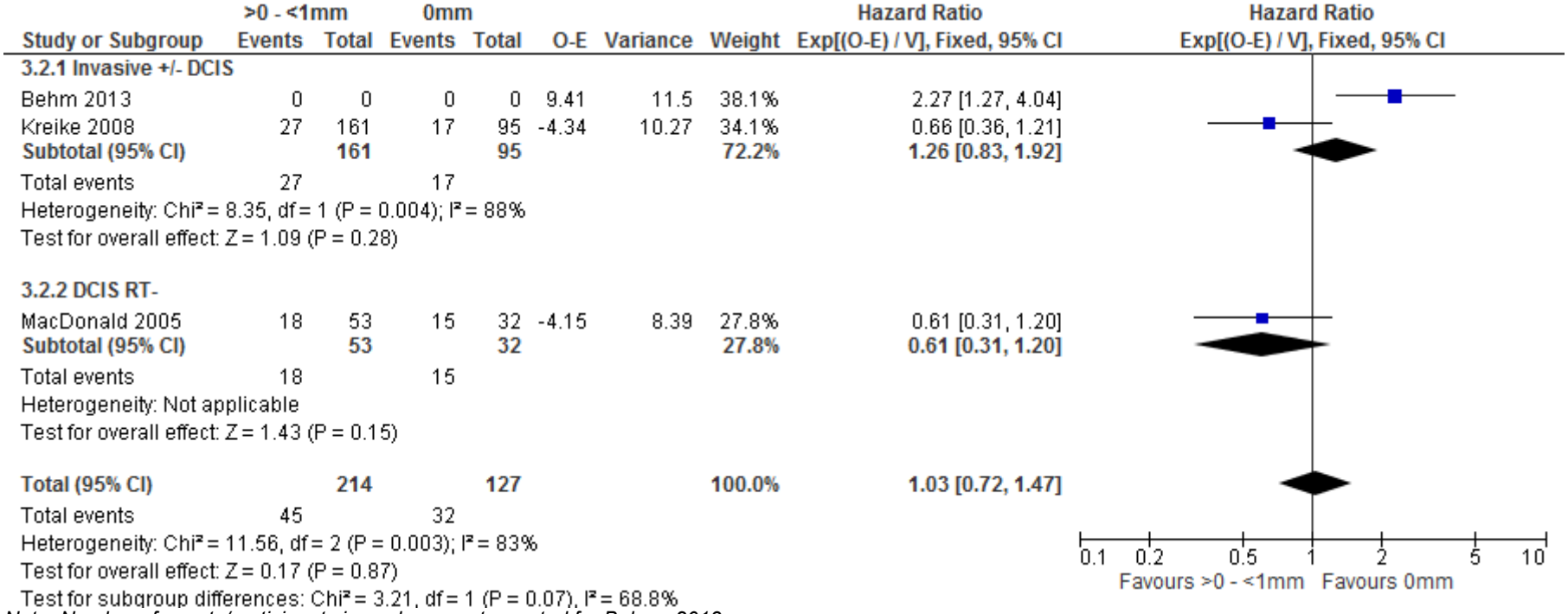


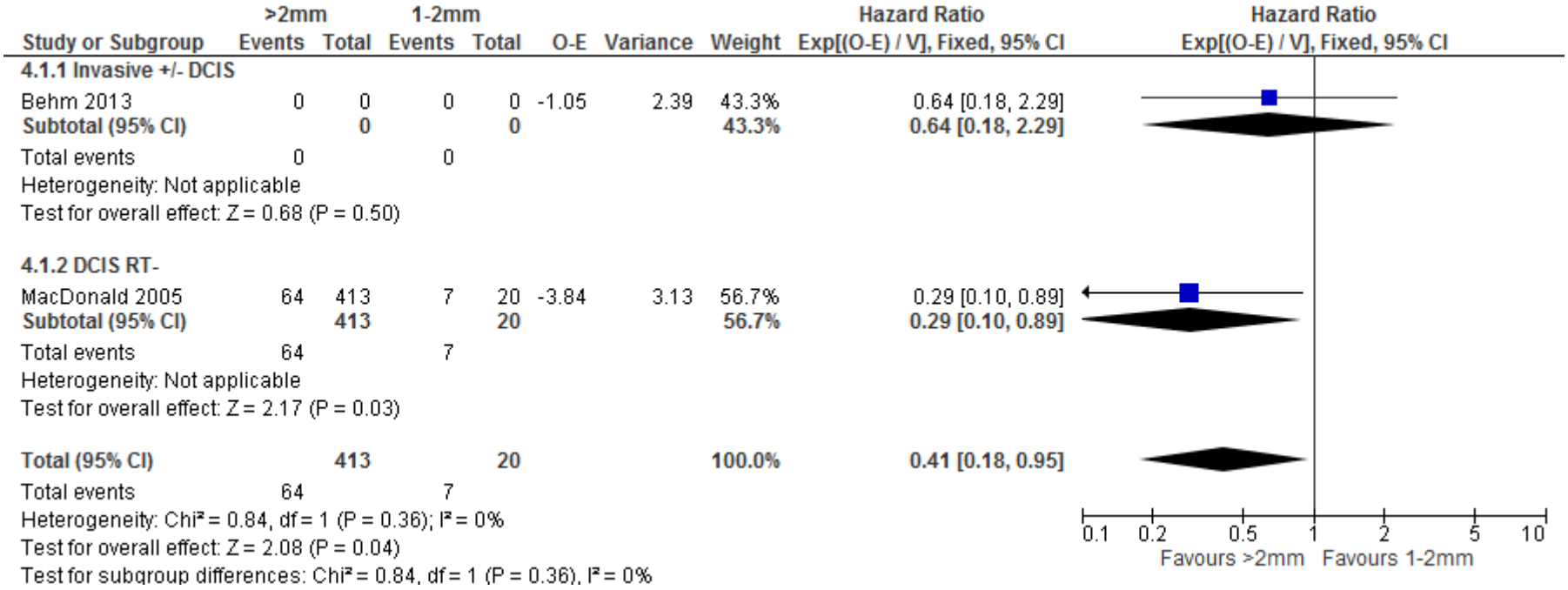
Figure 6: Local recurrence rate at 5 to 13.3 year follow-up



Note. Number of events/participants in each arm not reported for Behm, 2013

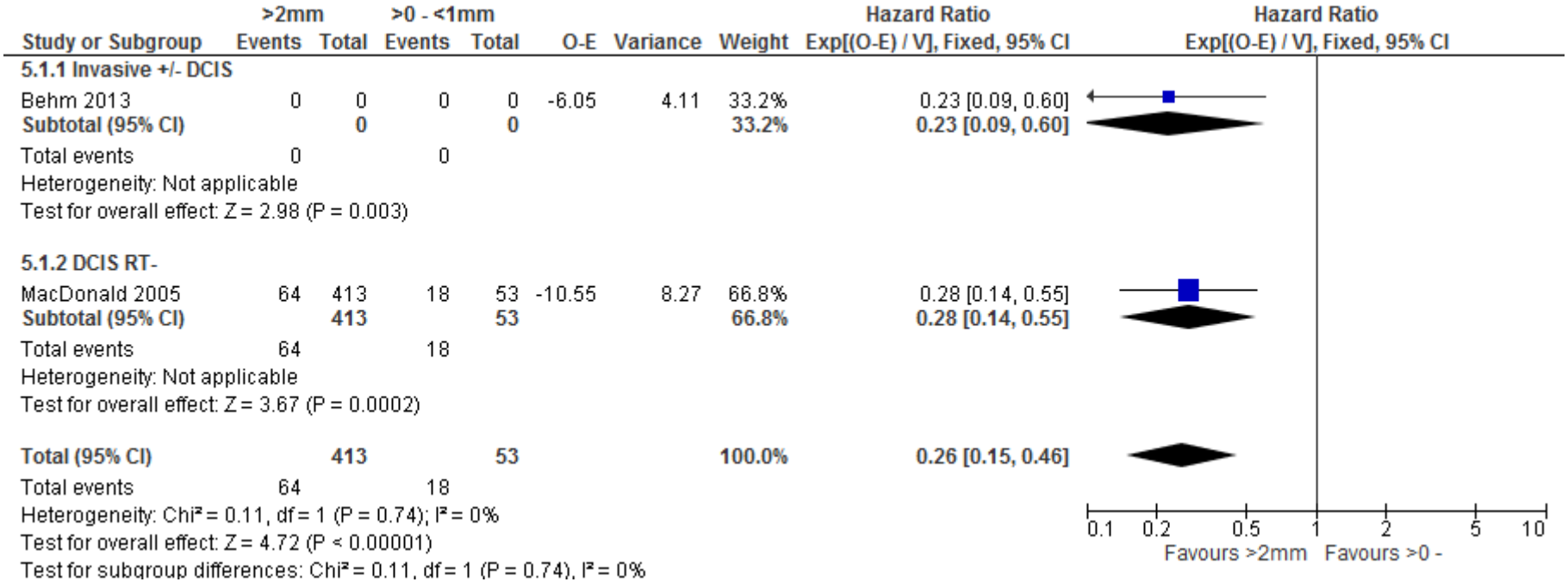
Comparison 4. >2 mm surgical margins versus 1-2 mm surgical margins

