CLINICAL TRIAL

Factors predicting in-breast tumor recurrence after breast-conserving surgery

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Abstract *Purpose*: The main objectives of this study were to identify risk factors for local in-breast tumor recurrence after breast-conservation and to evaluate the impact of IBTR (in-breast tumor recurrence) on overall survival. *Methods*: A total of 335 consecutive patients with 346 invasive and in situ breast cancers were treated with breast conserving therapy. Univariate and multivariate statistical analysis were performed and survival rates were calculated and analyzed using the Kaplan–Meier method. *Results*: With a median follow-up period of 70.6 months 14 patients (4%) developed an IBTR. Overall survival and the disease-free 8-year actuarial survival of patients were 95% and 93%, respectively. The overall survival of patients with tumour recurrence on any site was significantly shorter than of those without recurrence (64% versus 85% after 8 years of follow-up; $P < 0.0001$). Similarly, overall survival was significantly reduced in patients with distant metastases compared to all others without distant disease (88% versus 40% after 8 years; $P < 0.0001$). In contrast, overall survival of patients who experienced IBTR did not differ significantly from the group of patients who never developed IBTR (87% versus 70% after 8 years of follow-up). By univariate analysis, lobular carcinoma, high grade tumours, multifocality, concomitant LCIS and DCIS, the absence of estrogene and progesterone receptor status, as well as R1-status, were significant predictors of IBTR. By multivariate analysis, only R1-status ($P < 0.002$) and the presence of LCIS around the invasive tumour ($P < 0.03$) remained as significant factors predicting IBTR. *Conclusions*: Concomitant lobular carcinomas in situ, as well as R1 surgical status are independent significant risk factors for in breast tumor recurrence after breast conserving therapy.

Introduction

Surgical therapy for breast cancer has significantly developed over the past three decades. During the 1970s, Fisher in New York and Veronesi in Milano, Italy, revolutionized the surgical treatment with the paradigm shift from the standard modified radical mastectomy towards breast conservation (i.e. lumpectomy and adjuvant radiotherapy). The results of two large randomized controlled series have firmly established the principle of breast conservation being equally safe and effective as mastectomy for the majority of patients with stage I and II disease [1, 2], while achieving cosmetically superior results. Moreover, 20 and 25-year follow-up series for breast conserving therapy have further confirmed that, compared to mastectomy, breast conserving therapy (BCT) achieved an identical survival rate [3, 4].

During breast conservation (also known as lumpectomy, segmental mastectomy or wide local excision), the tumor is removed with a disease free margin. Although the minimal size of tumor free resection margin is not definitively identified, there is compelling evidence that positive resection margins lead to an increased rate of local in-breast recurrence [5–7].

Two etiologic types of ipsilateral, so-called in-breast tumor recurrence (IBTR) exist:(i) True local recurrences develop from cancer cells that have not been completely

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removed during surgery; (ii) new primary tumors are defined as new cancers arising from the residual ipsilateral breast parenchyma [8].

Adjuvant percutaneous radiation therapy significantly reduces the rate of local recurrences, and data from this overview published in 2002 indicate that the addition of radiation therapy also improves overall survival [9].

While radiotherapy clearly reduces the rate of IBTR, the following factors have been attributed to increase the risk of IBTR: Young age at the time of primary therapy [10, 11], high tumor grade [12–15], specific histological types, for example concomitant LCIS [16], lympho-vascular invasion [10, 12–15, 17], extensive intraductal component (EIC) [10, 13, 14, 17–20] and the lack of adjuvant systemic therapy like hormone- and chemotherapy [1, 21]. Concerning EIC, two main studies have demonstrated, that providing clear margins, there is no increased rate of local recurrence in patients with EIC [5, 6].

The objective of our study was to analyze a prospectively maintained database for factors influencing postoperative IBTR and survival.

Materials and methods

Between January 1990 and December 2004, 335 patients with 346 invasive and in situ breast cancers were treated with breast conserving therapy at the Department of Surgery, University Hospital Basel. All patient's data have prospectively been entered into a computerized database. Bilateral tumors were observed in 11 patients (3.3%). At the time of diagnosis, the patients had a median age of 54.2 years (range 41.5–81.3 years).

The surgical procedure consisted of a quadrantectomy or lumpectomy with axillary nodal staging for invasive cancers. Axillary lymph node dissection of level 1 and 2 was performed during the first study period until 1998. In 1999, sentinel lymph node procedure was introduced at the University Hospital Basel [22]. After a validation period, standard axillary lymph node dissection was only performed if macrometastases were found in the excised sentinel lymph node or when the sentinel lymph node could not reliably be identified.

