ASSOCIATION OF BREAST SURGERY

ASSOCIATION OF BREAST SURGERY GUIDELINES

THE MANAGEMENT OF RADIAL SURGICAL MARGINS IN RELATION TO BREAST CONSERVATION SURGERY FOR INVASIVE BREAST CANCER

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Association of Breast Pathology

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UK Breast Cancer Group

Association of Breast Surgery Guidelines

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EXECUTIVE SUMMARY

In recent years, the outcomes of invasive breast cancer treatment have improved. One of the biggest positive impacts is likely to be advances in systemic therapy such as the use of adjuvant and neo-adjuvant chemotherapy and treatments targeting the HER-2 receptor. This is in addition to real gains in breast cancer imaging and tumour localisation for breast conserving surgery and improvements in the accuracy and delivery of radiotherapy to target microscopic residual disease.

Surgery continues to play a vital role in the treatment of invasive cancer. In breast conserving surgery (BCS), completeness of macroscopic tumour excision is necessary to keep local recurrence rates low. However, the absolute requirement for a specified 'safe' margin width around the excised tumour has been the subject of much debate. The impact on the patient of margin re-excision from a psychological and cosmetic point of view can be considerable and has significant cost implications for NHS providers. Not only this, but the precision and accuracy of a second operation on a breast where the incision can be remote from the cancer site and the healing process is well under way, may be considered questionable.

Many international guidelines accept 'no tumour at ink' as the standard of care, based on a meta-analysis by Houssami and colleagues1 that was published in 2014. This standard has been adopted by the following European and North American bodies:

- St Galen Consensus 2015 ratified in 2017 as standard of care.
- NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines in Oncology for the USA, 2019.
- 2014 SSO/ASTRO Margins Guidelines for Stage 1 & 2 Invasive Breast Cancer.

More recently, in 2022 a systematic review and meta-analysis investigating the effect of margin status and survival outcomes after BCS was published in the British Medical Journal (BMJ) by Bundred and colleagues2. The Bundred analysis reached different conclusions from the Houssami study and suggested that a 1mm margin may be preferable to 'no tumour on ink'. In response, the ABS commissioned a critical analysis by professional systematic reviewers at the Sheffield Centre for Health and Related Research (ScHARR) (Appendix 1) to independently review both the Houssami and Bundred meta-analyses and investigate why their findings differed.

This document will summarise the evidence for breast conserving surgery as well as the factors linked to local recurrence. The findings of the ScHARR review will be discussed and updated recommendations for the management of surgical margins after breast conserving surgery for invasive breast cancer presented.

On the 16th of January 2024, the National Institute for Health and Care Excellence (NICE) updated their recommendations for further surgery after breast-conserving surgery for invasive disease in the Early and locally advanced breast cancer: diagnosis and management guidance. The revised recommendations from NICE and the ABS are now broadly similar. This harmonisation is welcome and will help clinical teams and patients make pragmatic decisions about re-excising surgical margins.

Background

The evidence base for BCS is extensive and dates back 50 years. In the 1970s, Umberto Veronesi led a clinical trial (the Milan I trial) which compared mastectomy and BCS (quadrantectomy) plus whole breast radiotherapy (WBRT). This trial demonstrated no difference in overall survival or disease-free survival although it found higher rates of local recurrence with BCS surgery (8.8 versus 2.3%) at 20 years follow up[3]. Similar survival results were obtained by Bernard Fisher in the USA in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B 06 trial[4]. A subsequent meta-analysis of these (and other) trials by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) in 1995 concluded that there was no significant difference in rates of local recurrence when comparing mastectomy with BCS+WBRT and no difference in all-cause mortality between mastectomy compared to BCS +WBRT[5].

More recent data show that local recurrence rates are falling after BCS+WBRT[6]. Modern comparisons, albeit using non-randomised data, which may be subject to confounding factors, show that BCS+WBRT gives superior outcomes compared to mastectomy even in the presence of adverse tumour biology[7]. Modern survival rates with BCS+WBRT were at least equivalent to mastectomy in large series where case mix adjustment for stage, age and grade was performed[8]. It has been consistently shown that BCS+WBRT is associated with enhanced quality of life compared with mastectomy even when reconstruction is performed[9]. Consequently, the practice of BCS+WBRT has become part of standard care for breast cancer with rates rising steadily across Europe[10]. Some have even queried whether it is appropriate to offer the choice of mastectomy to women for whom breast conservation is feasible[11].

