# Significance of resection margin as a risk factor for local control of early stage breast cancer

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**Introduction.** Breast conserving surgery combined with sentinel node biopsy represents currently the gold standard of treatment for early breast cancer. Although breast conserving surgery has been a widely accepted method for many years, there remain some highly controversial unresolved issues. The present analysis focused on the resection margin as one of the key factors for local control of the disease.
**Methods.** Patient disease free survival and overall survival were collected from patients undergoing breast conserving surgery from 2004 to 2009 at the Department of Surgery Atlas hospital Zlin, Czech Republic. All patients with resection margin less then 5 mm were re-resected to achieve this clear resection margin of 5mm or more. Disease free survival (more specifically local relapse free survival, metastasis free survival and regional free survival) and overall survival were assessed.
**Results.** The data on 330 patients were analyzed and 286/330 cases had complete follow-up. After a median follow-up of 70 months, 7 patients with isolated local relapse were identified (2.44%), 13 patients with distant metastasis without local relapse (4.54%) and 2 patients with relapse in the axilla without local relapse in the breast (0.7%).
**Conclusion.** The final decision about the extent of resection margin remains controversial but based on the data on local control presented here it seems reasonable to increase the criteria for a clear resection margin to 5 mm.

**Key words:** breast cancer, resection margin, local relapse

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## INTRODUCTION

In patients with early stage breast cancer, breast conserving surgery followed by adjuvant radiotherapy represents a safe therapeutic alternative to the rather mutilating modified radical mastectomy[1-2]. This approach has been thoroughly investigated and is supported by many randomized studies. Today it is accepted as the gold standard[3-4]. Adjuvant radiotherapy together with clear surgical resection margins both significantly decrease the local relapse rate and consequently, improve overall survival. They remain the principal factor that determines local relapse rate[5]. The primary objective of breast surgery is to obtain clear resection margins and, at the same time, achieve favorable cosmetic outcome. It is self-evident that surgery can significantly decrease patient quality of life[6]. Although the clinical team has to weigh carefully the cosmetic outcome, the biology of the tumor should also be considered. The decision on treatment strategy should be made by a multidisciplinary team including surgeon with training in oncological surgery, medical oncologist, radiation oncologist, radiologist and pathologist[7]. Despite the fact that for the treatment of early stage breast cancer, radical mastectomy or modified radical mastectomy have been replaced by breast saving procedures, including quandrantectomy, lumpectomy and tumorectomy, these new techniques have raised some questions that have not yet been resolved. One of the principal issues is the extent of clear resection margins[6]. As mentioned above, a clear resection margin is one of the key factors determining local relapse and, at the same time, the cosmetic outcome. However, the exact extent of resection margin remains controversial. Positive resection margins, i.e. tumor cells present in resection line, represent a generally accepted indication for re-resection. However, in the case the resection margin is between 1 mm to 10 mm, there are no clear recommendations and clinical teams are usually follow institutional guidelines[7]. The reason for the absence of consensus is the lack of randomized trials. The published data are often contradictory and confusing. Importantly, re-resections increase morbidity as well as the cost of the surgery. Local relapse rate is a reliable indicator of the long-term success of local management. At the Department of Surgery, Atlas Hospital, Zlin where this study was conducted, re-resection is routinely performed if the free resection margin achieved is less than

5 mm. Although there is a strong feeling that this approach may impact the local relapse rate, the proof for this practice has been missing. At the same time, long term experience and patient feedback indicate that an acceptable cosmetic outcome may still be achieved in the majority of patients even if the 5 mm free resection margin rule is followed. It should be kept in mind that the final therapeutic outcome is the result of multidisciplinary collaboration between the specialists involved and even if the surgeon performs outstanding surgery, satisfactory outcome will not be achieved if radiotherapy or systemic adjuvant treatment are suboptimal, or vice versa[7]. The aim of this retrospective study was to investigate whether the 5mm free resection margin has any impact on local relapse rate by comparing our data with that published on resection margin and local relapse rate.

## PATIENTS AND METHODS

A prospective database at the Department of Surgery Atlas Hospital Zlin included breast cancer patients undergoing breast conserving surgery between the years 2004 and 2009. Breast cancer diagnosis was established before surgery with core-cut biopsy. Two principal breast-saving procedures performed included lumpectomy and quadrantectomy. In the case of lumpectomy, all six sides of the tumor specimen were assessed for resection margins. In the case of quadrantectomy, four sides were assessed as the fifth side is constituted of subcutaneous tissue and, in the case of close proximity, skin was also resected. The sixth side was pectoral fascia.