Figure 7: Local recurrence



Comparison 5. >2 mm surgical margins versus >0 to <1 mm surgical margins

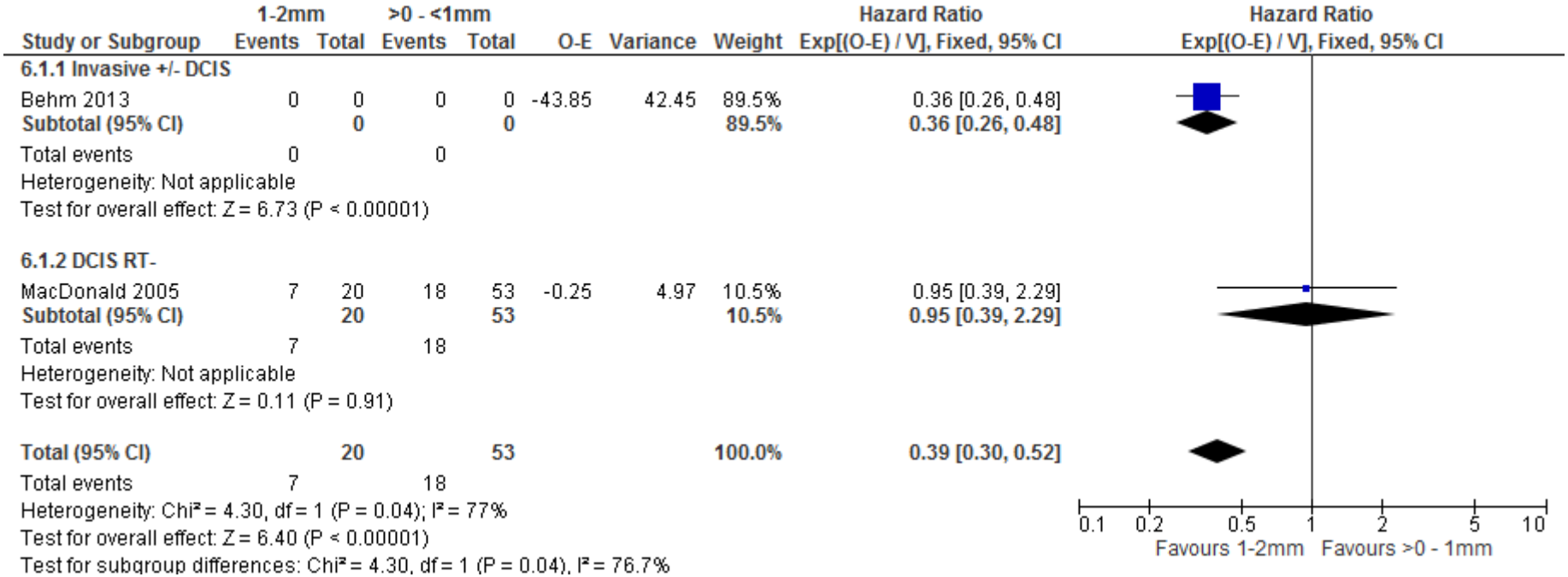
Figure 8: Local recurrence rate at 5 year follow-up



Note. Number of events/participants in each arm not reported for Behm, 2013

Comparison 6. 1-2 mm surgical margins versus >0 - <1 mm surgical margins

Figure 9: Local recurrence rate at 5 year follow-up



Note. Number of events/participants in each arm not reported for Behm, 2013

Appendix F – GRADE tables

Table 10: Clinical evidence profile: Comparison 1: >2 mm surgical margins versus 0 mm surgical margins

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	>2 mm	0 mm	Relative (95% CI)	Absolute	Quality	Importance
Re-operation rate (immediate re-excision)												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	6/11 (54.5%)	234/400 (58.5%)	RR 0.93 (0.54 to 1.61)	41 fewer per 1000 (from 269 fewer to 357 more)	VERY LOW	CRITICAL
Local recurrence - Whole sample (5 to 10 year follow-up)												
2	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	271/2924 (9.3%)	25/144 (17.4%)	HR 0.51 (0.34 to 0.77)	81 fewer per 1000 (from 37 fewer to 111 fewer)	VERY LOW	CRITICAL
Local recurrence - Invasive +/- DCIS (5 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	Serious[4]	Not calculable[5]	None	-	-	HR 0.52 (0.11 to 2.44)	-	number of events was not reported - insufficient information to judge	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**>2 mm**	**0 mm**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
											imprecision, and therefore overall quality	
Local recurrence - DCIS RT+ (8.5 year follow-up)												
2	Observational studies	No serious risk of bias	Serious[6]	No serious indirectness	Serious[2]	None	133/1756 (7.6%)	19/141 (13.5%)	HR 0.59 (0.35 to 0.98)	53 fewer per 1000 (from 3 fewer to 85 fewer)	VERY LOW	CRITICAL
Local recurrence - DCIS RT- (5 to 10 year follow-up)												
2	Observational studies	Serious[3]	Very serious[7]	No serious indirectness	Serious[2]	Strong association[8]	213/1431 (14.9%)	25/72 (34.7%)	HR 0.25 (0.17 to 0.35)	246 fewer per 1000 (from 209 fewer to 277 fewer)	VERY LOW	CRITICAL

DCIS, ductal carcinoma in situ; HR, hazard ratio; RR, Risk ratio; RT, radiotherapy
[1] <100 events and 95% CI crosses both boundaries for no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values
[2] <300 events
[3] Unclear whether method of selection was appropriate and whether different margin groups were comparable
[4] Population: unclear what proportion received radiotherapy
[5] Number of events were not reported - insufficient information to judge imprecision
[6] Significant heterogeneity - I squared value 78% - not possible to further explore heterogeneity as no additional subgroups of interest were identified by the GC. Estimated effects for both studies in same direction
[7] Significant heterogeneity - I squared value 85% - not possible to further explore heterogeneity as no additional subgroups of interest were identified by the GC. Estimated effects for both studies in same direction and exceed threshold for clinically meaningful difference
[8]HR (and 95% CI) <0.5

Table 11: Clinical evidence profile: Comparison 2: 1-2 mm surgical margins versus 0 mm surgical margins

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	>2 mm	0 mm	Relative (95% CI)	Absolute	Quality	Importance
Local recurrence (5 year follow-up)												
2	Observational studies	Serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	7/20 (35%)	15/32 (46.9%)	HR 0.78 (0.6 to 1.02)	79 fewer per 1000 (from 153 fewer to 7 more)	VERY LOW	CRITICAL
Local recurrence - Invasive +/- DCIS (5 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	Serious[2]	[4]	None	-	-	HR 0.81 (0.61 to 1.07)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
Local recurrence - DCIS RT- (5 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	7/20 (35%)	15/32 (46.9%)	HR 0.58 (0.23 to 1.44)	162 fewer per 1000 (from 333 fewer to 129 more)	VERY LOW	CRITICAL

DCIS, ductal carcinoma in situ; HR, hazard ratio; RT, radiotherapy
[1] Unclear whether method of selection was appropriate or whether different margin groups were comparable
[2] Population: unclear what proportion of received radiotherapy for Behm 2013
[3] <300 events
[4] Number of events were not reported - insufficient information to judge imprecision