The current ABS guidelines (2015), advise a 1mm margin around both invasive and in situ disease. This is in contrast with other European and North American guidelines where, for invasive cancer, no tumour at ink is acceptable. The US Society for Surgical Oncology (SSO), American Society for Radiation Oncology (ASTRO)[12] and National Comprehensive Cancer Network (NCCN) guidelines (2020) are similar, advising no tumour at ink. Dutch National guidelines permit focal positivity of 4mm or less on pathology review, although generally advise a radiotherapy boost especially in pre-menopausal women[13].

To reduce the likelihood of close margins, accurate pre-operative assessment of size is important and considered best practice. The Royal College of Radiologists recommend use of additional imaging such as MRI in cases of lobular cancer (where breast conserving surgery is being considered), suspicion of multifocal disease, mammographically occult disease and if there is discrepancy between the clinical and standard imaging estimate of size[14].

Various techniques have also been explored to try and achieve clear margins intra-operatively. However, initial methods such as frozen section and imprint cytology have not been widely adopted due to intra-operative time constraints and the need for skilled and expensive technicians and increasingly time pressured pathologists. Other technologies involve investment in expensive equipment. Many of these methods are still in development and subject to evaluation in clinical trials but may be able to reduce rates of re-excision in the future[15].

Whilst pathologists examine the margins of specimens more thoroughly than in the past, it should be noted that pathological assessment of margins is limited, with a sampling approach rather than assessment of the entire margin. The Royal College of Pathologists have rigorous guidelines about the handling and assessment of margins[16]. This details how the margins should be inked, processed and reported to a standardised level, which is then subject to quality controls. The accuracy of these margin assessments depends upon good communication between the operating surgeon and the reporting pathologist and include factors such as accurate specimen orientation.

Indications for Breast Conserving Surgery (BCS)

The basis for BCS is to remove the breast cancer, whilst simultaneously preserving the aesthetic of the breast. It is almost always combined with either whole breast radiotherapy (WBRT) or partial breast radiotherapy (either external beam or intra operative) to treat the 'halo' of subclinical tumour deposits which may extend many centimetres away from the known primary. This has been elegantly shown by several studies where detailed examination of mastectomy specimens examined peri-tumoral tissue[17,18]. One key study found that if a 2cm margin is taken around a cancer, 47% of patients would have residual tumour foci and even with a 10cm margin, 10% of patients would have residual microscopic tumour foci[17]. Clearly the fact that BCS has such a high rate of local control means that foci of disease are effectively treated by combinations of radiotherapy and systemic therapies. Omission of one, but not both, of these elements may be acceptable in some patient subgroups. For example, in some older patients with oestrogen receptor positive cancers it may be safe to omit radiotherapy, as shown in the PRIME II trial[19,20].

The cosmetic success of BCS depends upon the volume of tissue needing to be removed versus the size of the breast[21]. Absolute contraindications to breast radiotherapy and therefore BCS include previous breast or mantle radiotherapy (although there may be some rare exceptions to this), pregnancy (unless close to term and radiotherapy can be offered after delivery), homozygous ATM mutation carriers, inability to lie flat or abduct the arm and a pacemaker or implantable device in the radiation field. Relative contraindications include the Li- Fraumeni Syndrome (where there is a higher risk of inducing second cancers[22]) and scleroderma or systemic lupus erythematosus where the rates and severity of late radiotherapy toxicity are higher[23].

The indications for BCS have expanded with the advent of oncoplastic techniques and the wider use, and increasing efficacy of, neoadjuvant systemic therapy. As oncoplastic techniques have evolved, the ability to remove larger volumes of breast tissue, whilst maintaining (or even enhancing) the aesthetics of the breast, has improved.