Adjuvant chemotherapy or hormonal therapy was performed according to the newest St. Gallen consensus available at the time of treatment [23]. Generally, patients with advanced stage carcinomas were offered an adjuvant chemotherapy, neoadjuvant chemotherapy or in selected cases both of them.

The majority of patients (82.6%) underwent adjuvant radiation therapy to the breast; 4 Patients (1.2%) were treated in a neoadjuvant setting by breast irradiation; 54 patients did not receive radiation; this either because of

denial from the patient or histological subtypes. Radiation therapy was administered with a total dose of 50.4 Gy to the whole breast (5×1.8 Gy weekly). Patients younger than 60 years with R0 excision received an additional boost dose of 10 Gy (5×2 Gy for one week) to the tumor bed. Patients with close margins (<3 mm) received a boost dose of 20 Gy (5×2 Gy weekly) to the tumor bed irrespective of age. Patients older than 60 years with R0 excision received no additional boost dose on contrary to patients with close margins (<3 mm) excision who received a boost dose of 20 Gy (5×2 Gy weekly). Boost doses were only applied to the tumor bed. Radiation therapy to the whole breast was administered using photons, and to the tumor bed using electrons.

In order to classify also the tumors with skin infiltration according to latest standards, the new TNM classification was used [24].

This study has been approved by the regional Ethical Committee responsible for the University Hospital Basel.

Statistical analysis was performed with the STATISTICA software package (Statsoft Inc. Tulsa, Oklahoma, U.S.A.). The Mann–Whitney-U test was used for univariate analysis of continuous variables when comparing two independent groups, and the chi-squared test for 2×2 categorical tables. Clinical and pathological factors that have been tested significantly by univariate analysis underwent multivariate analysis using the Cox regression model. Survival curves were calculated according to the Kaplan–Meier life-table method with differences in survival curves tested by the log-rank test. Patient's characteristics are listed and described in Table 1.

Results

Median follow-up was 70.6 months (range 7–190 months). 11 out of 346 patients (3.2%) suffered from distant metastases and 14 (4.0%) had developed IBTR. The overall survival and the disease-free 8-year actuarial survival of patients were 95% and 93%, respectively (Fig. 1).

The overall survival of patients with tumour recurrence on any site was significantly shorter than of those without recurrence (64% versus 85% after 8 years of follow-up; $P < 0.0001$; Fig. 2). Similarly, overall survival was significantly reduced in patients with distant metastases compared to all other patients without distant disease (88% versus 40% after 8 years; $P < 0.0001$; Fig. 3). In contrast, overall survival of patients who experienced IBTR did not differ significantly from the group of patients who never developed IBTR (87% versus 70% 8 years of follow-up), as shown in Fig. 4.

By univariate analysis, lobular carcinoma, high grade tumours, multifocality, concomitant LCIS and DCIS, the

Table 1 Cases characteristics ($N = 346$)

Characteristics	No.	%
Age group (years)		
Median age		
20–40	24	6.9
40–60	161	46.5
60–80	149	43.1
>80	12	3.5
Staging		
T1	210	60.7
T2	97	28.0
T3	1	0.3
T4	6	1.7
Tis	28	8.1
Unknown	4	1.2
Node status		
N0	249	71.9
N1	71	20.5
N2	10	2.9
N3	3	0.9
NX	10	2.9
Unknown	3	0.9
M status		
M0	331	95.7
M1	1	0.3
Mx	13	3.6
Unknown	1	0.4
Grading		
G1	75	21.7
G2	151	43.6
G3	98	28.3
Unknown	22	6.4
Histopathological type		
Invasive ductal	233	67.3
Invasive lobular	37	10.7
Tubular	19	5.5
Mucinous	10	2.9
Medullary	10	2.9
Invasive ductulolobular	8	2.3
Non invasive Adenoca	29	8.4
R-status (including peritumoral DCIS)		
R0	320	92.5
R1	25	7.2
R2	1	0.3
Lymphovascular invasion		
Yes	79	22.8
No	265	76.6
Unknown	2	0.6

Table 1 continued

Characteristics	No.	%
Extensive intraductal component		
Yes	24	6.9
No	310	89.6
Unknown	12	3.5
Localisation		
Left breast	181	52.3
Right breast	165	47.7
Axillary dissection		
Yes	201	58.1
No	137	39.6
Unknown	8	2.3
ER status		
Yes	264	76.3
No	54	15.6
Unknown	28	8.1
PR status		
Yes	222	64.2
No	100	28.9
Unknown	24	6.9
Hormone therapy		
Yes	240	69.4
No	87	25.1
Unknown	19	5.5
Chemotherapy		
Neoadjuvant	3	0.9
Adjuvant	60	17.3
Neoadjuvant + Adjuvant	2	0.6
No	280	80.9
Unknown	1	0.3
Radiotherapy		
Neoadjuvant	4	1.2
Adjuvant	288	83.2
No	54	15.6

absence of estrogene and progesterone receptor status, as well as R1-status, were significant predictors of IBTR. In contrast, nodal status was not a predictive factor for IBTR (Tables 2, 3).

