

# Local control in 118 consecutive high-risk breast cancer patients treated with breast-conserving therapy

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**Abstract.** Although negative surgical margins are an important prognostic factor in the breast-conserving treatment of breast cancer, the required width of these margins is still under debate. To define the risk of in-breast recurrence in subgroups of patients with a local high-risk situation, local control was evaluated in all patients with close or positive margins treated at one institution between 1995 and 2000. A total of 118 patients (67% T1, 30% T2, 52% N0) were identified as having had positive or close margins ( $\leq 4$  mm) at the time of initial surgery. Of these, 65% had no tumor cells at the initial margin, 35% had a positive or questionable margin. Re-excisions were performed in 42%. The median (range) whole-breast radiotherapy dose, tumor bed boost dose and total dose were 50 (46.8-56) Gy, 15 (8-20) Gy and 65.8 (54-71) Gy, respectively. Thirty-six percent received adjuvant chemotherapy. Local (in-breast) control was calculated by the Kaplan-Meier method and compared between subgroups. The 5-year local control for the whole group was 94%. The rates for selected subgroups were:  $<56$  years 89.4% vs.  $>56$  years 98.1% ( $p=0.073$ , univariate analysis); pT1 95.9% vs. pT2 88.6% (not significant, n.s.); pN0 96.6% vs. pN+ 90.8% (n.s.); initial margin free of tumor cells 95.5% vs. initial margin involved or questionable 90.7% (n.s.), no re-excision 96.7% vs. one or more re-excisions 90.6% (n.s.); adjuvant chemotherapy 81.7% vs. no adjuvant chemotherapy 100% ( $p=0.007$ ). We conclude that among patients with close or positive margins, older patients achieved high local control rates with a median tumor-bed boost to 66 Gy. Younger patients and patients who received adjuvant chemotherapy (due to the presence of histopathological risk factors)

were at increased risk of in-breast recurrence and should be considered for intensified local treatment.

## Introduction

The surgical resection margin represents an important risk factor for local recurrence in breast cancer treated with breast-conserving surgery and post-operative radiotherapy (1,2). Although there is an international consensus that clear margins should be obtained by surgery before the initiation of radiotherapy, the definition of such negative margins varies, due to the different inclusion criteria applied in the randomized trials establishing the standard of breast-conserving therapy (3-7). In a recent international survey of 1133 radiation oncologists, the definition of 'no tumor cell at the margin' was considered an adequate description of a 'negative margin' by 46% of North Americans, but only 28% of Europeans, whereas the most frequently chosen definition among European radiation oncologists was 'no tumor cell within 5 mm of the margin' (8). The national treatment guideline of the German Cancer Society calls for a margin of 1 mm or more from the invasive or intraductal tumor component (9).

To elucidate the risk of in-breast recurrence in subgroups of patients with initially close or positive margins, with or without re-excision, we performed a retrospective analysis of local control in 118 consecutive women with a high-risk post-operative margin status.

## Materials and methods

**Patients and treatment.** The database of all breast cancer patients treated with a breast-conserving approach at the Department of Radiation Oncology, University of Würzburg, Germany, between 1995 and 2000 was searched for those patients in whom 'close margins' or 'positive margins', regarding invasive carcinoma cells, were documented for the initial surgical procedure. In 47 of 118 patients (39.8%) thus registered, the margin of the initial resection was stated in mm. In these, the margin was always  $\leq 4$  mm ( $\leq 2$  mm in 43 of 47). The remaining patients were classified by the pathologists as having had 'close', 'very close' or 'positive' margins without a statement regarding the exact margin width. In cases where the surgical and pathology reports (including those of re-resection) did not permit us to judge whether

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Table I. Patients characteristics of n=118 patients treated with breast-conserving therapy.

