Ann Surg Oncol (2019) 26:3931–3938
https://doi.org/10.1245/s10434-019-07641-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

The Impact of Margin Status on Breast Conservation Rates

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ABSTRACT

Background. Contemporary data indicate that breast conservation treatment (BCT) results in superior survival outcomes compared with mastectomy. However, positive margins after lumpectomy have implications for local control, and re-excisions are recommended to achieve negative margins. The need for reoperations after an initial attempt at BCT is associated with higher chance of conversion to mastectomy. Achieving negative margins at the first therapeutic surgical procedure is therefore critical to optimise BCT rates and survival outcomes.

Methods. A compilation of scientific reports on BCT, margin status, rates of reoperation, and the impact on BCT rates was reviewed. Re-excision rates after initial lumpectomy is variable to a staggering degree and reported to be between 0 and 100%. High reoperation rates (ROR) are associated with higher likelihood of conversion to mastectomy, which may not confer favourable treatment outcomes. Although widely agreed that decreasing ROR is a desirable objective, there is controversy regarding the need for its urgent implementation as a quality metric. Critics of this cite challenges related to how this can be achieved and its attendant ramifications. On the other hand, without the appropriate incentive for quality improvement of surgical treatment of breast cancer, patients may be subject to poorer overall outcomes.

Discussion. Techniques and approaches are discussed in this article to enable a reduction in positive margin status, and therefore ROR. The rationale for achieving ROR of 10–20% are explicated, as well as the impact this would have on BCT rates, which translates to better survival outcomes for women with breast cancer.

First Received: 26 April 2019;
Published Online: 3 September 2019

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Following the seminal reports of the randomised, control trials (RCTs) comparing breast conservation treatment (BCT) and mastectomy in the 1980s, the National Institute of Health issued a consensus statement recommending BCT as the preferred modality of surgical therapy for early onset breast cancer.[1–4] Despite the clear non-inferiority of BCT to mastectomy, which formed the basis for this consensus at that time, there was wide variability in adopting BCT among different centres. Some institutions reported significantly higher mastectomy rates than others.[5,6] Recently, a significant number of retrospective and prospective trials with more than 500,000 patients (Table 1) suggested that BCT may no longer be simply non-inferior to mastectomy in terms of survival outcomes. These studies report that BCT may confer superior survival to mastectomy.[7–22] Due to the persuasive data now available, there have been uniform calls internationally to increase BCT rates.[23–25] The National Accreditation Program for Breast Centers/American College of Surgeons' (NAPBC/ACS) accreditation criteria to have a minimum standard (50%) for BCT rates for breast centres is consistent with this policy.[26] It therefore would be logical to implement other benchmarks that contribute to this ultimate objective.

Positive margins at lumpectomy have a negative impact on BCS rates. Because margin positivity is associated with an increased risk of local recurrence, a re-excision is mandatory for optimum disease control.[27] However, a significant proportion of women who wish to have BCT actually undergo mastectomy for positive margins at first lumpectomy.[28,29] Because contemporary data (Table1) suggests inferior survival outcomes with mastectomy, efforts should be directed toward a reduction in mastectomy rates. Positive margins after the first therapeutic surgical procedure warrants re-excision, which worsens cosmetic outcomes and increases the likelihood of a patient electing to undergo a subsequent mastectomy for margin clearance. Consequently, increased mastectomy rates could result in poorer survival outcomes on a population

TABLE 1 Studies comparing outcomes for breast conservation treatment and mastectomy