By multivariate analysis, the R1-status ($P < 0.002$) and the presence of LCIS around the invasive tumour ($P < 0.03$) remained as significant factors predicting IBTR (Table 4).

The treatment of IBTR consisted of mastectomies (9 out of 14) or yet another breast conservation (4 out of 14). Due to denial of therapy, one patient's IBTR was not treated at
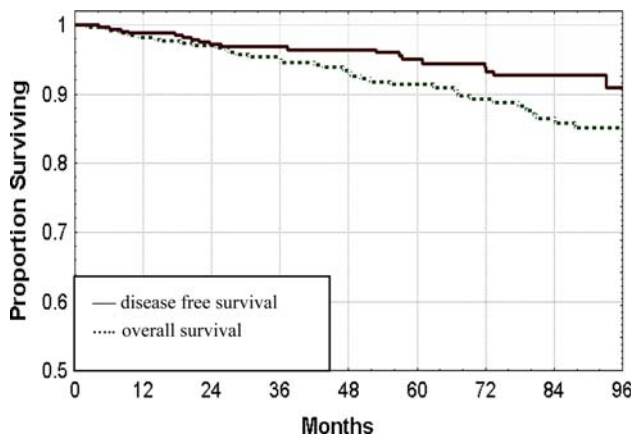
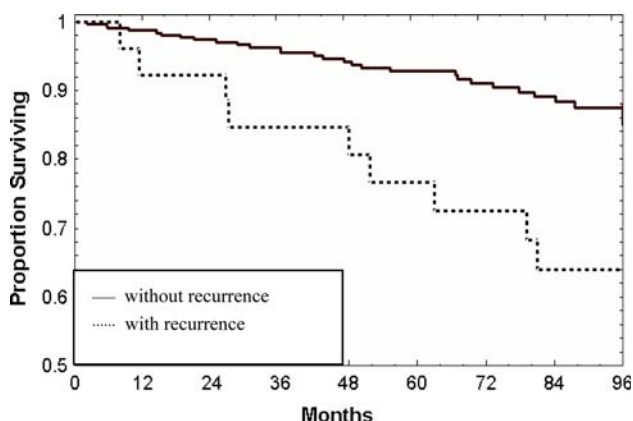**Fig. 1** Overall survival and the disease-free actuarial survival

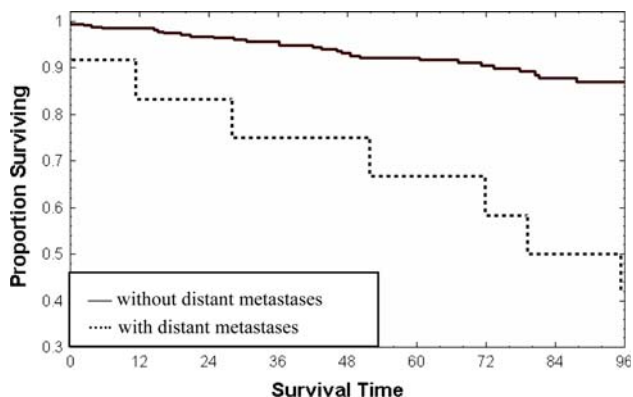**Fig. 2** Overall survival of patients with tumour recurrence on any site and without recurrence

Fig. 3 Overall survival in patients with distant metastases and all other patients without distant disease
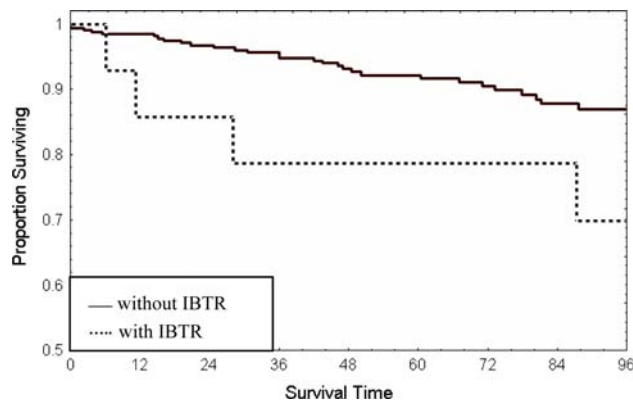
Fig. 4 Overall survival of patients with IBTR and without IBTR