Table 12: Clinical evidence profile: Comparison 3: >0 - <1 mm surgical margins versus 0 mm surgical margins

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	>2 mm	0 mm	Relative (95% CI)	Absolute	Quality	Importance
Re-operation rate (immediate re-excision)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	2/21 (9.5%)	20/42 (47.6%)	RR 0.2 (0.05 to 0.78)	381 fewer per 1000 (from 105 fewer to 452 fewer)	LOW	CRITICAL
Local recurrence (5 to 13.3 year follow-up)												
3	Observational studies	Serious[3]	Very serious[4]	No serious indirectness	Serious[2]	None	45/214 (21%)	32/127 (25.2%)	HR 1.03 (0.72 to 1.47)	6 more per 1000 (from 63 fewer to 95 more)	VERY LOW	CRITICAL
Local recurrence - Invasive +/- DCIS (5 to 13.3 year follow-up)												
2	Observational studies	Serious[5]	Very serious[6]	Serious[7]	Serious[2]	None	27/161 (16.8%)	17/95 (17.9%)	HR 1.26 (0.83 to 1.92)	41 more per 1000 (from 28 fewer to 136 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**>2 mm**	**0 mm**	**Relative (95% CI)**	**Absolute**		
Local recurrence - DCIS RT- (5 year follow-up)												
1	Observational studies	Serious[8]	No serious inconsistency	No serious indirectness	Serious[2]	None	18/53 (34%)	15/32 (46.9%)	HR 0.61 (0.31 to 1.2)	149 fewer per 1000 (from 291 fewer to 63 more)	VERY LOW	CRITICAL

DCIS, ductal carcinoma in situ; HR, hazard ratio; RR, risk ratio; RT, radiotherapy
[1] Unclear whether different margin groups were comparable
[2] <300 events
[3] Unclear whether different margin groups were comparable and unclear whether method of selection was appropriate for 2 of the 3 studies
[4] Significant heterogeneity - I squared value 83% - heterogeneity explored in subsequent subgroup analysis based on cancer type and treatment
[5] Unclear whether different margin groups were comparable and unclear whether method of selection was appropriate for 1 of the 2 studies
[6] Significant heterogeneity - I squared value 88% - not possible to further explore heterogeneity as no additional subgroups of interest were identified by the GC
[7] Unclear what proportion received radiotherapy for 1 of the 2 studies
[8] Unclear whether different margin groups were comparable and unclear whether method of selection was appropriate

Table 13: Clinical evidence profile: Comparison 4: >2 mm surgical margins versus 1-2 mm surgical margins

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**>2 mm**	**0 mm**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Local recurrence (5 year follow-up)												
2	Observational studies	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	64/413 (15.5%)	7/20 (35%)	HR 0.41 (0.18 to 0.95)	188 fewer per 1000 (from 14 fewer to 275 fewer)	VERY LOW	CRITICAL
Local recurrence - Invasive +/- DCIS (5 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	Serious[2]	[4]	None	-	-	HR 0.64 (0.18 to 2.29)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
Local recurrence - DCIS RT- (5 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	64/413 (15.5%)	7/20 (35%)	HR 0.29 (0.1 to 0.89)	233 fewer per 1000 (from 32 fewer to 308 fewer)	VERY LOW	CRITICAL

DCIS, ductal carcinoma in situ; HR, hazard ratio; RT, radiotherapy

[1] Unclear whether method of selection was appropriate and if different margin groups were comparable

[2] *Unclear what proportion received radiotherapy from Behm 2013*
[3] *<300 events*
[4] *Number of events not reported so cannot determine imprecision*

Table 14: Clinical evidence profile: Comparison 5: >2 mm surgical margins versus >0 - <1 mm surgical margins

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**>2 mm**	**0 mm**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Local recurrence (5 year follow-up)												
2	Observational studies	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	64/413 (15.5%)	18/53 (34%)	HR 0.26 (0.15 to 0.46)	237 fewer per 1000 (from 166 fewer to 279 fewer)	VERY LOW	CRITICAL
Local recurrence - Invasive +/- DCIS (5 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	Serious[2]	[4]	None	-	-	HR 0.23 (0.09 to 0.6)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
Local recurrence - DCIS RT- (5 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	64/413 (15.5%)	18/53 (34%)	HR 0.28 (0.14	230 fewer per 1000	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	>2 mm	0 mm	Relative (95% CI)	Absolute	Quality	Importance
									to 0.55)	(from 136 fewer to 283 fewer)		

DCIS, ductal carcinoma in situ; HR, hazard ratio; RT, radiotherapy
[1] Unclear whether method of selection was appropriate and if groups were comparable
[2] Unclear what proportion received radiotherapy for Behm 2013
[3] <300 events
[4] Number of events not reported so imprecision cannot be determined

Table 15: Clinical evidence profile: Comparison 6: 1-2 mm surgical margins versus >0 - <1 mm surgical margins

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	>2 mm	0 mm	Relative (95% CI)	Absolute	Quality	Importance
Local recurrence (5 year follow-up)												
2	Observational studies	Serious[1]	Serious[2]	Serious[3]	Serious[4]	None	7/20 (35%)	18/53 (34%)	HR 0.39 (0.3 to 0.52)	190 fewer per 1000 (from 146 fewer to 223 fewer)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**>2 mm**	**0 mm**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Local recurrence - Invasive +/- DCIS (5 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	Serious[3]	[5]	None	-	-	HR 0.36 (0.26 to 0.48)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
Local recurrence - DCIS RT- (5 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[4]	None	7/20 (35%)	18/53 (34%)	HR 0.95 (0.39 to 2.29)	11 fewer per 1000 (from 173 fewer to 201 more)	VERY LOW	CRITICAL

DCIS, ductal carcinoma in situ; HR, hazard ratio; RT, radiotherapy
[1] Unclear whether method of selection was appropriate and if groups were comparable
[2] Significant heterogeneity - I squared value 77% - heterogeneity not present in subsequent subgroup analysis based on cancer type and treatment
[3] Unclear what proportion received radiotherapy for Behm 2013
[4] <300 events
[5] Number of events not reported so cannot determine imprecision

Appendix G – Economic evidence study selection

See Supplement 1: Health economics literature review for details of economic study selection.

Appendix H – Economic evidence tables

No economic evidence was identified for this review question.

Appendix I – Health economic evidence profiles

No economic evidence was identified for this review question.

Appendix J – Health economic analysis

No health economic analysis was carried out for this review question.

Appendix K – Excluded studies

Clinical studies

Excluded studies - 1.1 Do tumour-free tissue margins wider than 0 mm reduce local recurrence for people with invasive breast cancer and/or ductal carcinoma in situ (DCIS) treated with breast conserving surgery?	
Study	**Reason for Exclusion**
Abner, A., Positive margins do not obviate breast-conservation surgery, American Family Physician, 47, 1254, 1993	Abstract >2 years old
Adams, B. J., Zoon, C. K., Stevenson, C., Chitnavis, P., Wolfe, L., Bear, H. D., The role of margin status and reexcision in local recurrence following breast conservation surgery, Annals of Surgical Oncology, 20, 2250-2255, 2013	No comparison of different margin widths
Aktas, A., Yeniay, L., Kapkac, M., Yilmaz, R., Prognostic factors affecting ipsilateral tumor recurrence and distant metastasis after breast-conserving surgery, European journal of cancer, 57, S113, 2016	Abstract only - insufficient information
Ang, S. C., Tapia, G., Davidson, E. J., Kahramangil, B., Mak, C., Carmalt, H., Warrier, S., Positive anterior margins in breast conserving surgery: Does it matter? A systematic review of the literature, Breast, 27, 105-108, 2016	Margin width categories inconsistent with protocol/local recurrence not reported
Aristei, C., Leonardi, C., Stracci, F., Palumbo, I., Luini, A., Viale, G., Cristallini, E. G., Cavaliere, A., Orecchia, R., Risk factors for relapse after conservative treatment in T1-T2 breast cancer with one to three positive axillary nodes: results of an observational study, Annals of oncology, 22, 842-7, 2011	Margin status not defined
Barthelmes, L., Al Awa, A., Crawford, D. J., Effect of cavity margin shavings to ensure completeness of excision on local recurrence rates following breast conserving surgery, European journal of surgical oncology, 29, 644-648, 2003	Margin width categories inconsistent with protocol
Besana-Ciani, I., Greenall, M. J., The importance of margins status after breast conservative surgery and radiotherapy in node positive patients: a follow-up of 10-15 years, International Seminars in Surgical Oncology, 5, 13, 2008	Margin width categories inconsistent with protocol
Bijker, N., Peterse, J. L., Duchateau, L., Julien, J. P., Fentiman, I. S., Duval, C., Di Palma, S., Simony-Lafontaine, J., De Mascarel, I., Van de Vijver, M. J., Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-in-situ: Analysis of European Organization for Research and Treatment of Cancer Trial 10853, Journal of Clinical Oncology, 19, 2263-2271, 2001	Margin width categories inconsistent with protocol