Mean $\pm$ SD age (range)	56 $\pm$ 12 years (28-88)
T stage	
T1	67%
T2	30%
T3	1%
T4	2%
N stage	
N0	52%
N1	36%
N2	4%
Nx	8%
Grading	
G1	3%
G2	58%
G3	24%
n.a.	15%
Estrogen receptor	
Positive	67%
Negative	33%
Initial surgical margin status	
No tumor cells at margin	65%
Margin involved/questionable	35%
Initial surgical margin width, median (range)	1 (0-4) mm
Final surgical margin (including reexcision)	
No tumor cells at margin	73%
Margin involved questionable	27%
Number of reexcisions	
None	58%
One	35%
Two	7%

there were actually tumor cells at the resection margin, the status was considered 'questionable'. The n=118 patients thus identified represent 12.1% out of a total number of 968 patients treated with radiotherapy as part of a breast-conserving approach during the respective time period. Clinical charts of the radiation oncology and gynecology departments, including surgical and pathology reports, were reviewed for patient and treatment characteristics.

Patient characteristics of the n=118 consecutive patients fulfilling the above criteria are given in Table I. Treatment characteristics are listed in Table II. The median total dose to

Table II. Treatment characteristics of n=118 patients treated with breast-conserving therapy.

Total RT dose whole breast, median (range)	50 (46.8-56) Gy
Boost technique	
Electrons	95%
Interstitial brachytherapy	5%
Total RT boost dose, median (range)	15 (8-20) Gy
Cumulative total RT dose, median (range)	65.8 (54-71) Gy
Chemotherapy	
CMF	20%
EC	16%
Hormonal therapy	
Tamoxifen	50%
Other	9%

the whole breast was 50 (46.8-56) Gy. Tangential photon techniques were used, the predominant photon energies were 5 MV (38%) and 10 MV (53%). Fraction doses were 1.8 Gy (14%) or 2 Gy (86%). The median total boost dose was 15 (8-20) Gy, in 95% of patients given via electrons, resulting in a median total dose of 65.8 (54-71) Gy. A total dose of 60-70 Gy was received by 93.2% of patients. Thirty-six percent of patients received chemotherapy, 59% hormonal therapy. The mean follow-up interval was 6.6 $\pm$ 1.4 years.

*Statistical analyses.* To determine the rate of in-breast recurrence, follow-up notes in these charts were reviewed and treating gynecologists and general physicians were contacted. In cases of known or suspected in-breast recurrences, detailed information including mammograms and further surgical and pathology reports was reviewed.

Local control was calculated for the whole group and subgroups according to the Kaplan-Meier method. In-breast recurrence was considered an event. Patients who died without in-breast recurrence or were alive without in-breast recurrence were censored at the respective time interval. Local control of subgroups was compared by Wilcoxon rank test. Selected parameters were tested in a multivariate Cox regression model. Patients consented to anonymous data analysis as part of the treatment contract with the university hospital.

## Results

A total of eight in-breast recurrences were observed, resulting in a crude local control rate of 93.2%. The actuarial 5-year local control rate, according to Kaplan-Meier, was 94%. When subgroups according to patient or treatment charac-

Parameter	5-year local control (%)	p-value
Age (years)		
≤56	89.4	0.073
>56	98.1	
T stage		
pT1	95.9	0.16
pT2	88.6	
N stage		
pN0	96.6	0.7
pN+	90.8	
Grading		
G2	93.6	0.34
G3	89.5	
Initial margin		
No tumor cells at margin	95.5	0.40
Involved/questionable	90.7	
Final margin		
No tumor cells at margin	94.7	0.56
Involved/questionable	91.8	
Estrogen receptor		
Positive	93.8	0.58
Negative	94.6	
Re-excision		
None	96.7	0.6
One or more	90.6	
Total RT dose (Gy)		
≤60	96.5	0.22
>60	92.7	
Adjuvant chemotherapy		
Yes	81.7	0.007
No	100	
Adjuvant hormonal therapy		
Yes	93.7	0.4
No	94.4	

