

Margins! Margins. Margins? How Important Is Margin Status in Breast-Preserving Therapy?

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Keywords

Breast cancer · Breast preservation · Margins · Surgery · Radiotherapy

Summary

Margin status is surely a prognostic factor in patients undergoing breast-conserving therapy, but its impact is probably overestimated in case of adequate adjuvant radiotherapy. Radiotherapy improves local control after excision of the primary tumor in all subgroups of patients. There is, in contrast, no evidence that a certain margin width or a re-resection improves local control.

Schlüsselwörter

Brustkrebs · Brusterhaltung · Resektionsränder · Operation · Radiotherapie

Zusammenfassung

Die pathohistologisch bestimmte Resektionsradikalität ist ein wichtiger prognostischer Faktor in der brusterhaltenden Therapie. Die Weite des freien Resektionsrandes hat allerdings bei adjuvanter Radiotherapie nur geringen Einfluss auf die Rezidivrate und die Bedeutung wird vermutlich überschätzt. Es gibt keinen Hinweis darauf, dass eine bestimmte Weite des freien Resektionsrandes nötig ist, und der Wert einer Nachresektion bei R0-Situation ist nicht belegt.

Introduction

Margin status has been an issue of controversial debates in the past years. The importance of clear margins after tumor-ectomy for breast cancer has been highlighted in large prospective trials already in the beginning of breast-conserving therapy [1, 2]. In an early investigation from Boston, patients with negative, close, focally positive, and more than focally positive margins had local recurrence rates of 0%, 4%, 6% and 21% [2]. The assessment of margins has therefore been considered as a critical part of breast-preserving treatment, and a lot of progress has been made over the past years with regard to standardization of surgical procedures and pathological examination. This standardization is probably the most important factor for the significant reduction in local relapse rate from 1–2% per year in series of the 1980s to an annual recurrence rate of 0.5–1% in recent years.

Although the general impact of margin status on local control is not under debate, there exists a broad variation between surgeons upon the definition of optimal and minimal

margin width, with the acceptance of smaller margins by more experienced surgeons [3]. Despite these uncertainties, measurement of margin width has been incorporated as a quality criterion in treatment guidelines for breast cancer [4]. The following article tries to define the role of margin status with emphasis on adjuvant radiotherapy, with the objective to optimize the combination of surgery and radiotherapy.

Theoretical Considerations

Tumor cells have the ability to invade the surrounding normal tissue. Isolated tumor cells or small foci of tumor cells are routinely found in the normal tissue around a tumor. These microscopic findings are even present in tumors that macroscopically appear to have a sharp border to the surrounding normal tissue. The well-known data from Holland demonstrate that the probability of finding tumor cells decreases with increasing distance from the macroscopic tumor [5, 6]. These residual cells are considered as the source for a local

recurrence if left after tumorectomy. It is therefore likely that the risk for a local recurrence after surgery decreases with increasing margin width.

Radiotherapy can destroy tumor cells. The probability of local tumor control is a function of the number of clonogenic tumor cells, the radiosensitivity of these tumor cells, and the radiation dose. For a given radiosensitivity and a certain radiation dose, the chance of tumor control therefore depends on the amount of tumor cells in the target volume. If a standard dose of radiotherapy is prescribed, this dose should be to control a certain number of tumor cells on a microscopic level. If the initial surgery has already reduced the number of cells below this threshold, more surgery (e.g. a re-resection) with further reduction of tumor cells will not necessarily further increase local control.

There are several clinical data supporting these theoretical assumptions. Rudloff and coworkers found an in-breast tumor recurrence rate of 28%, 21%, and 19% for lesions excised with margins of < 1 mm, 1–9 mm, and ≥ 10 mm, respectively, and risk reductions of 83% ($p = 0.002$), 70% ($p = 0.05$), and 24% ($p = 0.55$) in these subgroups [7].

Impact of Margin Status

Margin status is surely a prognostic factor. Involved margins are associated with a significant increased risk of failure. This is especially true for patients treated with surgery alone, without adjuvant radiotherapy.

In patients undergoing radiotherapy, the impact of margin status is less clear. Various studies have demonstrated that involved margins are associated with an increased risk for local recurrence [8, 9]. However, the hazard ratio is relatively low. Recent data from large studies and population-based registries suggest that the risk for a local recurrence is increased by a factor of 2 or less, which means that the impact of an R1 resection is comparable to or less than that of a radiation boost (tables 1 and 2) [10, 11]. In the large European Organisation for Research and Treatment of Cancer (EORTC) boost trial, margin status (free versus close versus involved) had no impact on the local recurrence rate [12].

How Important Is Margin Width?

Several guidelines for breast cancer treatment recommend a certain width of free margins, e.g. a free margin of 1 mm for the invasive tumor and 5 mm for the intraductal component in the current German guideline [13]. However, the impact of the margin width is probably overestimated [14]. A larger margin is associated with decreased failure risk, but the advantage decreases with increasing width and is small and mostly insignificant (table 3). On the basis of large data sets, an optimal margin width of about 2 mm has recently been

recommended for ductal carcinoma in situ and invasive cancers in patients undergoing excision and adjuvant radiotherapy [8].