Excluded studies - 1.1 Do tumour-free tissue margins wider than 0 mm reduce local recurrence for people with invasive breast cancer and/or ductal carcinoma in situ (DCIS) treated with breast conserving surgery?	
Study	**Reason for Exclusion**
Bodilsen, A., Offersen, B. V., Christiansen, P., Overgaard, J., Pattern of relapse after breast conserving therapy, a study of 1519 early breast cancer patients treated in the Central Region of Denmark 2000-2009, Acta OncologicaActa Oncol, 55, 964-969, 2016	Margin width categories inconsistent with protocol
Bonnier, P., Body, G., Bessenay, F., Charpin, C., Fetissof, F., Beedassy, B., Lejeune, C., Piana, L., Prognostic factors in ductal carcinoma in situ of the breast: results of a retrospective study of 575 cases. The Association for Research in Oncologic Gynecology, European Journal of Obstetrics, Gynecology, & Reproductive Biology, 84, 27-35, 1999	Margin width categories inconsistent with protocol
Bosma, S. C. J., Van Der Leij, F., Van Werkhoven, E., Bartelink, H., Wesseling, J., Linn, S., Rutgers, E. J., Van De Vijver, M. J., Elkhuizen, P. H. M., Very low local recurrence rates after breast-conserving therapy: Analysis of 8485 patients treated over a 28-year period, Breast cancer research and treatment, 156, 391-400, 2016	Margin width categories inconsistent with protocol
Boyages, J., Delaney, G., Taylor, R., Predictors of local recurrence after treatment of ductal carcinoma in situ: A meta-analysis, Cancer, 85, 616-628, 1999	Contains studies that do not compare margin widths - no new studies identified
Braunstein, L. Z., Brock, J. E., Chen, Y. H., Truong, L., Russo, A. L., Arvold, N. D., Harris, J. R., Invasive lobular carcinoma of the breast: local recurrence after breast-conserving therapy by subtype approximation and surgical margin, Breast cancer research and treatment, 149, 555-564, 2015	Margin width categories inconsistent with protocol
Butler-Henderson, K., Lee, A. H., Lenzo, N. P., Price, R. I., Epidemiology of ductal carcinoma in situ in Western Australia: implications for surgical margins and management, Breast Cancer, 22, 641-647, 2015	No comparison of different margin widths
Cabioglu, N., Hunt, K. K., Buchholz, T. A., Mirza, N., Singletary, S. E., Kuerer, H. M., Babiera, G. V., Ames, F. C., Sahin, A. A., Meric-Bernstam, F., Improving local control with breast-conserving therapy: A 27-year single-institution experience, Cancer, 104, 20-29, 2005	Margin width categories not defined/inconsistent with protocol
Carter, D., Margins of 'lumpectomy' for breast cancer, Human Pathology, 17, 330-332, 1986	Commentary/narrative review
Cefaro,G.A., Genovesi,D., Marchese,R., Ursini,L.A., Cianchetti,E., Ballone,E., Nicola,M.D., Predictors of local recurrence after conservative surgery and whole-breast irradiation, Breast Cancer Research and Treatment, 98, 329-335, 2006	Margin status not defined
Chuwa, E. W. L., Tan, V. H. S., 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 Journal of Surgery, 78, 42-48, 2008	Margin width categories inconsistent with protocol
Cutuli, B., Cohen-Solal-le Nir, C., De Lafontan, B., Mignotte, H., Fichet, V., Fay, R., Servent, V., Giard, S., Charra-Brunaud, C., Lemanski, C., Auvray, H., Jacquot, S., Charpentier, J. C., Breast-conserving therapy for	Margin status not defined

Excluded studies - 1.1 Do tumour-free tissue margins wider than 0 mm reduce local recurrence for people with invasive breast cancer and/or ductal carcinoma in situ (DCIS) treated with breast conserving surgery?	
Study	**Reason for Exclusion**
ductal carcinoma in situ of the breast: The French Cancer Centers' experience, International Journal of Radiation Oncology Biology Physics, 53, 868-879, 2002	
Demirci, S., Broadwater, G., Marks, L. B., Clough, R., Prosnitz, L. R., Breast conservation therapy: The influence of molecular subtype and margins, International Journal of Radiation Oncology Biology Physics, 83, 814-820, 2012	Insufficient presentation of results for analysis
DiBiase, S. J., Komarnicky, L. T., Schwartz, G. F., Xie, Y., Mansfield, C. M., The number of positive margins influences the outcome of women treated with breast preservation for early stage breast carcinoma, Cancer, 82, 2212-2220, 1998	Margin status categories inconsistent with protocol
Dixon, J. M., Thomas, J., Kerr, G. R., Williams, L. J., Dodds, C., Kunkler, I. H., Macaskill, E. J., A study of margin width and local recurrence in breast conserving therapy for invasive breast cancer, European journal of surgical oncology, 42, 657-664, 2016	Margin width categories inconsistent with protocol
Dunne, C., Burke, J. P., Morrow, M., Kell, M. R., Effect of margin status on local recurrence after breast conservation and radiation therapy for ductal carcinoma in situ, Journal of Clinical Oncology, 27, 1615-20, 2009	Contains studies with insufficient follow-up and/or sample size - no new studies identified
Fowble, B., The significant of resection margin status in patients with early-stage invasive cancer treated with breast-conservation therapy, Breast Journal, 4, 126-131, 1998	Overview
Fowble, B., Hanlon, A. L., Fein, D. A., Hoffman, J. P., Sigurdson, E. R., Patchefsky, A., Kessler, H., Results of conservative surgery and radiation for mammographically detected ductal carcinoma in situ (DCIS), International Journal of Radiation Oncology Biology Physics, 38, 949-957, 1997	Insufficient presentation of results
Freedman, G., Fowble, B., Hanlon, A., Nicolaou, N., Fein, D., Hoffman, J., Sigurdson, E., Boraas, M., Goldstein, L., Patients with early stage invasive cancer with close or positive margins treated with conservative surgery and radiation have an increased risk of breast recurrence that is delayed by adjuvant systemic therapy, International Journal of Radiation Oncology Biology Physics, 44, 1005-1015, 1999	Insufficient presentation of results
Freedman,G.M., Anderson,P.R., Li,T., Nicolaou,N., Locoregional recurrence of triple-negative breast cancer after breast-conserving surgery and radiation, Cancer, 115, 946-951, 2009	No comparison between margin widths
Freyvogel, M., O'Rourke, C., Valente, S., Fanning, A., Dietz, J., A comparison of treatment outcomes for patients with close or positive DCIS margins after mastectomy for early stage breast cancer, Annals of Surgical Oncology, 1), S72, 2015	Abstract only - insufficient information