In all patients treated with breast saving surgery, sentinel node biopsy procedure or axillary dissection were performed, and in the case of metastasis in the sentinel lymph node, axillary dissection followed. In the case of non-palpable lesions, the surgeon was present during ultrasonography examination, marking on the skin the tumor location. The institutional guidelines mandate free resection margins of 5 mm or more because, as outlined above, these clear margin are believed to impact disease free survival. In the case the resection margin was positive for tumor cells or less than 5 mm, a re-resection was completed. During the re-resection procedure, only affected cavity walls were re-resected. If re-resection did not achieve a free resection margin of 5 mm or more, mastectomy was subsequently performed. In all patients treated with breast saving surgery, adjuvant radiotherapy followed together with adjuvant chemotherapy or hormonal therapy according to the National Comprehensive Cancer Network guidelines. For adjuvant radiotherapy, linear accelerator Elekta synergy was used, using 3-D conformal planning, energy 6-18 MeV or Microselectron brachytherapy equipment for tumor bed boosting. The radiotherapy dose was 50 Gy for whole breast with additional boost for tumor bed (either 16 Gy in 2 Gy fractions using external beam radiotherapy or 12 Gy in 1 fraction using interstitial brachytherapy technique). All patients were followed for local and distant relapse over a 3 month interval during the first 3 years, at a 6 month interval in the next 2 years and then yearly. Clinical examination was performed during each visit, mammography yearly, liver ultrasound and chest X-ray yearly. Tumor markers CEA and Ca 15-3 were determined. Other tests and examinations were performed as clinically indicated. Disease free survival and overall survival data were collected after a minimum of a 5 year follow up. All patients lost from the database were contacted and questioned for cancer status. General practitioners were contacted in the case of patient death to find out the exact cause of death. However, since the information gathered from general practitioners and patients over the phone were considered unreliable, we have not included these patients in the final analysis for local relapse calculation despite the fact that all contacted patients were disease free.

## RESULTS

The data on 330 breast cancer patients between 2005 and 2008 who underwent breast conserving surgery at the Department of Surgery, Atlas Hospital, Zlin, Czech Republic were analyzed in the present study. Most patients had T1 and T2 tumors and only one patient had T3 disease. Twenty-four patients with in situ carcinoma and 9 patients who underwent neoadjuvant chemotherapy before the surgical procedure were also included. The mean age of the patients was 59 years, ranging from 25 to 88 years. All patients met the general indication criteria for breast-conserving surgery at this department, including tumor size of less than 5 cm (one patient with marginal T3), no distant metastasis, no multicentric tumor, and willingness to undergo adjuvant radiotherapy. In the case of T3 tumors neoadjuvant chemotherapy was administered and 9 patients after neoadjuvant chemotherapy were included in the analysis. Tumor characteristics are summarized in Table 1. Lumpectomy was performed in 111 patients, and

**Table 1.** Tumor characteristics.

| | Number of patients |
|---|---|
| TNM Stage | |
| 0 (TIS) | 19 |
| I | 101 |
| IIA | 63 |
| IIB | 33 |
| IIIA | 5 |
| IIB | 0 |
| IIIC | 9 |
| **Tumor Size** | |
| TIS | 24 |
| pT1mic | 2 |
| pT1a | 7 |
| pT1b | 69 |
| pT1c | 151 |
| pT2 | 76 |
| pT3 | 1 |
| **Total number** | **330** |

TIS – tumor in situ – non invasive cancer

quadrantectomy in 219 patients. After careful assessment of tumor resection margin, the margin was less then 5mm in 78 cases (23.6%). Re-resection followed in these patients, and in 31 cases the re-resection specimen contained tumor cells. After s database search, we identified 286 patients (286/330) who were undergoing regular check-ups or for whom the data on death or disease progression were available. Forty-four patients were lost to the follow-up due to movement to another city and hospital or for unknown reasons that obviated obtaining relevant clinical information on the status of the disease. As mentioned above, all patients lost to follow up, were contacted over the phone or the general practioner was contacted to find out the status of the disease. No cases of local or distant relapse were identified. The median follow-up of these patients was 70 months. After 70 months of follow up, 7 patients with isolated local relapse were identified (2.4%), 13 patients with distant metastasis without local relapse (4.5%), and 2 patients with regional relapse in the axilla without local relapse in the breast (0.7%). After 5 years of follow-up, 6 local relapses (2.0%), 11 distant relapses without local relapse (3.9%) and 2 regional relapses in axillary nodes (0.7%) were identified. After reviewing all seven patients with local relapse, we found that 2 patients had rejected the recommended adjuvant radiotherapy. All patients with local or regional (nodal) relapse were indicated for surgical therapy followed by radiotherapy in the case the radiotherapy was not performed as part of the primary breast cancer treatment. Only in one patient was local relapse followed early by distant metastasis, and systemic treatment was preferred over local treatment in this case.

