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*ORIGINAL ARTICLE*

# Significance of the resection margin and risk factors for close or positive resection margin in patients undergoing breast-conserving surgery

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## Summary

***Purpose:*** *While positive resection margin (RM) in women undergoing breast-conserving surgery (BCS) represents a clear indication for re-resection, there is no unequivocal recommendation regarding the extent of the clear RM. The aim of this study was to define the optimal extent of the RM and the risk factors for close or positive RM.*

***Methods:*** *Patients scheduled for BCS had diagnosis confirmed before BCS (lumpectomy and quadrantectomy) by core biopsy. Sentinel lymph node biopsy followed BCS, and in case of positive findings axillary lymph node dissection followed. According to RM patients were categorized into 4 groups: 1) Patients with positive RM; 2) Clear RM < 2 mm; 3) Clear RM of 2-5 mm; and 4) RM > 5 mm. In the first 3 groups where re-resection was indicated, the presence of tumor cells in the re-resection specimen was determined. All patients were followed for local recurrence.*

***Results:*** *330 patients undergoing BCS were studied. Median follow up was 39.6 months (range 12-70). Lumpectomy was performed in 111 cases and quadrantectomy in 219. In 19 cases the final procedure was mastectomy due to the impossibility to achieve negative RM. In 78 cases re-resection followed the primary procedure due to close or positive RM. Clear RM was < 2 mm in 12 cases (15%), 2-5 mm in 56 (72%) and positive margin in 10 (13%). Positive re-resection specimen was detected in 31 cases (39.7%) (in 10 cases with positive RM after primary procedure, in 3 with negative margin < 2 mm and in 18 with 2-5 mm margin). The re-resection rate according to the location of the primary tumor was 77% (n=60) in the upper outer quadrant, 8% (n=6) in the lower outer quadrant, 6% (n=5) in the upper inner quadrant, 4% (n=3) in the lower inner quadrant, and 5% (n=4) in centrally located tumors. Multicentric/multifocal tumor was diagnosed in 16 cases from which re-resection was indicated in 12 cases (75%). The number of re-resection according to tumor size was as follows: Tis 8 cases (30.7%), T1a none, T1b 14 (20.2%), T1c 34 (22.5%), T2 22 (28%). Re-resection was performed in 8 cases (31%) of ductal carcinoma in situ (DCIS), in 53 (22%) of ductal carcinoma, in 10 (37%) of lobular carcinoma, and in 7 (15%) of other histology. Five cases with local relapse were detected during follow up.*

***Conclusion:*** *The generally recommended clear RM of 1-5 mm is not sufficient because of the high number of positive specimens in the case of clear RM of 2-5 mm. The risk factors for close or positive RM are multicentric tumors and upper outer location of the primary tumor. Longer follow up will be needed to analyze local relapse rate according to RM status.*

**Key words:** breast cancer, breast-conserving surgery, resection margin

## Introduction

BCS is a generally accepted alternative to mastectomy in the treatment of early breast cancer. Although prospective trials have demonstrated that survival rates after BCS are identical to those after mastectomy [1], higher rate of local recurrence in BCS remains a significant issue [2]. The local relapse rate increases with time. The main risk factor for local relapse is a positive RM, and during long term follow up the relapse rate doubles in the case of positive RM [3]. However, there is no consensus regarding definition of clear RM. It is

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generally recommended to obtain at least 1-2 mm margin [4,5]. Proper pathological examination of RM is time-consuming, making the perioperative examination difficult. Barthelmes et al. calculated that a 6 μm resection slide through the largest diameter of a 2 cm tumor represents only 1% of the tumor surface. The complete examination of the tumor surface would require 3000 such slides [6]. The RM is examined for the presence of tumor cells directly in the specimen or the shaving of the cavity [1,6-11]. In case of tumor cells being present in the resection line, re-resection is indicated. The re-resection rate may be up to 60% [6,8,9,12]. Re-resection increases the risk of wound infection, prolongs the duration of hospitalization and increases the treatment cost.

The primary aim of this study was to define the optimal RM; the secondary aim was to define the factors which increase the rate of positive RM [13,14].

## Methods

In this prospective study included were 330 breast cancer patients undergoing BCS from January 2004 to December 2009 at the Department of Surgery, Atlas Hospital, Zlin. This number represents 82.9% of all breast operations performed during that period. The Local Ethics Committee approved the study and all patients were asked to sign informed consent.