Excluded studies - 1.1 Do tumour-free tissue margins wider than 0 mm reduce local recurrence for people with invasive breast cancer and/or ductal carcinoma in situ (DCIS) treated with breast conserving surgery?	
Study	**Reason for Exclusion**
Gage, I., Schnitt, S. J., Nixon, A. J., Silver, B., Recht, A., Troyan, S. L., Eberlein, T., Love, S. M., Gelman, R., Harris, J. R., Connolly, J. L., Pathologic margin involvement and the risk of recurrence in patients treated with breast-conserving therapy, Cancer, 78, 1921-1928, 1996	Insufficient presentation of results
Garvey, E. M., Senior, D. A., Pockaj, B. A., Wasif, N., Dueck, A. C., McCullough, A. E., Ocal, I. T., Gray, R. J., Rates of residual disease with close but negative margins in breast cancer surgery, Breast, 24, 413-417, 2015	No comparison of margin width for local recurrence
Gojkovic Horvat, A., Gugic, J., Ratosa, I., Majdic, E., Marinko, T., Paulin Kosir, S. M., Jugovec, V., Korosec, P., Demsar, A., Grasic Kuhar, C., Local recurrence after breast conserving surgery for ductal carcinoma in situ, Breast, 24, S130, 2015	Conference poster - insufficient presentation of results
Guinot, J. L., Tortajada, M. I., Santos, M. A., Torres, A., Moreno, A., Fernandez, J., Santamaria, P., Domingo, C., Arribas, L., Long-term outcome with HDR brachytherapy boost to preserve the breast when margins are close or involved, Brachytherapy, 15, S47, 2016	Abstract only - insufficient information
Houssami, N., Macaskill, P., Luke Marinovich, M., 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, Annals of Surgical Oncology, 21, 717-730, 2014	Contains studies with insufficient follow-up - no new studies identified
Houssami, N., Macaskill, P., Marinovich, M. L., Dixon, J. M., Irwig, L., Brennan, M. E., Solin, L. J., Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy, European journal of cancer, 46, 3219-32, 2010	Contains studies inconsistent with protocol - no new studies identified
Hunt, K. K., Sahin, A. A., Too much, too little, or just right? Tumor margins in women undergoing breast-conserving surgery, Journal of Clinical Oncology, 32, 1401-1406, 2014	Case study
Jobsen, J. J., Riemersma, S., van der Palen, J., Ong, F., Jonkman, A., Struikmans, H., The impact of margin status in breast-conserving therapy for lobular carcinoma is age related, European journal of surgical oncology, 36, 176-181, 2010	Margin width categories inconsistent with protocol
Jobsen, J. J., Van Der Palen, J., Ong, F., Meerwaldt, J. H., Differences in outcome for positive margins in a large cohort of breast cancer patients treated with breast-conserving therapy, Acta Oncologica, 46, 172-180, 2007	Margin width categories inconsistent with protocol
Jobsen, J. J., Van Der Palen, J., Ong, F., Meerwaldt, J. H., The value of a positive margin for invasive carcinoma in breast-conservative treatment in relation to local recurrence is limited to young women only, International Journal of Radiation Oncology Biology Physics, 57, 724-731, 2003	Margin width categories inconsistent with protocol

Excluded studies - 1.1 Do tumour-free tissue margins wider than 0 mm reduce local recurrence for people with invasive breast cancer and/or ductal carcinoma in situ (DCIS) treated with breast conserving surgery?	
Study	**Reason for Exclusion**
Johnson, A. T., Henry-Tillman, R., Suzanne Klimberg, V., Breast conserving surgery: Optimizing local control in the breast with the assessment of margins, Breast Disease, 12, 35-41, 2001	Book chapter
Kestin, L. L., Goldstein, N. S., Lacerna, M. D., Balasubramaniam, M., Martinez, A. A., Rebner, M., Pettinga, J., Frazier, R. C., Vicini, F. A., Factors associated with local recurrence of mammographically detected ductal carcinoma in situ in patients given breast-conserving therapy, Cancer, 88, 596-607, 2000	Insufficient presentation of results
Kim, J. Y., Park, K., Kang, G., Kim, H. J., Gwak, G., Shin, Y. J., Predictors of recurrent ductal carcinoma in situ after breast-conserving surgery, Journal of Breast Cancer, 19, 185-190, 2016	Margin width categories inconsistent with protocol
Kini, V. R., Vicini, F. A., Frazier, R., Victor, S. J., Wimbish, K., Martinez, A. A., Mammographic, pathologic, and treatment-related factors associated with local recurrence in patients with early-stage breast cancer treated with breast conserving therapy, International Journal of Radiation Oncology Biology Physics, 43, 341-346, 1999	Insufficient presentation of results
Kitchen, P. R. B., Cawson, J. N., Moore, S. E., Hill, P. A., Barbetti, T. M., Wilkins, P. A., Power, A. M., Henderson, M. A., Margins and outcome of screen-detected breast cancer with extensive in situ component, ANZ Journal of Surgery, 76, 591-595, 2006	No comparison of margin widths
Kuah, S., Choo, B. A., Chan, M. Y. P., Tan, E. Y., Factors predicting for local recurrence after wide local excision, Annals of the Academy of Medicine Singapore, 45 (9 Supplement 1), S249, 2016	Abstract only - insufficient information
Kurtz, J. M., Jacquemier, J., Amalric, R., Brandone, H., Ayme, Y., Hans, D., Bressac, C., Spitalier, J. M., Why are local recurrences after breast-conserving therapy more frequent in younger patients?, Journal of Clinical Oncology, 8, 591-598, 1990	Insufficient presentation of results
Lamattina, J. C., Guixa, H. G., Wernicke, M., Lorusso, C., Orti, R., Local recurrence after conservative treatment in breast cancer, Breast Disease, 8, 131-139, 1995	Case-control study - insufficient presentation of results
Law, T. T., Kwong, A., Surgical margins in breast conservation therapy: How much should we excise?, Southern Medical Journal, 102, 1234-1237, 2009	Non-systematic review
Lee,J., Lee,S., Bae,Y., Multiple margin positivity of frozen section is an independent risk factor for local recurrence in breast-conserving surgery, Journal of Breast Cancer, 15, 420-426, 2012	Margin width categories inconsistent with protocol
Leong, C., Boyages, J., Jayasinghe, U. W., Bilous, M., Ung, O., Chua, B., Salisbury, E., Wong, A. Y., Effect of Margins on Ipsilateral Breast Tumor Recurrence after Breast Conservation Therapy for Lymph Node-Negative Breast Carcinoma, Cancer, 100, 1823-1832, 2004	Margin width categories inconsistent with protocol

Excluded studies - 1.1 Do tumour-free tissue margins wider than 0 mm reduce local recurrence for people with invasive breast cancer and/or ductal carcinoma in situ (DCIS) treated with breast conserving surgery?	
Study	**Reason for Exclusion**
Livi, L., Paiar, F., Saieva, C., Scoccianti, S., Dicosmo, D., Borghesi, S., Agresti, B., Nosi, F., Orzalesi, L., Santini, R., Barca, R., Biti, G. P., Survival and breast relapse in 3834 patients with T1-T2 breast cancer after conserving surgery and adjuvant treatment, Radiotherapy and oncology, 82, 287-293, 2007	Margin status not defined
Lupe, K., Truong, P. T., Alexander, C., Lesperance, M., Speers, C., Tyldesley, S., Subsets of women with close or positive margins after breast-conserving surgery with high local recurrence risk despite breast plus boost radiotherapy, International Journal of Radiation Oncology Biology Physics, 81, e561-e568, 2011	Insufficient presentation of results
Maishman, T., Cutress, R. I., Hernandez, A., Gerty, S., Copson, E. R., Durcan, L., Eccles, D. M., Local Recurrence and Breast Oncological Surgery in Young Women With Breast Cancer: The POSH Observational Cohort Study, Annals of Surgery., 22, 2016	Over 50% of sample had mastectomy - results not presented separately for mastectomy and breast-conserving therapy
Mamounas, E. P., Dvorak, T., Lumpectomy margins: everything old is new again?, Surgical OncologySurg Oncol, 24, 5-8, 2015	Commentary
Mansfield, C. M., Komarnicky, L. T., Schwartz, G. F., Rosenberg, A. L., Krishnan, L., Jewell, W. R., Rosato, F. E., Moses, M. L., Haghbin, M., Taylor, J., Ten-year results in 1070 patients with stages I and II breast cancer treated by conservative surgery and radiation therapy, Cancer, 75, 2328-2336, 1995	Insufficient presentation of results
Margenthaler, J. A., Suzanne Klimberg, V., Margin status following partial mastectomy: One size does not fit all!, Oncology, 25, 2011	Review of paper
Marinovich, M. L., Azizi, L., Macaskill, P., Irwig, L., Morrow, M., Solin, L. J., Houssami, N., The Association of Surgical Margins and Local Recurrence in Women with Ductal Carcinoma In Situ Treated with Breast-Conserving Therapy: A Meta-Analysis, Annals of Surgical Oncology, 23, 3811-3821, 2016	Contains studies with insufficient follow-up/margin categories inconsistent with protocol - no new studies identified
Marinovich, M. L., Azizi, L., Macaskill, P., Irwig, L., Morrow, M., Solin, L. J., Houssami, N., The association of surgical margins and local recurrence in women with ductal carcinoma in situ treated with breast conserving therapy: A meta-analysis, Journal of Clinical Oncology, 34, no pagination, 2016	Conference poster - full text already identified
McCloskey, S. A., Botnick, L. E., Rose, C. M., Malcolm, A. W., Ozohan, M. L., Mena, R., Llamas, L., Tao, M. L., Long-term outcomes after breast conservation therapy for early stage breast cancer in a community setting, Breast Journal, 12, 138-144, 2006	Margin status not defined
Me, A., Akbari, M., Zirakzadeh, H., Nafissi, N., Heidari, A., Hosseinizadegan Shirazi, F., Margin Status Influence on the Outcome of Patients Treated with Breast Conserving Surgery, Iranian Journal of Cancer Prevention, 4, 177-82, 2011	Margin width categories inconsistent with protocol