Factors affecting local recurrence rates:

There is increasing evidence that local recurrence rates (LRR) are falling. In a Dutch population of women under 40 with early-stage breast cancer, Van Laar and colleagues reviewed the 5-year LRR from 1988 -2010 and demonstrated a reduction in LRR over that period[6]. They concluded that this observed reduction in LRR was multifactorial but probably strongly influenced by the increased use and effectiveness of systemic therapy and radiotherapy and not the extent of the pathological margin around the breast cancer.

Other factors known to impact on rates of local recurrence include age, tumour biology, tumour grade, vascular invasion and the use of, and type, of radiotherapy. Nodal status may affect local recurrence rates after breast conserving surgery but the evidence base linking nodal status and local recurrence rates is more consistent after mastectomy.

1. Age

There have been concerns that the LRR is higher in younger women with BCS and again this may be due to the higher rates of triple negative breast cancers (TNBC) in these patients and the higher prevalence of pathogenic gene mutation carriers[24]. The rate is still low, and outcomes are largely impacted by adjuvant therapies. In the POSH study of young women with breast cancer (under age 40 years), positive margins 'tumour on ink' were associated with significantly worse overall survival and distant disease-free interval but not local recurrence interval[25].

2. Tumour Biology

Biological factors influence the rate of local recurrence, regardless of whether patients have BCS or mastectomy[26,27]. However, it is difficult to determine whether close versus wide margins have an impact that varies with tumour biology as no studies to date have stratified by disease biology.

Lowery and colleagues performed a systematic review, including data from over 12 000 patients, and found

that LRR rates were higher in patients with TNBC and HER2 positive cancers compared to luminal subtypes for both BCS and mastectomy patients [28]. The LRR in these patients is likely to be modified by adjuvant therapy rather than type of surgery.

Grade is also important with one study finding a LRR with grade 3 cancers of 7% compared to 3.5% for grade 2 and 1.0% for grade 1[26]. Genetic factors are also important with evidence suggesting women with BRCA gene mutations may have a slightly increased LRR compared to non-carriers after breast conservation surgery[29] although this is not found in all series, and some of these cases may represent new primary cancers.

Multigene assays are also useful in predicting high recurrence risk, not just systemically but also locally, for example women with a high Oncotype DX score have a higher LRR rate compared to women with a low score[30]. A study from Radosa and colleagues, of 1,930 women with TNBC, found that type of surgery (mastectomy versus breast conservation) was not significantly associated with a difference in local or distant recurrence rates[7].

Systemic therapy
The role of systemic therapy in local disease control is well established. The NSABP B-13 chemotherapy (methotrexate + 5FU) versus no chemotherapy trial showed a reduction in LRR from 13% to 2.6% with chemotherapy for example[31].

Endocrine therapy also reduces the risk of LRR in women with ER positive cancers. This was first shown in the NSABP B-14 trial, which compared Tamoxifen versus placebo and found it reduced the LRR rate from 14% to 4%[32].

Similarly, targeted HER2 directed therapies reduce the LRR rate. The NSABP B31 trial of trastuzumab versus none found a reduction in LRR from 2.8% to 1.7%[33]. Other studies have found the LRR rate to fall from 10% to 1% with the use of anti HER-2 treatment[34].

3. Radiotherapy and boost
Data from multiple trials consistently demonstrate that WBRT reduces the rate of LRR after BCS [35]. The addition of a boost to the tumour bed is also effective at further reducing the risk of LRR in high-risk women from 13 to 9%[36]. Omission of radiotherapy may be acceptable in older women with low-risk cancers when taking appropriate adjuvant systemic therapy, as has been shown in the PRIME II trial[19,20]. There is a small increased risk of local recurrence in these women, but no effect on overall survival[18]. For some low-risk women, partial breast radiotherapy can be used as an alternative to whole breast radiotherapy and has been shown to be non-inferior in terms of local relapse at five years[37], although this rarely applies in the UK.