*Inclusion criteria*

The main study inclusion criteria were women with indication for BCS. Indication for BSC: 1) Tumor size T1, T2; 2) Patients have agreed to receive radiotherapy; 3) No distant metastasis (Table 1).

The patients were divided into 3 groups according to the RM: 1) Positive RM signifying tumor cells in the resection line; 2) Clear RM < 2 mm; and 3) Clear RM 2-5 mm.

*Operations*

The surgical procedures were divided into lumpectomy and quadrantectomy with regard to the tumor size. Lumpectomy included resection of the tumor with 1.5 cm RM. All 6 sides of the specimen were pathologically examined. Quadrantectomy was conducted in larger tumors with the same margin including skin and fascia pectoralis and the pathologist examined only 4 sides (5th side of the quadrantectomy specimen is the skin and 6th side m. pectoralis). In all procedures axillary nodes were examined either with sentinel lymph node biopsy or axillary dissection. In case of positive sentinel lymph node biopsy, axillary node dissection followed. Re-re-

**Table 1.** Tumor characteristics and re-resections

| *Characteristics* | *N* | *%* | *Re-resection, N* | *%* |
|---|---|---|---|---|
| Surgery | 330 | 100 | 78 | 100 |
| Stage | | | | |
| 0 | 19 | 6 | 9 | 11.5 |
| I | 101 | 30 | 28 | 35.9 |
| IIA | 63 | 49 | 20 | 25.6 |
| IIB | 33 | 10 | 13 | 16.7 |
| IIIA | 5 | 2 | 5 | 6.4 |
| IIIB | 0 | 0 | 0 | 0 |
| IIIC | 9 | 3 | 3 | 3.9 |
| Histology | | | | |
| DCIS | 26 | 8 | 8 | 31 |
| Ductal Ca | 232 | 70 | 53 | 22 |
| Lobular Ca | 27 | 8 | 10 | 37 |
| Others | 45 | 14 | 7 | 15 |
| Pathological tumor size | | | | |
| Tis | 24 | 7 | 8 | 10 |
| PT1mic | 2 | 0.6 | 0 | 0 |
| pT1a | 7 | 2 | 0 | 0 |
| pT1b | 69 | 21 | 14 | 18 |
| pT1c | 151 | 46 | 34 | 44 |
| pT2 | 76 | 23 | 22 | 28 |
| pT3 | 1 | 0.4 | 0 | 0 |
| Positive nodes | 98 | 29.6 | 41 | 52.6 |
| Lymphatic/vascular invasion - positive | 75 | 22.7 | 22 | 28.2 |
| Estrogen receptor positive | 195 | 59 | 47 | 60.2 |
| Progesterone receptor positive | 204 | 61.8 | 54 | 69.2 |
| Her 2/neu positive | 42 | 12.7 | 8 | 10.3 |
| Grade | | | | |
| 1 | 64 | 19.4 | 12 | 15.3 |
| 2 | 185 | 56 | 52 | 66.7 |
| 3 | 81 | 24.6 | 14 | 18 |

Ca: carcinoma, mic: microinvasive carcinoma

section was carried out in all cases when the histologically verified clear margin was < 5 mm and repeat surgery was carried out until a margin of at least 5 mm was obtained. In case no clear margin was obtained after second re-excision, mastectomy was performed. Operations were performed by one surgeon, and only in few cases by two surgeons. Standard adjuvant therapy followed in all patients with invasive tumors and, if indicated, also in tumors *in situ*. Adjuvant therapy included radiotherapy with minimal dose of 50 Gy and tumor bead boost of 16 or 10 Gy, and adjuvant chemotherapy or hormonal therapy administered according to the standard guidelines. Histopathological classification (hematoxylin-eosin staining), immunohistochemical staining, including hormone receptor expression, Ki67 expression and Her-2 status were routinely determined.

*Statistical considerations*

Association between clinical and pathological parameters, including tumor location, age, multicentricity and multifocality, histopathological classification, tumor size, and whether re-resection was performed (yes vs. no) were examined using the Fisher's exact test. The data of categorical variables were directly entered into a 2×2 contingency table. The data of continuous variables were first dichotomized and then entered into 2×2 contingency tables. Subsequently, the analyses were performed using NCSS Software (Number Cruncher Statistical Systems, Kaysville, UT, USA), and the decision on statistical significance was based on $p < 0.05$. Fisher's exact test is only available for 2×2 tables, and is based on the following rationale: given the marginal frequencies in the table, and assuming that in the population the two factors in the table are not related, how likely is it to obtain cell frequencies as uneven or worse than the ones that were observed? For small *n*, this probability can be computed exactly by counting all possible tables that can be constructed based on the marginal frequencies. Thus, the Fisher's exact test computes the exact probability under the null hypothesis of obtaining the current distribution of frequencies across cells, or one that is more uneven. Both one-sided and two-sided probabilities can be calculated.