Author/year of publication	Centre/country	Treatment period	No. of patients	Type of study	Comparison of survival	Comparison of local control	BCT rate	Conclusion and relevant comments
Hwang et al.[7]	Duke University, USA	1990–2004	112,154 Stages I, II	Retrospective California Cancer Registry	HR for OS BCS + RT: 0.72 (0.68–0.76) Mx: 1.0	NR	55%	BCS + RT associated with higher breast cancer specific survival at almost 10-year follow up For every potential confounding factor related to mortality evaluated, women with Mx more likely to die with 3 years
Agarwal et al.[8]	University of Michigan, USA	1998–2008	132,149 < 4 cm < 4 LN+	Retrospective, SEER	HR for survival ($p < 0.001$) BCS + RT: 1.0 Mx: 1.31 (1.25–1.39) Mx + RT: 1.47 (1.34–1.61)	NR	70%	Patients with BCT improved breast cancer specific survival
van Hezewijk et al.[9]	Multicentre trial, various countries (TEAM trial)	2001–2006	9231 ER, PR + ve	Prospective	HR 5-year OS: ($p < 0.001$) BCS + RT: 1.0 Mx: 1.22 (1.02–1.47)	HR for LRR ($p = 0.01$) BCS + RT 1.0 Mx 1.53 (1.10–2.11)	54.1%	Significantly higher LRR in patients with Mx only
Martin et al.[10]	Australian National University	1995–1999	2787	Retrospective	Hazard of death reduced by 55.88%	NR	51.5%	Patients with BCS better survival than mastectomy
Horvind et al.[11]	Cancer Registry of Norway	2005–2011	9547	Retrospective Norway Registry	HR of death at 6 year BCT: 1.0 Mx: 1.7 (1.3–2.4)	NR	61.1%	Women treated with BCT have significantly better breast cancer-specific survival
Saadatmand et al.[12]	Erasmus University Medical Centre	1999–2012	173,797	Retrospective The Netherlands Cancer Registry	HR for 5-year overall mortality BCT: 0.87 (95% CI 0.81–0.93) Mx: 1.0 (Reference)	NR	48% (1999–2005) 54% (2006–2012)	Comparison of 2 cohorts of patients from 1999–2005 to 2006–2012
van der Heiden-van der Loo et al.[13]	Netherlands Comprehensive Cancer Organisation	2003–2006	40,892	Retrospective The Netherlands Cancer Registry	NR	5-year IBTR BCS (+RT): 2.38% Mx: 3.45%	54.9%	IBTR rates may be used as an outcome indicator on a national level for international comparison
van Maaren et al.[14]	Netherlands Comprehensive Cancer Organisation	2000–2004	37,207	Retrospective The Netherlands Cancer Registry	HR for 10-year overall mortality BCT: 0.81 (95% CI 0.78-0.85) Mx: 1.0 (Reference)	NR	58%	Significantly higher 10 year distant metastasis-free survival for BCS + RT in T1N0 stage cancer

TABLE 1 continued

Author/year of publication	Centre/country	Treatment period	No. of patients	Type of study	Comparison of survival	Comparison of local control	BCT rate	Conclusion and relevant comments
Plichta et al.[15]	Massachusetts General Hospital	1996–2008	584 < 40 yrs old	Retrospective Single centre	10-year DFS BCT: 89% Mx: 79%	10-year LRR BCT: 4% Mx: 8.7%	57.4%	BCT oncologically safe for young breast cancer patients
Nandakumar et al.[16]	Indian National Cancer Registry	2006–2008	9903	Observational registry-based	5-year survival BCT: (stage I, II, III) 96.0%, 94.0%, 87.1% Mx: (stage I, II, III) 91.0%, 85.8%, 69.0%	NR	Stage I,II,III: 55.8%, 33.5%, 15.0%	Significantly decreased survival with mastectomy
Christiansen et al.[17]	Danish Cancer Co-operative Group	1995–2012	58,331	Retrospective registry-based	RR for mortality Primary mastectomy: 1.20 BCS first, then mx: 1.08 BCS (reference): 1.0		BCS (final): 49%	Patient who underwent attempt at BCS prior to mastectomy had a considerably better outcome than those primarily assigned to mastectomy
Wang et al.[18]	Single institution analysis (China)	1999–2014	6137 Stage I	Retrospective	5-year overall survival BCS + RT: 99.1% Mx: 96.1% ($p = 0.001$)	5-year DFS BCS + RT: 95.3% Mx: 90.2%	BCS + RT 21.1%	BCS + RT provided better outcomes than mastectomy and should be preferred treatment option
Corradini et al.[19]	Various European Centres	1998–2014	7565 T1–2, N0–1	Matched cohort, Patients outside clinical trials	Local recurrence-free survival (HR) BCT: 1.517 (CI: 1.092–2.108) Mx: 1.0	10-year metastatic disease-free survival BCT: 89.4% Mx: 85.5%	BCS + RT 84.8%	Patients treated with BCS and RT had an improved outcome compared to mx alone with respect to local control, distant control and overall survival. Patients should be encouraged to receive BCS with RT.
Lazow et al.[20]	National Cancer Database	2004–2014	11,859 Younger than 40 year	Retrospective Multiple regression	HR for 10-year survival BCT versus unilateral Mx: 2.36 BCT versus bilateral Mx: 2.30		42.8%	Unilateral or bilateral mastectomy associated with a small but significant decrease in 10-year overall survival relative to BCT