Surgical margin status and local control: recent systematic review evidence
Numerous studies have found that the only statistically significant margin is that between a positive margin and a clear (not at ink) margin in terms of LRR[38]. There have also been many studies that have tried to determine what the optimal minimal resection margin width should be for BCS but here the evidence is less clear, and it should be noted that none are randomised trials. All are observational studies and hence subject to bias despite adjustment attempts. Some common sources of bias are as follows:

1. Surgeons may be more inclined to re-excise narrow margins in higher risk cases including younger women and adverse clinicopathological features.
2. Elderly women and those with multiple co-morbidities may not have margin re-excision because of concerns about the risks of further surgery. This group will also be less likely to get systemic therapies and radiotherapy than younger and fitter patients.
3. Extensive invasive disease at the margins is more likely to be identified pathologically, whilst smaller islands or multiple scattered foci of disease at margins may be missed on histopathological assessment.
4. Lobular cancers may pose a challenge as they can have a diffuse growth pattern and therefore be difficult to accurately size pre-operatively with conventional imaging.
5. Use of radiotherapy and boost may be more likely in certain subgroups such as larger tumours, lymph node metastases and younger women.
6. Systemic therapy use may also vary between patient groups.
7. Variation between breast units in terms of surgery, imaging and pathology protocols.

The large meta-analysis conducted by Houssami and colleagues in 2014[1], investigated the rate of local recurrence in more than 28,000 women across 33 studies who had BCS for invasive cancer. Positive margins were defined as the presence of (invasive or in-situ) cancer at the resection or inked margin. Negative margins were defined as the absence of tumour within a specified distance (mm) of the resection margin, with a close margin indicating presence of tumour within that distance but not at the resection margin.

There were 1506 recurrences with an overall local recurrence mean rate of 5.3% at 79 months. The relative risk of recurrence was 2.44 for those with a positive margin (tumour at ink) versus a negative margin, and 1.74 for those with a close (within a specified negative margin width) versus a negative margin. This rate was further reduced by almost a half with the addition of chemotherapy. When they analysed their data, they found that clear margins were better than both involved AND close margins in terms of LRRs (they did not comment on survival rates in this study). However, they were unable to identify a minimum threshold margin width to qualify as clear although there was a trend for a reduced rate of local recurrence as margins increased from 1 to 2 to 5mm. As this trend was not significant, they concluded that no tumour at ink was the acceptable minimal margin although this conclusion may not have been fully justified based on the data presented in the paper.

In 2022, a systematic review and meta-analysis performed by Bundred and colleagues was published in the BMJ[2]. Positive margins were defined as the presence of (invasive or in situ) cancer at the resection margin with this category defined as tumour at the inked margin and the margin distance 0 mm. Close margins were defined as

being within 2mm of the inked margin and clear margins defined as more than 2mm from the inked margin. Bundred and colleagues concluded that margin widths should be at least 1mm and that positive or close margins (<2mm) were linked to higher rates of breast cancer local recurrence as well as distant recurrence.

The publication of the Bundred meta-analysis prompted the ABS to commission the ScHARR Systematic Review Group to critically appraise both the Houssami and Bundred meta-analyses to support the development of up-to-date ABS consensus guidelines regarding the management of surgical margins for patients having BCS for invasive breast cancer.

ScHARR Report

The analysts from ScHARR confirmed that both meta-analyses were performed to a high standard but used different methodologies and included different articles. In particular, three key articles that were not published at the time of the Houssami review were included by Bundred and permitted margin width stratification.

Both studies agreed that negative margins reduce the probability of local recurrence. However, Houssami and colleagues concluded that increasing the distance for defining negative margins was not significantly associated with reduced odds of local recurrence. Conversely, Bundred and colleagues concluded that close margins are associated with increased local and distant recurrence compared with negative (wider) margins and that surgeons should aim to achieve a minimum clear margin of at least 1mm.

The main methodological differences between the two meta-analyses are presented in table 1.

The overall assessment was that both reviews used reasonable methods of analysis, with differences in included studies, slight differences in eligibility and methods of stratification for margin width that may account for their slightly different conclusions.

Comparison of the findings are presented in table 2.

Conclusions:

For local recurrence; both studies find that clear margins are better than involved margins and both suggest that widely clear margins are better than close margins but whilst Houssami and colleagues cannot identify a margin threshold and states that any margin is adequate, Bundred and colleagues selected 1mm, albeit based on very little evidence specific to this threshold.

For distant disease and survival; this was not explored by the Houssami study, but Bundred and colleagues find in favour of clear and wider margins. Most studies that look at the link between local recurrence and subsequent death do not identify a difference in survival

Table 1. Summary of the main methodological differences between the Houssami and Bundred meta-analyses.