## Results

The average patient age was 59 years (range 25-88). Median follow up was 38 months (range 12-70). Lumpectomy was performed in 111 (34%) cases and quadrantectomy in 219 (66%). If the clear RM was < 5 mm, re-resection followed, till clear RM > 5 mm was obtained. In case the re-resection clear margin was < 5 mm mastectomy followed. Re-resection was indicated in 78 out of 330 patients (23.6%). In patients undergoing lumpectomy, re-resection was indicated in 27 (24%) cases. Re-resection after quadrantectomy was necessary in 51 (23%) cases. Of the whole group of 330 patients undergoing BCS, positive axillary nodes were detected in 98 (29.6%) patients. In the group of 78 re-resections the sentinel node was positive in 39 (50%) cases. Positive RM was observed in 10 (13%) cases, clear RM < 2 mm in 12 (15%) cases, and clear RM 2-5 mm in 56 (72%) cases. Positive re-resection margin was diagnosed in 31 (39.7%) cases from 78 re-resections and was followed by repeat resection (Table 2). In case the re-resection clear margin was < 5 mm, mastectomy followed. No more than 2 re-resections were performed. BCS as a final surgical procedure was performed in 311 (94%) cases; mastectomy followed in 19 (5.7%.) patients in whom no clear margin could be obtained. In all 19 patients, mastectomy contained residual tumor cells. Re-resection of the cavity was performed only for the positive sides to avoid unacceptable cosmetic effect. In 51 (65%) cases only one side of the cavity was positive for tumor cells. Only 4 patients had 4 positive sides. There was no case with > 4 positive sides.

Risk factors for close or positive resection margins (Table 3).

*Localization of the tumor*

Re-resection or mastectomy were performed in tumors located in the upper outer quadrant (77%), in the lower outer quadrant (8%), in the upper inner quadrant (6%), in the lower inner quadrant (4%) and in 5% in tumors with central location.

*Age*

Six patients were < 35 years (range 25-34). The tumor size in this group was 4-33 mm and re-resection was performed in 3 (50%) ($p=0.09$). In one case no clear margin by re-resection was achieved and mastectomy was carried out.

*Neoadjuvant chemotherapy*

BCS after neoadjuvant chemotherapy was performed in only 9 cases and in 2 of them re-resection followed.

**Table 2.** Indications for re-resection and mastectomy

| *Re-resection or mastectomy* | *Number of cases (%)* | *Number of specimens positive for tumor cells (%)* |
|---|---|---|
| Positive margin | 10 (13) | 10 (32) |
| Clear margin < 2 mm | 12 (15) | 3 (10) |
| Clear margin 2-5 mm | 56 (72) | 18 (58) |

**Table 3.** Risk factors for close or positive resection margin

| *Risk factors* | *p-value* |
|---|---|
| Location of the tumor in UOQ | 0.02 |
| Age < 35 years | 0.09 |
| Multicentric/multifocal carcinoma | < 0.00001 |
| DCIS | 0.13 |
| Tumor size | 0.13 |

UOQ: upper outer quadrant, DCIS: ductal carcinoma in situ

*Multicentricity and multifocality*

Multicentric/multifocal carcinoma was found in 16 cases and in 12 of them re-resection followed, (75% of all multifocal/multicentric cases, $p < 0.00001$) and 15.3% of all re-resections.

*Histopathological classification*

Re-resection was performed in 8 out of 26 cases of DCIS (31%), in 53 (22%) cases of ductal carcinoma, in 10 (37%) cases of lobular carcinoma, and with in 7 out of 45 (15%) cases with other histologies.

*Tumor size*

The risk of re-resection was higher in DCIS compared to invasive tumors, but this difference did not reach statistical significance ($p=0.13$). In general, the risk of re-resection increased with T stage: Tis: 8 (30.7%), T1a: 0 (0%), T1b: 14 (20.2%), T1c: 34 (22.5%), T2: 22 (28%).