Excluded studies - 1.1 Do tumour-free tissue margins wider than 0 mm reduce local recurrence for people with invasive breast cancer and/or ductal carcinoma in situ (DCIS) treated with breast conserving surgery?	
Study	**Reason for Exclusion**
Medeiros, K., Peddi, P., Zhou, M., Chu, Q., Can radiation therapy adequately address positive surgical margins in elderly women (>70 years) with stage I ER+ breast cancer?, Journal of Clinical Oncology, 34, no pagination, 2016	Conference poster - insufficient information
Meijnen, P., Oldenburg, H. S. A., Peterse, J. L., Bartelink, H., Rutgers, E. J. Th, Clinical outcome after selective treatment of patients diagnosed with ductal carcinoma in situ of the breast, Annals of Surgical Oncology, 15, 235-243, 2008	Margin width categories inconsistent with protocol
Meric, F., Mirza, N. Q., Vlastos, G., Buchholz, T. A., Kuerer, H. M., Babiera, G. V., Singletary, S. E., Ross, M. I., Ames, F. C., Feig, B. W., Krishnamurthy, S., Perkins, G. H., McNeese, M. D., Strom, E. A., Valero, V., Hunt, K. K., Positive surgical margins and ipsilateral breast tumor recurrence predict disease-specific survival after breast-conserving therapy, Cancer, 97, 926-933, 2003	Margin status not defined
Merrill, A. L., Tang, R., Plichta, J. K., Rai, U., Coopey, S. B., McEvoy, M. P., Hughes, K. S., Specht, M. C., Gadd, M. A., Smith, B. L., Should New "No Ink On Tumor" Lumpectomy Margin Guidelines be Applied to Ductal Carcinoma In Situ (DCIS)? A Retrospective Review Using Shaved Cavity Margins, Annals of Surgical Oncology, 23, 3453-3458, 2016	Outcomes outside scope
Morrow, M., Harris, J. R., Schnitt, S. J., Surgical margins in lumpectomy for breast cancer - Bigger is not better, New England journal of medicine, 367, 79-82, 2012	Narrative review
Nakamura, S., Woo, C., Silberman, H., Streeter Jr, O. E., Lewinsky, B. S., Silverstein, M. J., Breast-conserving therapy for ductal carcinoma in situ: A 20-year experience with excision plus radiation therapy, American journal of surgery, 184, 403-409, 2002	Insufficient presentation of results
Neuschatz, A. C., DiPetrillo, T., Safaii, H., Price, L. L., Schmidt-Ullrich, R. K., Wazer, D. E., Long-term follow-up of a prospective policy of margin-directed radiation dose escalation in breast-conserving therapy, Cancer, 97, 30-39, 2003	Insufficient presentations of results/margin width categories inconsistent with protocol
Niwinska, A., Galecki, J., Nagadowska, M., Michalski, W., The analysis of the outcome and the risk factors of failure in early breast cancer patients after breast conserving therapy, Nowotwory, 55, 122-129, 2005	Insufficient presentation of results
Noguchi, S., Koyama, H., Kasugai, T., Tsukuma, H., Tsuji, N., Tsuda, H., Akiyama, F., Motomura, K., Inaji, H., A case-control study on risk factors for local recurrences or distant metastases in breast cancer patients treated with breast-conserving surgery, Oncology, 54, 468-474, 1997	Margin width categories inconsistent with protocol

Excluded studies - 1.1 Do tumour-free tissue margins wider than 0 mm reduce local recurrence for people with invasive breast cancer and/or ductal carcinoma in situ (DCIS) treated with breast conserving surgery?	
Study	**Reason for Exclusion**
Obedian, E., Haffty, B. G., Negative margin status improves local control in conservatively managed breast cancer patients, Cancer Journal from Scientific American, 6, 28-33, 2000	Insufficient presentation of results
Ohsumi, S., Sakamoto, G., Takashima, S., Koyama, H., Shin, E., Suemasu, K., Nishi, T., Nakamura, S., Iino, Y., Iwase, T., Ikeda, T., Teramoto, S., Fukutomi, T., Komaki, K., Sano, M., Sugiyama, K., Miyoshi, K., Kamio, T., Ogita, M., Long-term results of breast-conserving treatment for early-stage breast cancer in Japanese women from multicenter investigation, Japanese Journal of Clinical Oncology, 33, 61-67, 2003	Margin status not defined
Oouchi, A., Sakata, K., Masuoka, H., Tamakawa, M., Nagakura, H., Someya, M., Nakata, K., Asaishi, K., Okazaki, M., Okazaki, Y., Ohmura, T., Hareyama, M., Hori, M., Shimokawara, I., Okazaki, A., Watanabe, Y., Yamada, T., Yuyama, T., Satoh, T., Hirata, K., The treatment outcome of patients undergoing breast-conserving therapy: the clinical role of postoperative radiotherapy, Breast Cancer, 16, 49-57, 2009	Margin width categories inconsistent with protocol
Park, C. C., Mitsumori, M., Nixon, A., Recht, A., Connolly, J., Gelman, R., Silver, B., Hetelekidis, S., Abner, A., Harris, J. R., Schnitt, S. J., Outcome at 8 years after breast-conserving surgery and radiation therapy for invasive breast cancer: Influence of margin status and systemic therapy on local recurrence, Journal of Clinical Oncology, 18, 1668-1675, 2000	Insufficient presentation of results
Park, S., Ahn, S. D., The effect of escalating boost dose in breast cancer patients with involved resection margin, Radiotherapy and oncology, 119, S557, 2016	Abstract only - insufficient information
Park, S., Park, H. S., Kim, S. I., Koo, J. S., Park, B. W., Lee, K. S., The impact of a focally positive resection margin on the local control in patients treated with breast-conserving therapy, Japanese Journal of Clinical Oncology, 41, 600-608, 2011	Margin width categories inconsistent with protocol
Perez, C. A., Breast conservation therapy in patients with stage T1-T2 breast cancer: current challenges and opportunities, American Journal of Clinical Oncology, 33, 500-10, 2010	Margin width categories inconsistent with protocol
Perez, C. A., Conservation therapy in T1-T2 breast cancer: past, current issues, and future challenges and opportunities, Cancer journal (Sudbury, Mass.), 9, 442-453, 2003	Margin width categories inconsistent with protocol
Peterson, M. E., Schultz, D. J., Reynolds, C., Solin, L. J., Outcomes in breast cancer patients relative to margin status after treatment with breast-conserving surgery and radiation therapy: The University of Pennsylvania experience, International Journal of Radiation Oncology Biology Physics, 43, 1029-1035, 1999	Insufficient presentation of results