Methodology	Houssami 2014	Bundred 2022
Search strategy	Similar	Similar. Bundred included all articles retrieved in Houssami, but not all were included in the final analysis. More recent search so more articles included overall
Search dates	1965-2013	1980-2021
Included articles	33 identified and all analysed	68 identified but only 27 analysed
Common articles	9 included in both reviews but did not include more recent articles than 2014 due to earlier analysis/search date	9 included in both reviews, but 24 of the Houssami studies are excluded due to either not having minimum 60 month follow up or not reporting hazard ratios
Inclusion criteria	Stage 1-2 Breast cancer in >90% of cases All had BCS All had radiotherapy Relative outcomes reported using a range of metrics	Stages 1-3 breast cancer All had BCS Only 94% had radiotherapy Had to report a hazard ratio
Risk of bias assessment	No formal reporting but stated all were of adequate quality	Formally assessed using ROBINS risk of bias tool. No studies excluded despite scores being low to moderate for most studies
Effect of individual studies		Some of the analyses are based on a small number or even a single study
Length of follow up	Minimum specified of 4 years. Median of 6.6 years	Minimum specified 5 years, median reported 7.4 years
Outcomes examined	Local recurrence only	Local and distant recurrence and overall survival
Statistical analysis	Modelling approach where margin status (+/-) and margin width and margin status used as model covariates	Cox proportional model approach with subgroup analysis of different margin widths where data available
Adjustment for covariates between groups	Age, year of recruitment, endocrine therapy, re excision rate, Local recurrence type (first or any)	Adjusted versus non adjusted hazard ratios were examined between studies. Presented separate analysis of both adjusted and unadjusted results (adjustments for age, stage, grade, chemo, radiotherapy, node status, published after 2010)

Table 2. Comparison of the findings of the 2 meta-analyses.

Finding	Houssami	Bundred
Local recurrence according to margin category (involved, close, clear)	Higher LRR if margins positive or close compared to clear. Higher risk of local recurrence if close than if clear	Higher LRR if margins positive or close compared to clear. Higher risk of local recurrence if close than if clear
Local recurrence according to margin width	Used a modelling approach to explore margin widths and determines that increasing the width of the negative margin did not reduce risk of LRR with non-significant P values, although there was a non-significant trend in favour of greater widths	Wider margins compared with narrower significant (looking at 0.1-2 versus 2mm, and 0.1-1 versus >2 and 1.1-2 versus >2), although 0.1-1mm versus >1mm was not analysed, despite being the recommended threshold
Distant recurrence	Not analysed	Higher risk with both positive and close margins
Overall Survival	Not analysed	Higher risk with positive and close margins
Adjusted analyses (for variables such as age/ radiotherapy/systemic therapy etc)	Did not influence results	Did influence results and some of the previously significant findings were no longer significant due to smaller numbers, although trends in the same direction

until about 15 years after diagnosis (radiotherapy versus no radiotherapy studies for example). In this case median follow up was only 7 years so this finding is surprising. In addition, for failure of local control to contribute to death, it would be expected that local recurrence would be the first event rather than distant recurrence without initial local recurrence. In addition, we know that the included studies will have had sources of bias (detailed earlier in this section) that will not have been fully adjusted for.

It is therefore likely that there may be a benefit to taking a wider margin than no tumour at ink. However, the rates of local recurrence are falling, despite narrower margins and are generally now very low. Re-excising margins, especially if a mastectomy is required, has a negative impact on patient quality of life.

The evidence that close margins (<2mm) negatively impact on survival is weak and may reflect the observational and therefore potentially biased nature of the data.

Overall, the data strongly suggests that whilst microscopic residual disease is frequently present out to 10cm from the primary cancer, minimal clear margins at the time of BCS are associated with excellent rates of local disease control following appropriate adjuvant therapies. This indicates that these microscopic foci may be adequately treated by adjuvant radiotherapy and systemic therapies. Data also shows that re-excision in the face of clear margins, however small, rarely yields identifiable disease (6.5% if margin close versus 36% if grossly involved in one series[39]) and is not an adequate justification for putting the patient through the morbidity of further surgery in most cases.