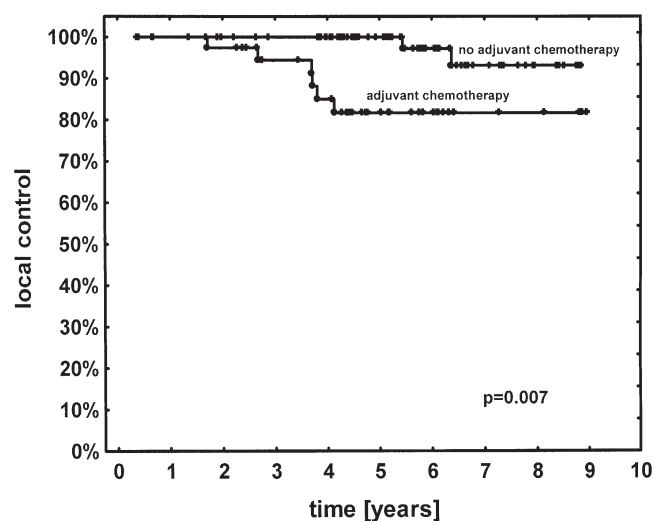


Figure 1. Local control according to administration of adjuvant chemotherapy.

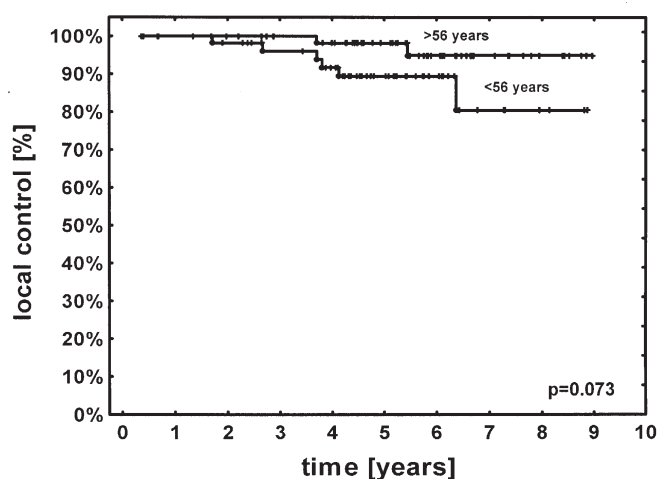


Figure 2. Local control according to age group.

significance ( $p=0.073$ ). Lower local control rates were also seen in patients with other prognostic factors (higher T or N stage, higher grading, higher radiotherapy dose) but these differences were not significant.

When the two parameters with  $p<0.1$  were entered into a multivariate Cox model, administration of chemotherapy remained of borderline significance ( $p=0.062$ ) whereas age lost significance ( $p=0.63$ ). In a model with these parameters and the known risk factors total RT dose, final resection margin and T stage, the administration of chemotherapy ( $p=0.11$ ) and the other factors were not significant.

## Discussion

In the present analysis of in-breast tumor control after breast-conserving treatment in patients registered as having had 'close' or 'positive' margins, a rather low local recurrence rate of 6% at five years was observed. Obviously, the low number of events in this six-year experience from a high-

teristics were compared (Table III), only the administration of adjuvant chemotherapy was associated with significantly increased local recurrence rates on univariate analysis (Fig. 1). Younger patients ( $<56$  years) also had higher local recurrence rates (Fig. 2), this finding was of borderline

volume university department represents a limitation of statistical analysis of prognostic factors for in-breast control. In subgroup analyses, only the administration of adjuvant chemotherapy was linked, on univariate analysis, to a significantly increased local recurrence rate of 18.3% at five years. Interestingly, not a single in-breast recurrence was observed after five years in patients not receiving adjuvant chemotherapy. This association of local control and chemotherapy administration was lost on multivariate analysis and is, therefore, most likely due to the selection of patients for adjuvant chemotherapy who had a combination of risk factors such as higher T stage, higher N stage, higher grading, younger age and negative estrogen receptor status. Except for estrogen receptor status, each of these factors alone was associated with a slightly, but not significantly, lower local control rate. The association of younger age (<56 years) alone with local control was of borderline significance on univariate analysis ( $p=0.073$ ).