Excluded studies - 1.1 Do tumour-free tissue margins wider than 0 mm reduce local recurrence for people with invasive breast cancer and/or ductal carcinoma in situ (DCIS) treated with breast conserving surgery?	
Study	**Reason for Exclusion**
Pezner, R. D., Wagman, L. D., Ben-Ezra, J., Odom-Maryon, T., Breast conservation therapy: Local tumor control in patients with pathologically clear margins who receive 5000 cGy breast irradiation without local boost, Breast cancer research and treatment, 32, 261-267, 1994	Margin width categories inconsistent with protocol
Rauschecker, H. F., Sauerbrei, W., Gatzemeier, W., Sauer, R., Schauer, A., Schmoor, C., Schumacher, M., Eight-year results of a prospective non-randomised study on therapy of small breast cancer, European journal of cancer, 34, 315-323, 1998	Margin width categories inconsistent with protocol
Russo, A. L., Arvold, N. D., Niemierko, A., Wong, N., Wong, J. S., Bellon, J. R., Punglia, R. S., Golshan, M., Troyan, S. L., Brock, J. E., Harris, J. R., Margin status and the risk of local recurrence in patients with early-stage breast cancer treated with breast-conserving therapy, Breast cancer research and treatment, 140, 353-361, 2013	Margin width categories inconsistent with protocol
Sagara, Y., Barry, W. T., Vaz-Luis, I., Aydogan, F., Brock, J. E., Winer, E. P., Golshan, M., Metzger-Filho, O., Effect of margin width on local recurrence in invasive lobular carcinoma treated with multimodality therapy, Cancer Research. Conference: 37th Annual CTRC AACR San Antonio Breast Cancer Symposium. San Antonio, TX United States. Conference Start, 75, 2015	Abstract only - insufficient information
Sahoo, S., Recant, W. M., Jaskowiak, N., Tong, L., Heimann, R., Defining negative margins in DCIS patients treated with breast conservation therapy: The University of Chicago experience, Breast Journal, 11, 242-247, 2005	Insufficient presentation of results
Santiago, R. J., Wu, L., Harris, E., Fox, K., Schultz, D., Glick, J., Solin, L. J., Fifteen-year results of breast-conserving surgery and definitive irradiation for Stage I and II breast carcinoma: The University of Pennsylvania experience, International Journal of Radiation Oncology Biology Physics, 58, 233-240, 2004	Insufficient presentation of results
Scepanovic, D., Lukacovicova, M., Hurakova, A., Pobijakova, M., The influence of surgical margins on local control after breast conserving surgery and postoperative radiotherapy, Radiotherapy and Oncology, 96, S248-S249, 2010	Conference abstract >2 years old
Schnitt, S. J., Abner, A., Gelman, R., Connolly, J. L., Recht, A., Duda, R. B., Eberlein, T. J., Mayzel, K., Silver, B., Harris, J. R., The relationship between microscopic margins of resection and the risk of local recurrence in patients with breast cancer treated with breast- conserving surgery and radiation therapy, Cancer, 74, 1746-1751, 1994	Insufficient presentation of results
Schouten van der Velden, A. P., van Vugt, R., Van Dijck, J. A. A. M., Leer, J. W. H., Wobbes, T., Local Recurrences After Different Treatment Strategies for Ductal Carcinoma In Situ of the Breast: A Population-	Insufficient presentation of results

Excluded studies - 1.1 Do tumour-free tissue margins wider than 0 mm reduce local recurrence for people with invasive breast cancer and/or ductal carcinoma in situ (DCIS) treated with breast conserving surgery?	
Study	**Reason for Exclusion**
Based Study in the East Netherlands, International Journal of Radiation Oncology Biology Physics, 69, 703-710, 2007	
Schuck, A., Konemann, S., Heinen, K., Rube, C. E., Hesselmann, S., Reinartz, G., Schuller, P., Micke, O., Schafer, U., Willich, N., Microscopic residual disease is a risk factor in the primary treatment of breast cancer, Strahlentherapie und Onkologie, 178, 307-313, 2002	Margin status not defined
Shah, C., Wilkinson, J. B., Keisch, M., Beitsch, P., Arthur, D., Lyden, M., Vicini, F. A., Impact of margin status on outcomes following accelerated partial breast irradiation using single-lumen balloon-based brachytherapy, Brachytherapy, 12, 91-98, 2013	Insufficient presentation of results
Shin, E., Takatsuka, Y., Okamura, Y., Fukuda, K., Mishima, H., Tono, T., Yagyu, T., Kobayashi, K., Kikkawa, N., Takeda, M., Kurata, A., Otani, M., Strategy for breast conserving treatment--analysis of recurrence and prognosis after breast cosnserving treatment, Gan to kagaku ryoho, Cancer & chemotherapy. 23 Suppl 1, 92-99, 1996	Non-English language
Shin, E., Takatsuka, Y., Okamura, Y., Kobayashi, T., Nishisho, I., Kikkawa, N., Kawahara, K., Kurata, A., Otani, M., Takeda, M., Risk factors for local recurrence after breast-conserving therapy, International Journal of Clinical Oncology, 4, 230-235, 1999	Margin status not defined
Shoker, B., Margin width influencing local recurrence in ductal carcinoma in situ, Breast Cancer Research, 1 (1) (no pagination), 1999	Margin width categories inconsistent with protocol
Smith, S. L., Truong, P. T., Lu, L., Lesperance, M., Olivotto, I. A., Identification of patients at very low risk of local recurrence after breast-conserving surgery, International Journal of Radiation Oncology Biology Physics, 89, 556-562, 2014	Insufficient presentation of results
Smitt, M. C., Nowels, K. W., Zdeblick, M. J., Jeffrey, S., Carlson, R. W., Stockdale, F. E., Goffinet, D. R., The importance of the lumpectomy surgical margin status in long term results of breast conservation, Cancer, 76, 259-267, 1995	Insufficient presentation of results
Smitt, M. C., Nowels, K., Carlson, R. W., Jeffrey, S. S., Predictors of reexcision findings and recurrence after breast conservation, International Journal of Radiation Oncology Biology Physics, 57, 979-985, 2003	Insufficient presentation of results
Solin, L. J., Fourquet, A., Vicini, F. A., Haffty, B., Taylor, M., McCormick, B., McNeese, M., Pierce, L. J., Landmann, C., Olivotto, I. A., Borger, J., Kim, J. S., De la Rochefordiere, A., Schultz, D. J., Mammographically detected ductal carcinoma in situ of the breast treated with breast-conserving surgery and definitive breast	Insufficient presentation of results