## DISCUSSION

The data show that meticulous attention to tumor resection margins during breast cancer surgery with re-resection in the case of tumor resection margins of less than 5 mm as well as the use of adjuvant radiation therapy and systemic treatment, results in a very low local relapse rate. Among 286 patients with complete follow-up data, 7 patients with local relapse were identified after a median follow-up of 70 months which means the local relapse rate of 2.45%. To be able compare our results with published data, a 5 year disease free interval was assessed. After 60 months of follow up, 6 local relapses were identified (2.0%), 11 distant metastasis without local relapse (3.9%), 2 regional relapses (in axillary lymph nodes) without local relapse (0.7%). This relapse rate compared favorably with other published data. After analysis of 533 stage I and stage II breast cancer patients with close margins or negative margins and 7% local relapse rate at 8 years, Park et al. concluded that pathological margin status together with adjuvant therapy are the major predictors of local relapse[8]. Kunos et al. did a retrospective study of 341 stage I and II breast cancer patients to determine the rate of local relapse in relation to resection margin. After 54 months of follow-up, the recurrence rate was 1.8% in the case of tumor free margin more than 2 mm versus 8.4% in patients with tumor free margin between 0 mm and 2 mm (ref.[9]). Kreike et al. reported an ipsilateral recurrence rate of 9.3% after 10 years and 13.8% after 15 years allowing us to conclude that resection margin and lymphovascular invasion are the most important factors for local recurrence[10]. Mirza et al. observed 6% local relapse rate after 9 years in patients with stage I and II disease[11]. Miles et al. studied the impact of age on local control in 3064 breast cancer patients with a median follow up of 8.9 years. The local recurrence rate was 11.4 % in patients younger than 40 years, 5.7% in patient group 40-49 years, 6.2% in patients 50-59 years of age, 60% in patients 60-69 years old and 6.2% in patients older than 70 years[12].

A weak point of the present analysis is a relatively high proportion of patients lost to follow-up that may evoke some uncertainty about the outcome in the whole cohort. However, the general practitioner or the patient was contacted in all these cases to rule out recurrent disease. Thus, the actual recurrence rate is even lower than in the cohort of patients with complete follow-up.

In breast cancer surgery, there are currently different recommendations regarding the resection margins, with some authors preferring the wider margins, underscoring the malignant nature of the disease, while others pointing out the growing importance of cosmetic outcome of the surgery. The recommended range of the clear resection margin between 1 and 10 mm is extremely wide, and guidelines agree only on the necessity of re-resection in case of positive margin[7,13,14,15]. In a previous study that aimed to determine what percentage of the cavity re-resection specimen contain tumor cells in the case re-resection is performed until clear resection margin of at least 5 mm is obtained, we reported that around 30% of specimen re-resected to achieve 5mm free resection margin will contain tumor tissue[16]. From these data, it is clear that resection margin less than 5 mm is definitely not sufficient to achieve tumor negative breast after surgical procedure[17-18]. The other important question is, however, whether obtaining free resection margin will have an impact on local recurrence rate and subsequently on overall survival of breast cancer patients[19-27]. All patients undergoing breast conserving surgery are indicated for adjuvant radiotherapy (considering that adjuvant radiotherapy may be omitted in older patients[28]). The effect of adjuvant radiotherapy for local tumor control is supported by a large number of randomized trials and its role currently seems to be unquestionable[29]. The outcome of early stage breast cancer patients is excellent with more then 90% surviving 5 years, but there may be still a space for improvement. This improvement may be achieved by more precise surgery aiming for wider clear resection margin that, together with adjuvant radiotherapy, could provide even better results as disease free survival and possibly overall survival. As mentioned above, after supportive data from a previous study we decided to evaluate the local relapse free survival in this group of patients in the case the clear resection margin 5 mm is achieved. We always have to keep in mind the importance of cosmetic outcome of breast surgery[18]. We also have to consider the fact that the isolated local relapse does not have to impact

the overall survival since the local relapse may be successfully treated by local surgery or radiotherapy. On the other hand, local relapse remains a negative prognostic indicator[30-31]. At the same time, local relapse may negatively affect the quality of life and, possibly, patient compliance during further follow-up or adjuvant treatment.

## CONCLUSION

The strategy of 5 mm resection margin is associated with very low local recurrence rate. However further research is needed to provide clear recommendations regarding optimal free resection margin during breast-conserving surgery.

## CONFLICT OF INTEREST STATEMENT

**Author's conflict of interest disclosure:** *None declared.*

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