In the time period under investigation, the local policy for radiotherapy after breast-conserving surgery was to give 50 Gy whole-breast and 10 Gy boost radiotherapy to patients with wide negative margins and 50 plus 16 Gy boost to patients with close or positive margins. There was, however, no fixed limit in mm to define 'close' margins and definitions of close or negative margins have not been uniformly applied in the international literature (8). For the purpose of the present analysis, only patients with margins described in the pathology report as involved, 'close' or 'very close' or were included. In the cases where margin width was stated in mm, this was always  $\leq 4$  mm, mostly  $\leq 2$  mm.

To compare the present results with published data, it must be considered that the majority of the 'high-risk' patients analyzed now would have been regarded as standard risk in some clinical trials in which only the absence of invasive carcinoma at the inked margin was required. This was the case in the EORTC 'boost vs. no boost' trial in which patients were randomized to receive a 16-Gy boost or no boost to the tumor bed after 50 Gy of whole-breast therapy (10). In the two arms of that trial, the re-excision rate was about 25% compared to 42% in the present series. In the boost arm, the total dose of which is comparable to the mean total dose of this series, the 5-year local control rate was 95.7%, with a strong age dependence ( $\leq 40$  years: 89.8%, 41-50 years: 94.2%, 51-60 years: 96.6%,  $\geq 61$  years: 97.5%). In the present series, where age groups were split at the median of 56 years, local control was similar to the EORTC data for the older group (98.1% at five years) but apparently worse for the under-56-year-olds (89.4%). This suggests that the margin status is especially critical in younger patients, whereas a boost dose of approximately 16 Gy can compensate for close margins in older patients.

Other authors have published the outcome of a strict 'margin-directed' policy in 498 patients, where boost doses were 10 Gy (margin  $>5$  mm), 14 Gy (2-5 mm) or 20 Gy (positive or  $<2$  mm) (11). In case of a re-excision showing no residual tumor no boost was given. With this approach, 12-year local control rates were 83% (positive margin), 91% (margin  $>0$  mm to 2 mm), 95% (2-5 mm), 100% ( $>5$  mm) and 94% (re-excision without residual tumor). These data confirm that increased boost doses cannot generally compensate

for positive or very close margins but also suggest that a negative histology on re-excision is not equivalent to initially wide negative margins.

In another recent analysis, the six-year local control after predominantly 50±10 Gy in 535 patients was 97% in patients with negative ( $>2$  mm) margins, but 83%, 78% and 15% in patients with positive, close ( $\leq 2$  mm) or indeterminate margins, respectively, emphasizing the recurrence risk associated with close or uncertain margin status in the context of standard boost doses (12).

Within our study cohort, young age is the one pre-treatment factor most strongly linked to poor local control. A subsequent analysis of the above-mentioned EORTC trial showed that young age was correlated with a higher prevalence of adverse prognostic factors (tumor size, grading, receptor status, initial incomplete resection in order to preserve the breast) but that only young age and radiotherapy dose remained significant in a multivariate analysis (13). The authors suggested, that the worse local control in younger patients might be explained by a different biologic and genetic background of these tumors. Molecular markers and gene expression profiling approaches to predict the probability of distant metastasis in individual breast cancer patients have been developed (14-16) and more recently the estimation of the local recurrence risk has been addressed in such studies (17). For patients 50 years or younger, an international randomized trial comparing boost doses of 16 and 26 Gy is currently recruiting patients (18).

In conclusion, a satisfactory local control rate of 94% at five years was achieved in 118 consecutive patients with close, uncertain or positive margins applying a mean total dose of 66 Gy. However, patients in whom adjuvant chemotherapy was administered and patients under 56 years of age achieved local control at five years only in 81.7 and 89.4%, respectively, suggesting that intensified local treatment should be considered in subgroups of patients with close or positive margins.

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