BCS Breast-conserving surgery/lumpectomy only; *BCT* breast-conservation treatment/lumpectomy with radiotherapy; *DFS* disease-free survival; *ER* oestrogen receptors; *HR* hazard ratio; *IBTR* ipsilateral breast tumour recurrence; *LN* lymph node status; *LR* local recurrence; *Mx* mastectomy; *NR* not Reported; *OS* overall survival; *PR* progesterone receptors; *RT* radiotherapy/radiation treatment; *SEER* Surveillance Epidemiology, and End Results database; *TEAM* Tamoxifen Exemestane Adjuvant Multicentre trial basis.[30,31] Hence, margin clear lumpectomy at the first operation should be our goal. Setting benchmarks for reoperation rates (ROR) for BCT would be a necessary and salutary step in optimising survival outcomes for breast cancer therapy.

However, contrary to this objective, recent reports argue against the implementation of re-excision rates as a quality metric.[32,33] In broad terms, paradoxically, the arguments put forth against this are: (1) the fear that its introduction would lead to the unwanted consequence of increased mastectomy rates by surgeons to reduce their re-excision rate, and (2) many factors involved in positive margins are beyond the surgeon's control. The first concern is overruled by simultaneous adherence to recommended standards for BCT rates and ROR.[26] This would naturally encourage greater use of BCT over mastectomy. The second challenge can be mitigated by various strategies previously published, which are to a great extent within the surgeon's control.[34] Using existing multidisciplinary approaches and current surgical technology, this article seeks to detail the methods that can be applied to enable the expedited implementation of a benchmark for re-excision rates.

ASSOCIATION OF MARGIN STATUS, RE-EXCISION, AND BCT RATES

Positive pathologic margins following breast-conserving surgery (BCS) are associated with poorer local control and therefore warrant a re-excision.[35–37] Re-excision, in turn, has been found to be associated with a higher probability of a decision to proceed with mastectomy.[28] Observations on the wide range of margin positive lumpectomy with disproportionate high rates of reoperations led to reports of "an epidemic of re-excisions."[38,39] According to published data, ROR for BCS may range from 0 to 70% with some reports indicating an alarmingly disparate rates of as high as 0–100%.[40,41] This vast variability is of great concern, because it exceeds rates for other commonly measured surgical outcomes, such as infection or margin positive rates in the surgical management of any malignancy.[38] It makes the reluctance to implement it as a quality metric by some experts perplexing. Measures to decrease variance in ROR should indeed take priority to decrease patient anxiety, surgical and cosmetic complications, and cost.

Several initiatives have already been introduced in an effort to address the issue of ROR. The American Society for Radiation Oncology (ASTRO) issued a consensus several years ago defining a negative margin following BCS as "no tumour on ink."[42] This definition abated the controversy on adequacy of margin width, and adherence to this requirement resulted in a reduction in ROR.[43] As reported, currently 63% and 81% of women with positive margins proceed to undergo a unilateral or bilateral mastectomy respectively.[28,29] The implementation of the ASTRO margin guidelines can be expected to decrease ROR and lead to a concomitant increase in BCT. An increase in BCT rates in women of all age groups, even those younger than age 40 years could potentially improve breast cancer-related survival on a population basis.[20,30,31]

In addition to refined margin status criteria, surgical techniques to achieve adequacy of resection may be adopted to minimise the need for re-excision. A plethora of techniques has been reported to augment conventional tactile means of assessing margins, which have been used successfully in various settings.

SURGICAL TECHNOLOGY FOR INTRAOPERATIVE MARGIN ASSESSMENT

Image-Assisted Techniques

The use of intraoperative ultrasound and oriented specimen radiographs have been reported with varied success. Conventional film-screened and digital mammography methods have been used with some success in decreasing positive margins with minimal impact on operation times.[44,45] Margin positivity using specimen mammography has been reported to be between 11.8% and 21.8%, down from 47.6% in one study.[44] Most recently, 3D intraoperative specimen mammography also shows excellent reduction in margin positive lumpectomy.[46] Also, although operator-dependent, intraoperative ultrasound resulted in positive margin rates of between 3.5 and 33.3%. These rates were lowered from 29–45 to 3.5% and 11% respective in two studies by Rahusen et al.[47] and Moore et al.,[48] respectively.