In the Netherlands, guidelines go a step further and do not require a re-excision of focally positive margins. A group retrospectively looked at the impact this has had on their ipsilateral breast tumour recurrence (IBTR) rate, 5-year disease-free survival (DFS) rate, and 10-year overall survival (OS) rate. They found that not re-excising focally positive margins had an impact on the LRR, but this did not translate into an effect on DFS or OS. On sub-group analysis, the risk was higher in younger women <50[40].

For most women, therefore we should aim to obtain a clear margin and, despite weak evidence to set a defined threshold, a 1mm margin seems reasonable. If a margin is less than 1 mm but not at ink, re-excision will probably not improve survival and is unlikely to result in local recurrence because of modern multimodal therapy.

Individual cases where the surgical margin is less than 1mm should be reviewed by multidisciplinary teams to ensure that there is concordance between expected and actual tumour size. In addition, pathological review is necessary to ensure that extensive disease is not found close to the cut surface. Other risk factors for higher LRR should also be considered such as poor disease biology and young age.

Patients without any of these adverse factors are likely to be adequately managed without re-excision of close margins. Those with adverse risk factors for local recurrence may benefit from re-excision of close margins. Treatment planning discussions with these patients should include the following pieces of relevant information:

1. *most re-excision operations have a very low yield of further disease;*
2. *the evidence base for re excision is not strong;*
3. *re-excision may have a negative impact on final cosmesis.*

Lastly, the data was presented at a session of the ABS Conference in May 2023 in Belfast, UK with a lengthy discussion (Available for ABS members to view on the website). A vote was taken from delegates present during the session and the consensus was that in general, the UK should continue with 1mm surgical excision margins for patients having BCS for invasive breast cancer and not change to 'no tumour on ink'. However, it was felt appropriate for treating clinicians and multi-disciplinary teams to selectively review cases with margins between 0 and 1 mm to allow patients to make individual decisions regarding margin re-excision of margins. It was also felt that more research was required before any definitive conclusions could be drawn.

RECOMMENDATIONS

These relate to the management of early-stage invasive breast cancer treatment, using breast conservation surgery with whole breast radiotherapy, where appropriate systemic treatment is accepted (endocrine or chemotherapy).

These guidelines apply to lesions where the predominant lesion is an invasive cancer rather than pure DCIS.

- Accurate pre-operative assessment of tumour size using conventional imaging. These will be supplemented by MRI of the breast where the primary tumour is lobular in nature and breast conserving surgery is planned. Further imaging with breast MRI or Contrast Enhanced Mammography may be used if the tumour is mammographically occult, or there is a size discrepancy between clinical and radiological estimates. Women <40 years old with difficult imaging interpretation and dense breasts may also be considered for further breast imaging, particularly if the size difference may mean a mastectomy is required rather than BCS.
- All surgical margins are assessed and commented on in the standard way. If there is no invasive cancer or DCIS within 1mm of the inked radial margins, they may be considered clear.
- In cases where invasive disease or DCIS is found within 1mm of the inked radial surgical margins and the patient does not have any other risk factors for local recurrence, following MDT review and after a risks and benefits discussion with the patient, radial margin re-excision can be omitted if both the patient and treating clinicians agree.
- In cases where invasive disease or DCIS is found within 1mm of the inked radial surgical margins and the patient has other risk factors for local recurrence or likely extensive residual disease (discordant tumour and pathology size, extensive malignant disease close to the margin, a 'cut off' appearance on pathology, and widespread multiple foci of LCIS, DCIS and/ or invasion) re-excision should be discussed.
- In cases where invasive disease or DCIS is found within 1mm of the inked radial surgical margins and the patient is unfit for further surgery or does not wish to undergo re-excision, following MDT review and after a risks and benefits discussion with the patient, margin re-excision can be omitted if both the patient and treating clinicians agree. Consideration should be given to the use of a radiotherapy boost to the tumour bed.
- In the very frail older woman with a limited life expectancy where invasive disease or DCIS is found within 1mm of the inked radial surgical margin there may be little benefit and some risk to life/ deterioration in quality of life by re-excising margins. Consideration should be given to use of endocrine therapy (if appropriate) and radiotherapy (plus/minus boost) as an alternative to further surgery.
- On-going, prospective auditing of positive margin and re-excision rates should be implemented in individual breast units. It is recommended that breast units identify and appoint a surgeon to lead this.