Excluded studies - 1.1 Do tumour-free tissue margins wider than 0 mm reduce local recurrence for people with invasive breast cancer and/or ductal carcinoma in situ (DCIS) treated with breast conserving surgery?	
Study	**Reason for Exclusion**
irradiation: Long-term outcome and prognostic significance of patient age and margin status, International Journal of Radiation Oncology Biology Physics, 50, 991-1002, 2001	
Solin, L. J., Fowble, B. L., Schultz, D. J., Goodman, R. L., The significance of the pathology margins of the tumor excision on the outcome of patients treated with definitive irradiation for early stage breast cancer, International Journal of Radiation Oncology Biology Physics, 21, 279-287, 1991	Insufficient presentation of results
Solin, L. J., Yeh, I. T., Kurtz, J., Fourquet, A., Recht, A., Kuske, R., McCormick, B., Cross, M. A., Schultz, D. J., Amalric, R., LiVolsi, V. A., Kowalyshyn, M. J., Torhorst, J., Jacquemier, J., Westermann, C. D., Mazoujian, G., Zafrani, B., Rosen, P. P., Goodman, R. L., Fowble, B. L., Ductal carcinoma in situ (intraductal carcinoma) of the breast treated with breast-conserving surgery and definitive irradiation: Correlation of pathologic parameters with outcome of treatment, Cancer, 71, 2532-2542, 1993	Insufficient presentation of results
Stadler, B., Staffen, A., Strasser, K., Wrba, F., Stanek, Ch, Prognostic factors for local recurrence in patients with limited surgery and irradiation of breast cancer, Strahlentherapie und Onkologie, 166, 453-456, 1990	Margin status not defined
Swanson, G. P., Rynearson, K., Symmonds, R., Significance of margins of excision on breast cancer recurrence, American Journal of Clinical Oncology: Cancer Clinical Trials, 25, 438-441, 2002	Follow-up <5 years
Touboul,E., Buffat,L., Belkacemi,Y., Lefranc,J.P., Uzan,S., Lhuillier,P., Faivre,C., Huart,J., Lotz,J.P., Antoine,M., Pene,F., Blondon,J., Izrael,V., Laugier,A., Schlienger,M., Housset,M., Local recurrences and distant metastases after breast-conserving surgery and radiation therapy for early breast cancer, International Journal of Radiation Oncology, Biology, Physics, 43, 25-38, 1999	Insufficient presentation of results
Tovar, J. R., Zandonade, E., Amorim, M. H., Factors associated with the incidence of local recurrences of breast cancer in women who underwent conservative surgery, International Journal of Breast Cancer, 2014, 639534, 2014	Margin status not defined
Tunon-De-Lara, C., De-Mascarel, I., Mac-Grogan, G., Stockle, E., Jourdain, O., Acharian, V., Guegan, C., Faucher, A., Bussieres, E., Trojani, M., Bonichon, F., Barreau, B., Dilhuydy, M. H., Dilhuydy, J. M., Mauriac, L., Durand, M., Avril, A., Analysis of 676 cases of ductal carcinoma in situ of the breast from 1971 to 1995: Diagnosis and treatment - The experience of one institute, American Journal of Clinical Oncology: Cancer Clinical Trials, 24, 531-536, 2001	Margin status not defined
Van Den Broek, N., Van Der Sangen, M. J. C., Van De Poll-Franse, L. V., Van Beek, M. W. P. M., Nieuwenhuijzen, G. A. P., Voogd, A. C., Margin status and the risk of local recurrence after breast-conserving treatment of lobular breast cancer, Breast cancer research and treatment, 105, 63-68, 2007	Margin status not defined

Excluded studies - 1.1 Do tumour-free tissue margins wider than 0 mm reduce local recurrence for people with invasive breast cancer and/or ductal carcinoma in situ (DCIS) treated with breast conserving surgery?	
Study	**Reason for Exclusion**
Vargas, C., Kestin, L., Go, N., Krauss, D., Chen, P., Goldstein, N., Martinez, A., Vicini, F. A., Factors associated with local recurrence and cause-specific survival in patients with ductal carcinoma in situ of the breast treated with breast-conserving therapy or mastectomy, International Journal of Radiation Oncology Biology Physics, 63, 1514-1521, 2005	Insufficient presentation of results
Vicini, F. A., Kestin, L. L., Goldstein, N. S., Baglan, K. L., Pettinga, J. E., Martinez, A. A., Relationship between excision volume, margin status, and tumor size with the development of local recurrence in patients with ductal carcinoma-in-situ treated with breast-conserving therapy, Journal of surgical oncology, 76, 245-254, 2001	Insufficient presentation of results
Vicini, F. A., Lacerna, M. D., Goldstein, N. S., Horwitz, E. M., Dmuchowski, C. F., White, J. R., Gustafson, G. S., Ingold, J. A., Martinez, A. A., Ductal carcinoma in situ detected in the mammographic era: An analysis of clinical, pathologic, and treatment-related factors affecting outcome with breast-conserving therapy, International Journal of Radiation Oncology Biology Physics, 39, 627-635, 1997	Insufficient presentation of results
Voogd, A. C., Nielsen, M., Peterse, J. L., Blichert-Toft, M., Bartelink, H., Overgaard, M., Van Tienhoven, G., Andersen, K. W., Sylvester, R. J., Van Dongen, J. A., Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: Pooled results of two large European randomized trials, Journal of Clinical Oncology, 19, 1688-1697, 2001	Margin width categories inconsistent with protocol
Vos, E., Siesling, S., Verhoef, C., Voogd, A., Koppert, L., Omitting a re-excision for a focally positive surgical margin after primary breast conserving surgery is safe, Annals of Surgical Oncology, 1), S26-S27, 2016	Abstract only - insufficient information
Wai, E. S., Lesperance, M. L., Alexander, C. S., Truong, P. T., Moccia, P., Culp, M., Lindquist, J., Olivotto, I. A., Predictors of local recurrence in a population-based cohort of women with ductal carcinoma in situ treated with breast conserving surgery alone, Annals of Surgical Oncology, 18, 119-124, 2011	Margin status not defined
Wang, S. Y., Chu, H., Shamliyan, T., Jalal, H., Kuntz, K. M., Kane, R. L., Virnig, B. A., Network meta-analysis of margin threshold for women with ductal carcinoma in situ, Journal of the National Cancer InstituteJ Natl Cancer Inst, 104, 507-16, 2012	Contains studies with insufficient follow-up - no new studies identified
Wazer, D. E., Jabro, G., Ruthazer, R., Schmid, C., Safaii, H., Schmidt-Ullrich, R. K., Extent of margin positivity as a predictor for local recurrence after breast conserving irradiation, Radiation Oncology Investigations, 7, 111-117, 1999	Margin width categories inconsistent with protocol
Whipp, E., Beresford, M., Sawyer, E., Halliwell, M., True local recurrence rate in the conserved breast after magnetic resonance imaging-targeted radiotherapy, International Journal of Radiation Oncology, Biology, Physics, 76, 984-90, 2010	Insufficient presentation of results

Economic studies

See Supplement 1: Health economics literature review for the list of excluded economic studies.

Appendix L – Research recommendations

What is the optimum tumour-free margin width after breast-conserving surgery for women with ductal carcinoma in situ (DCIS) and invasive breast cancer?

Why this is important

An important determinant of local recurrence is the surgical margin width (the distance from the breast cancer to the edge of the surgical excision). If the surgical margin is considered 'involved', then re-excision can take place as a further operation.

The threshold for considering if a margin is 'involved' is therefore important. If the margin is wide, then unnecessary re-excision can be avoided, whereas if the margin is narrow, local recurrence rate will be increased. From the evidence review, it was not possible to clearly define an optimum margin width between 0 mm and 2 mm to minimise local recurrence rates and minimise further surgery, and therefore it was felt this was an important topic for further research.

Table 16: Research recommendation rationale

Research question	What is the optimum tumour-free margin width after breast-conserving surgery for women with ductal carcinoma in situ (DCIS) and invasive breast cancer?
Importance to 'patients' or the population	Reduce local recurrence rates and optimise survival Minimise further surgery to where necessary Minimise cosmetic sequelae of more extensive/further surgery Reduce uncertainty
Relevance to NICE guidance	Ability to more clearly define an optimum margin width in future guidance
Relevance to the NHS	Reduce costs of local recurrence Reduce costs of further surgery including pathology
National priorities	Reduce variation in treatment Achieving world class cancer outcomes: A strategy for England 2015-2020 Improving outcomes strategy for cancer (2011) Cancer reform strategy (2007) National cancer survivorship initiative (2010)
Current evidence base	Current evidence was not clear and was graded as very low quality with high rates of imprecision
Equality	Applies to all patients with early breast cancer requiring surgery

Table 17: Research recommendation modified PICO table

Criterion	Explanation
Population	Adults (18 or over) with invasive breast cancer (M0) and/or DCIS who have undergone, or are due to undergo, breast conserving surgery with whole breast radiotherapy Exclusions – Neoadjuvant chemotherapy
Intervention	Margin width of 0 mm
Comparator	Margin widths of • >0-<1 mm

Criterion	Explanation
	• 1-2 mm • >2 mm
Outcome	Re-operation rate Local recurrence rate Patient satisfaction Overall survival Disease-free survival Treatment-related morbidity HRQoL Cosmetic result
Study design	Multicentre large observational cohort study
Timeframe	5 years
Additional information	Need to stratify by: Type of breast cancer: • Invasive breast cancer • DCIS Prognostic variables known to affect local recurrence rate: • Tumour size, grade, receptor status • Systemic treatments (chemotherapy, hormonal therapy, biological therapy) Presentation: • Screening • Symptomatic Breast radiotherapy Requirement for re-excision

HRQoL, health-related quality of life; M0, no distant metastases