Surgical Methods

Operative technical details can contribute to decreased ROR. Oncoplastic surgical techniques have been developed as a means to achieve good cosmetic outcomes following extensive cancer resections. In cases where standard breast-conserving surgery may not suffice to provide adequate margins, these techniques may be applied to allow clear margins and decrease the need for re-excision.[49] The use of added intraoperative shave margins as reported by Chagpar et al.[50,51] demonstrated a decrease in margin positive lumpectomy from 36 to 19% and may be associated with decreased operative costs. Another approach contributing to a reduction in ROR is the use of radioactive seed localisation (RSL).[52] A meta-analysis has shown that the use of RSL compared with conventional wire localisation resulted in a numerically lower margin positive rate.[53]

Pathologic Methods

Pathologic methods may range from gross inspection by the surgeon, macroscopic margin assessment by either surgeon or pathologist, touch smear cytology, or frozen-section (FS) analysis. Frozen-section analysis results in margin positive rates of 6–16%, which is the narrowest range across different practice settings compared with the other techniques.[54] However, frozen section is resource intensive and needs to be implemented with cost-effective outcomes in mind. Osborn et al. reported that compared with re-excision at a second sitting, the use of FS would be cost-effective if ROR was below 26%.[55] Because other studies have independently verified the efficacy of FS in reducing ROR, it remains a viable option in efforts to decrease ROR. In addition, standardisation of pathologic assessment, whether during intraoperative FS analysis or during standard paraffin sections, using perpendicular margins has also been shown to reduce the need for re-excision.[56]

Multidisciplinary Approach

Neo-adjuvant systemic chemotherapy or estrogen ablation (NAST) often are used for the treatment of locally advanced breast cancer. NAST also has been adopted for early-stage breast cancer to downstage tumour size and decrease ROR with BCT.[57] A reduction in tumour size intuitively improves the ability to achieve negative margins at the first oncologic surgical procedure. Certain tumour subtypes are known to be associated with higher ROR.[58] Administration of NAST according to histology may facilitate adequacy of resection. Hence, a multidisciplinary approach (MDC) involving radiologist, surgeons, pathologists, and medical oncologists has been shown to contribute to a reduction in ROR. Accordingly, Tevis et al.[59] reported a decrease of margin positive lumpectomy rates from 21 to 13.7% to 7.7% based on the extent of adoption of MDC-based intraoperative recommendations.

DISCUSSION

Achieving negative margin status while limiting ROR is a complex multifaceted issue. Actual ROR is thought to differ significantly from the achievable rates.[38] In this context, Dunham et al.[38] convincingly imply that there is room for reduction of both ROR as well as the disparity of rates between surgeons and centres. Landercasper et al.[57] also has highlighted that ROR should be audited as a quality indicator for breast centres. This would decrease patient anxiety, cost, and surgical complications associated with mastectomy and reconstruction resulting from margin positive lumpectomy. Re-excision rates of 20% can be achieved without the use of any elaborate surgical or technical methods.[60] It therefore is reasonable to take this as a reference point. The many methods that can be applied to achieve lower ROR than this have been detailed in the foregoing discussion. The best of these are summarized in the "Toolbox to reduce lumpectomy reoperations" proposed by the American Society of Breast Surgeons.(ASBrS).[34] In fact, a recent systematic review reported that the introduction of the definition of a negative margin status as "no ink on tumour" reduced re-excision rates to 14%.[61] It is hence not inconceivable that the use of "Toolbox techniques" will enable further reduction in ROR to 10% as endorsed by the ASBrS.