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REFERENCES

1. Houssami N, Macaskill P, Marinovich ML, Morrow M. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. Annals of surgical oncology. 2014;21(3):717-30.
2. Bundred JR, Michael S, Stuart B, Cutress RI, Beckmann K, Holleczek B, et al. Margin status and survival outcomes after breast cancer conservation surgery: prospectively registered systematic review and meta-analysis. Bmj. 2022;378:e070346.
3. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347(16):1227-32.
4. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347(16):1233-41.
5. Early Breast Cancer Trialists' Collaborative G. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. N Engl J Med. 1995;333(22):1444-55.
6. van Laar C, van der Sangen MJ, Poortmans PM, Nieuwenhuijzen GA, Roukema JA, Roumen RM, et al. Local recurrence following breast-conserving treatment in women aged 40 years or younger: trends in risk and the impact on prognosis in a population-based cohort of 1143 patients. Eur J Cancer. 2013;49(15):3093-101.
7. Radosa JC, Eaton A, Stempel M, Khander A, Liedtke C, Solomayer EF, et al. Evaluation of Local and Distant Recurrence Patterns in Patients with Triple-Negative Breast Cancer According to Age. Annals of surgical oncology. 2017;24(3):698-704.
8. Hartmann-Johnsen OJ, Karesen R, Schlichting E, Nygard JF. Survival is Better After Breast Conserving Therapy than Mastectomy for Early Stage Breast Cancer: A Registry-Based Follow-up Study of Norwegian Women Primary Operated Between 1998 and 2008. Annals of surgical oncology. 2015;22(12):3836-45.
9. Al-Ghazal SK, Fallowfield L, Blamey RW. Comparison of psychological aspects and patient satisfaction following breast conserving surgery, simple mastectomy and breast reconstruction. Eur J Cancer. 2000;36(15):1938-43.
10. Garcia-Etienne CA, Tomatis M, Heil J, Friedrichs K, Kreienberg R, Denk A, et al. Mastectomy trends for early-stage breast cancer: a report from the EUSOMA multi-institutional European database. Eur J Cancer. 2012;48(13):1947-56.
11. Johns N, Dixon JM. Should patients with early breast cancer still be offered the choice of breast conserving surgery or mastectomy? Eur J Surg Oncol. 2016;42(11):1636-41.
12. Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. Annals of surgical oncology. 2014;21(3):704-16.
13. Netherlands CCCt. Breast Cancer: Dutch Guidelines, V2.0. NABON. 2012.
14. https://www.rcr.ac.uk/system/files/publication/field_publication_files/bfcr199-guidance-on-screening-and-symptomatic-breast-imaging_0.pdf.
15. Pradipta AR, Tanei T, Morimoto K, Shimazu K, Noguchi S and Tanaka K. Emerging Technologies for Real-Time Intraoperative Margin Assessment in Future Breast-Conserving Surgery. Adv Sci. 2020; doi: 10.1002/advs.201901519.
16. Ellis IC, P. Deb, R. Girling, A. Hales, P. Hanby, A. Ibrahim, M. Lee, AHS. Liebmann, R. Mallon, E. Pinder, SE. Provenzano, E. Quinn, C. Rakha, E. Rowlands, D. Stephenson, T. . Pathology reporting of breast disease in surgical excision specimens incorporating the dataset for histological reporting of breast cancer. Royal College of Pathologists. 2016.
17. Holland R, Veling SH, Mravunac M, Hendriks JH. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. Cancer. 1985;56(5):979-90.
18. Vaidya JS, Vyas JJ, Chinoy RF, Merchant N, Sharma OP, Mittra I. Multicentricity of breast cancer: whole-organ analysis and clinical implications. Br J Cancer. 1996;74(5):820-4.
19. Kunkler IH, Williams LJ, Jack WJL, Cameron DA, Dixon JM. Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer. N Engl J Med. 2023;388(7):585-94.
20. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM, investigators PI. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol. 2015;16(3):266-73.
21. Cochrane RA, Valasiadou P, Wilson AR, Al-Ghazal SK, Macmillan RD. Cosmesis and satisfaction after breast-conserving surgery correlates with the percentage of breast volume excised. Br J Surg. 2003;90(12):1505-9.
22. Heymann S, Delaloge S, Rahal A, Caron O, Frebourg T, Barreau L, et al. Radio-induced malignancies after breast cancer postoperative radiotherapy in patients with Li-Fraumeni syndrome. Radiat Oncol. 2010;5:104.
23. Lin A, Abu-Isa E, Griffith KA, Ben-Josef E. Toxicity of radiotherapy in patients with collagen vascular disease. Cancer. 2008;113(3):648-53.