## Discussion

The primary aim of this study was to find the optimal clear RM, based on the presence of tumor cells in the re-resection specimen. The patients were divided into 3 groups: those with positive resection line, with RM< 2 mm, and RM 2-5 mm. The total number of re-resections was 78, (23.6% of all performed surgical procedures). The presence of tumor cells in the re-resection specimen was the reason for re-resections. We found positive re-resection specimens in 39.7% of all re-resections which correspond to published data (3-70%) [6,8,9,12]. Re-resection specimens in patients with positive RM contained tumor cells in 100%. With 2 mm clear RM the re-resection specimens contained tumor cells in 25% and with 2-5 mm in 32.1%. Mastectomy as final surgical procedure was performed in 7 cases and all specimens contained tumor cells. No case of mastectomy without finding of tumor cells in the specimen was observed in the present study. Papa et al. reported 18% and Keskek et al. 34% of mastectomy specimens negative for tumor cells after mastectomy [7,15]. These results demonstrate the role of primary mastectomy in some cases.

The secondary aim of our study was to find out the risk factors for close or positive RM and adjust the primary surgical procedure to avoid re-resections. Data published so far yielded conflicting results with regard to risk factors identification. The risk factors most often related with positive RM after BCS are tumor size, age, grade, multifocality and multicentricity, diagnostic biopsy, neoadjuvant chemotherapy, and lobular carcinoma histopathology [6,8,9,11,12,14-27]. The risk of re-resection significantly increases with tumor size. Cellini et al. reported increasing rate of residual tumor cells in the specimen after resection of tumors with diameter ≤ 2 cm [10]. On other hand, Tartter et al. noted higher number of re-resection in smaller tumors (1.4-1.7 cm) [18]. In the present study the number of re-resections increased with tumor size and was highest in T2 tumors (30%). Lobular carcinoma is often presented as risk factor for re-resection [7,19,21,26]. DCIS is also considered as risk factor [9,12,17,19,26]. Younger patients are more often asking for BCS even if the tumor size and histopathology are not favorable for this option [6,11,18]. Age under 35 years is generally considered as risk factor [28], however there are no data regarding optimal RM extent in younger patients [28]. In the present study the re-resection rate in patients under 35 years was 50%, with high rate of mastectomy and high rate of more positive sites of the specimen. The re-resection rate in patients younger than 35 years was not statistically significant, but the patient sample was small. BCS after neoadjuvant chemotherapy is a challenge, since the histopathological examination of the tumor specimen after chemotherapy is quite difficult. The B-18 study reported local relapse rate 10.7%, and in patients with pathological complete response 7.6%. However, in women previously planned for mastectomy, where the surgical procedure was changed to BCS after neoadjuvant chemotherapy, the local relapse rate was 16% compared with 6.9% in women scheduled in the first place for BCS [29]. Bonnadona et al. reported the same local relapse rate for patients after BCS with or without neoadjuvant chemotherapy - 7% [30]. Veronesi et al. found 5.9% local relapse rate after neoadjuvant chemotherapy followed by mastectomy and 21% in BCS [31]. In patients with multicentric/multifocal tumors re-resection was necessary in 75% of the cases; and multicentricity/multifocality was proven as a statistically significant risk factor [6,12,15,17]. Positive nodes, higher grade, lymphatic invasion, and triple negative phenotype are generally considered to decrease the probability of obtaining clear resection margin and the re-resection rate is higher [3,9,10]. The local relapse rate is important indicator of correct selection of patients for BCS and of quality of surgical care including adjuvant radiotherapy and systemic therapy. The local relapse rate in our study was low (1.51%), but the follow-up was short. Keskek et al. reported a similar cohort of 248 patients with median follow up of 38 months and local relapse rate of 2.8% [7].

## Conclusion

The presented data demonstrate that the generally recommended clear RM of 1-2 mm may not be sufficient because of the high number of positive specimens in the case of re-resection of tumors with clear RM 2-5 mm. Paradoxically, for RM 2-5 mm the specimens were positive in higher rate than in the case of clear RM < 2 mm. When re-resection is not performed because of clear RM after initial surgery with a margin less than 5 mm, 32.1% of such cases still harbor tumor tissue in the breast. The risk factors for close or positive RM are multicentricity, upper outer location of the primary tumor, while DCIS, lobular histology and T stage were associated with a trend of increased risk of re-resection. Longer follow up will be needed to analyse local relapse rates based on clear RM.

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