Impact of Re-Resection

Most guidelines recommend a re-resection in case of insufficient margin width in the pathological specimens [13]. However, there is no clear scientific basis for this recommendation. In particular, there are no prospective data – especially no data from randomized trials – that demonstrate a benefit of a re-resection in comparison to leaving the situation as it is. The impact of a positive margin status might suggest that changing an R1 status to an R0 status by a re-resection might improve local control. However, the prognostic impact must not necessarily result from the surgery but could be caused by different biological behavior, e.g. the more aggressive tumors are more likely to have an R1 resection. This would mean that an R1 resection is not a mechanistic problem but reflects a biological problem that cannot be solved by surgery alone. Nevertheless, a re-resection with the objective of achieving an R0 situation is justified due to the negative impact of an R1 status.

The situation is more difficult if the tumor has been completely removed with free margins in the initial excision. There are several arguments against a re-resection in these patients:

- In patients with an R0 resection, the difference in local failure rates between patients with close margins and patients with wider margins is small. In a retrospective investigation of 1,046 patients with close (≤ 2 mm free margin) or positive margins after first excision, the local control was 95% in patients with no further excision and 94% in patients with re-excision; residual tumor was found in one-third of re-excision specimens, but this was correlated to other unfavorable prognostic factors such as an extensive intraductal carcinoma component (EIC) and node positivity [15].
- In case of a re-resection, residual tumor is found in the re-resection specimen in about 30% of patients, irrespective of where the re-resection has been performed [16].
- Multiple resections may increase the uncertainty for optimal definition of the target volume of the radiotherapy boost. As the boost has a clear impact, its quality and efficacy should not be decreased by a less important procedure.

Impact of Radiotherapy and Impact of a Boost

Radiotherapy can effectively reduce the risk of local recurrence. The large Early Breast Cancer Trialist' Collaborative Group (EBCTCG) meta-analysis has demonstrated that radiotherapy to the whole breast after breast-preserving surgery prevents 2 out of 3 recurrences [17]. An additional boost

Table 1. Impact of margin status (R0 versus R1) and radiotherapy on local tumor recurrence in patients undergoing breast-conserving surgery

	Nodal-negative patients, no systemic therapy (n = 2232)	Nodal-positive patients with systemic therapy (n = 1250)
Impact of R1 resection versus R0 resection on local recurrence rate, hazard ratio	1.93, p = 0.01	0.99, p = 0.49
Impact of radiotherapy versus no radiotherapy on local recurrence rate, hazard ratio	4.13, p < 0.0001	2.67, p = 0.02
Population-based analysis from Denmark: Ewertz et al. 2008 [11].		

Table 2. Impact of margin status (R0 versus R1) on local tumor recurrence in patients undergoing breast-conserving surgery

	Local recurrence after 10 years	
	pN0 (n = 461)	pN+ (n = 312)
R0 resection	12%	12%
R1 resection	28%, p < 0.01	18%, n.s.
Besana-Ciani et al. 2008 [10]. n.s = Not significant.		

Table 3. Wider margins are not associated with significantly better local control after breast-conserving surgery for invasive breast cancer

	Impact on local tumor recurrence rate, hazard ratio (confidence interval)
> 1 mm versus ≤ 1 mm	0.69 (CI: 0.28–1.69), n.s.
> 2 mm versus ≤ 2 mm	0.90 (CI: 0.44–1.84), n.s.
Population-based analysis from Manitoba: Hardy et al. 2008 [21]. CI = Confidence interval, n.s. = not significant.	

Table 4. Summary on the impact of breast radiotherapy and a boost as compared to margin status on local recurrence rate after tumorectomy

Parameter		Reduction of local recurrence rate, hazard ratio	Significance
Breast XRT	45–50 Gy vs. no RT	~0.33	highly significant, LOE IA
Boost	Boost vs. no boost	~0.50	highly significant, LOE IA
Margin involvement	R0 vs. R1	~0.50–0.70	marginally significant, LOE II
Margin width in case of free margins	close versus wide	~0.80–1.00	not significant, LOE II
RT = Radiotherapy, LOE = level of evidence.			

with 10–16 Gy can further reduce the recurrence by a factor of about 2 [18]. Thus, radiotherapy is surely more important than the margin status. After complete tumor removal, radiotherapy is surely more important than additional surgical procedures (table 4). Moreover, radiotherapy can be delivered under defined quality criteria with high standards even on a nationwide basis [18, 19].

Summary and Recommendations

Optimal local control is a major goal in breast-preserving therapy. It increases not only the chance of breast preservation, but has an impact on overall survival at least in a subset

of patients. Radiotherapy (whole breast irradiation plus a boost) is the most important procedure for improving local control after complete tumor excision. There is currently no evidence that re-resections or a certain margin width improve local control significantly or in a comparable manner as radiotherapy. Therefore, optimal delivering of radiotherapy should not be compromised in the multidisciplinary treatment of breast cancer.

Disclosure Statement

The authors have no conflict of interest to declare.

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