As mentioned, apart from the emotional impact on the patient who has to undergo a reoperation, there are documented increased risks of complications and additional cost.[62,63] It has been estimated that achieving adequate margins through a single operation can result in substantial savings at a national level.[64,65] This has been verified through the use of FS analysis to minimise ROR.[65,66] Oncoplastic techniques combined with shave margins may also minimise positive margins in women with histology types like invasive lobular carcinoma, classically thought to require mastectomy.[58] The appropriate use of FS in conjunction with certain surgical techniques may reduce ROR to as low as 2.5%.[66] The intersection of these separate studies suggests that lowering ROR is cost-effective breast cancer surgical management likely to increase achievable BCT rates, which in turn can improve survival, reduce postoperative complication rates, avoid delay of adjuvant treatment, and provide better cosmesis and post treatment quality of life.[62–67]

Appropriate multidisciplinary-based therapy has led to better survival for women with breast cancer over historical treatment epochs.[68] However, it has been observed that survival has arrived at a plateau for at least one group of patients.[69] It is all the more critical now that efforts should be focussed on the application of appropriate therapeutic surgical strategies to allow further improvement in survival outcomes. There is sufficient contemporary data indicative of improved survival with BCT compared with mastectomy (Table 1). Population studies demonstrate a survival benefit of 4% in favour of BCT when conservation rates are 70%, but this advantage declines to 2% when BCT rates are 54%, consistent with instrumental variable estimates.[30,31,70] Because ROR has a deleterious impact on BCT rates, a persistently high ROR can drive survival outcomes down. It therefore follows that one potential way to enable higher survival among women with breast cancer

TABLE 2 List of objections to re-operation rate (ROR) as a quality metric and suggested counter-measures

	Objection	Suggested counter-measure	References
1	Absence of standardised definition of clear margin	Negative margin now defined as 'no ink on tumour', potentially avoiding 45% of re-excisions	42,43
2	Variability in specimen processing	Standardisation of processing using perpendicular margins and not en face margins	56
3	Adequacy of preoperative imaging	Standardisation by American College of Radiology certification	26
4	Known variation of positive margins based on histological type of cancer	Preoperative chemotherapy for tumour downstaging and use of oncoplastic surgical techniques as expounded in 'Toolbox'	57,58
5	Cosmetic concerns with greater tissue resection to achieve clear margins	Preoperative chemotherapy for tumour downstaging and use of oncoplastic surgical techniques as expounded in 'Toolbox'	34
6	Implementation of maximum ROR will lead to increased mastectomy rates	Concomitant application of both ROR and breast conservation therapy rates as quality measures. Use of techniques in 'Toolbox'	Current paper

is to ensure that ROR is minimised. As such, there is a pressing need to establish ROR as a quality metric for breast surgery. Because an ROR of 20% is reasonably attainable without any extraordinary means, the authors propose that this should be the minimum standard, whereas 10% remains the ideal ROR. Critical re-evaluation and revision of surgical and oncologic therapeutic processes is encouraged if this rate is not met, with conscious use of published "Toolbox" measures to achieve acceptable ROR.[34,60] In this regard, the author's published an algorithm used in their current practice.[70]

It has been suggested that the adoption of a target re-excision rate as a quality measure for BCT would lead to surgeons exploiting the system unfavourably for patients by performing more mastectomies to avoid being penalised by the adoption of such a standard.[31,32] This concern is set aside by current accepted and modest metrics for BCT rates.[26] It is critical that both ROR and BCT rates be integrated and concordant to avert the overemphasis of one practice standard over another. Reduction of ROR is therefore a laudable goal, which should be undertaken by all surgeons treating breast cancer and about which patients should be informed. The objections which have been raised against the implementation of ROR as a quality metric may be countered by practicable measures listed in Table 2. There is value in narrowing the variability in ROR not only in terms of health economics but also in its potential impact on survival, representing a quality improvement endeavour. The opportunity to break the cycle of high ROR in order to decrease mastectomy rates is consistent with best practice patterns. The trends that have become evident since the implementation of a consistent definition of margin status indicate that surgeons can exert significant control over ROR and policies can be introduced which incentivise surgeons to achieve successful BCT in a single operation, maintain low ROR, and attain high BCT rates.[61,70,71] When reasons are not yet clearly evident and research is in progress, available contemporary data (Table 1) is adequate to direct recommendations for best practice. This approach has been endorsed by organizations such as ESSO-EUSOMA and ICHOM Initiative. The ultimate objective for today's surgeon should be the appropriate de-escalation of breast cancer surgical therapy, which is based on robust current data and which has a demonstrable positive impact on survival outcomes.[72,73]

DISCLOSURE The authors declare that they have no conflict of interest.

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