24. Arvold ND, Taghian AG, Niemierko A, Abi Raad RF, Sreedhara M, Nguyen PL, et al. Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy. J Clin Oncol. 2011;29(29):3885-91.
25. Copson ER, Maishman TC, Tapper WJ, Cuttress RI, Greville-Heygate S, Altman DG et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. Lancet Oncol. 2018; 19: 169-180.
26. Rezai M, Kraemer S, Kimmig R, Kern P. Breast conservative surgery and local recurrence. Breast. 2015;24 Suppl 2:S100-7.
27. Chen J, Jiang P, Wang HJ, Zhang JY, Xu Y, Guo MH, et al. The efficacy of molecular subtyping in predicting postoperative recurrence in breast-conserving therapy: a 15-study meta-analysis. World J Surg Oncol. 2014;12:212.
28. Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ. Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. Breast Cancer Res Treat. 2012;133(3):831-41.
29. Pierce LJ, Phillips KA, Griffith KA, Buys S, Gaffney DK, Moran MS, et al. Local therapy in BRCA1 and BRCA2 mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy. Breast Cancer Res Treat. 2010;121(2):389-98.
30. Mamounas EP, Tang G, Fisher B, Paik S, Shak S, Costantino JP, et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. J Clin Oncol. 2010;28(10):1677-83.
31. Fisher B, Dignam J, Mamounas EP, Costantino JP, Wickerham DL, Redmond C, et al. Sequential methotrexate and fluorouracil for the treatment of node-negative breast cancer patients with estrogen receptor-negative tumors: eight-year results from National Surgical Adjuvant Breast and Bowel Project (NSABP) B-13 and first report of findings from NSABP B-19 comparing methotrexate and fluorouracil with conventional cyclophosphamide, methotrexate, and fluorouracil. J Clin Oncol. 1996;14(7):1982-92.
32. Fisher B, Dignam J, Bryant J, DeCillis A, Wickerham DL, Wolmark N, et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. J Natl Cancer Inst. 1996;88(21):1529-42.
33. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Jr., Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353(16):1673-84.
34. Kiess AP, McArthur HL, Mahoney K, Patil S, Morris PG, Ho A, et al. Adjuvant trastuzumab reduces locoregional recurrence in women who receive breast-conservation therapy for lymph node-negative, human epidermal growth factor receptor 2-positive breast cancer. Cancer. 2012;118(8):1982-8.
35. EBCTCG. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. Lancet. 2011; 378(9804):1707-1716.
36. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol. 2015;16(1):47-56.
37. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol. 2015;16(1):47-56.
38. Zavagno G, Goldin E, Mencarelli R, Capitanio G, Del Bianco P, Marconato R, et al. Role of resection margins in patients treated with breast conservation surgery. Cancer. 2008;112(9):1923-31.
39. Rivere AE, Chiasson KF, Corsetti RL, Fuhrman GM. An Assessment of Margins after Lumpectomy in Breast Cancer Management. Am Surg. 2016;82(2):156-60.
40. Vos EL, Siesling S, Baaijens MHA, Verhoef C, Jager A, Voogd AC, et al. Omitting re-excision for focally positive margins after breast-conserving surgery does not impair disease-free and overall survival. Breast Cancer Res Treat. 2017;164(1):157-67.

APPENDIX 1

A Critical Analysis of Two Systemic Reviews on Breast Cancer Surgical Margins
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