Discussion

Since Fisher [1] and Veronesi [2] have established the equality in outcome of breast-conserving surgery followed by radiation therapy compared to modified radical mastectomy, BCT has become standard of care for early breast cancer. The search for identification of relevant risk factors for local tumor relapse (i.e. IBTR) has widely been made but is still ongoing. The purpose of this study was to explore a prospectively maintained database of 346 consecutive patients with primary breast cancer undergoing BCT from 1990 to 2004 at the Department of Surgery, University Hospital Basel, and to examine potential risk factors for IBTR and their prognostic influence on patient's overall survival and also to compare them with published material.

In the current study we used an univariate and a multivariate analysis of the collected data material in order to detect factors predicting for the occurrence of IBTR. We found that several significant tumor characteristics were predictive for IBTR including lobular carcinoma, high tumor grade, R1-status, absence of estrogene and progesterone receptors and concomitant LCIS and DCIS using the univariate analysis. Multivariate analysis revealed that only concomitant LCIS and positive microscopic margins (R1-status) remained independent predictors of IBTR.

IBTR rate was 4% after a median follow-up of 70.6 months in our study. The previously reported percentage of IBTR varies from 1.3% [25] to 8.5% [26]. Cabioglu et al. [25], explain their low number (IBTR rate 1.3%) with a decrease of IBTR in patients <50 years within a specific time range in their observation period. In our study we couldn't find a lower incidence of IBTR in younger patients. We therefore assume it to be the reason for our higher IBTR rate.

Komoike et al. [26] reported patients treated before 1993 and described a 8.5% rate of IBTR within a median follow-up period of 107 months. This is a considerable longer median follow up compared to our study

all. In both groups, mastectomies and breast conservation, one second recurrence has been reported. The pattern of all recurrences is demonstrated in Table 5 and the course of disease of patients with IBTR is shown in Table 6.

Table 2 Analysed categorical factors according to in-breast tumour recurrence

Factors		IBTR (n = 14)		No IBTR (n = 332)		Statistical significance
		N	%	N	%	
Histology						
Lobular carcinoma		4	29	33	9.9	P < 0.03
All other carcinomas		10	71	299	91.1	
Grading						
G1 and G2		8	57	331	99.7	P < 0.0001
G3		6	43	1	0.3	
Multifocality						
Yes		4	29	25	7.5	P < 0.02
No		10	71	307	92.5	
Concomitant in situ carcinoma						
DCIS		11	89	151	45.5	P < 0.02
No DCIS		3	21	181	54.5	
LCIS		4	29	17	5.1	P < 0.0001
No LCIS		10	71	315	94.9	
Receptor status						
Estrogene	Positive	8	57	266	80.1	P < 0.02
	Negative	6	43	66	19.9	
Progesterone	Positive	5	36	236	71.1	P < 0.01
	Negative	9	64	96	28.9	
Margin status						
R 0		11	89	310	93.4	P < 0.04
R 1		3	21	22	6.6	
Nodal status						
N0		11	89	238	80.8	N.S.
N+		3	21	64	19.2	

Table 3 Analysed non-parametric factors according to in-breast tumour recurrence

Factors	IBTR		No IBTR		Significance
	Median (Min; Max)		Median (Min; Max)		
Patient age at operation (years)	54	(41.5; 81.3)	59	(29.7; 92.8)	N.S.
Tumour diameter (mm)	21.7	(20; 48)	16.0	(1; 73)	N.S.
Resection margin (mm)	3.5	(<1; 8)	2.0	(<1; 25)	N.S.

Table 4 Results from multivariate analysis

Variable	P value
EIC	0.65
Resection margin	0.47
Tumor size	0.24
Tumor grading	0.47
R-status	0.001
Nodal-status	0.07
Multifocality	0.71
Concomitant DCIS	0.36
Concomitant LCIS	0.025
Positive ER-status	0.29
Positive PR-status	0.41

Table 5 Anatomic distribution of tumour recurrence

Recurrence		Lymph node	IBTR	Distant metastases
Lymph node	4 (1.2)	2	1	1
IBTR	14 (4.0)	1	11	2
Distant metastases	11 (3.1)	1	2	8
Total	27 (7.8)	4	14	11

(70.6 months). Another study [27] matching well the median follow-up in Komoike's work is reporting an IBTR rate of 7.5%. They observed their patients until 1993 with a follow up period of 103.2 month. Nottage et al. [28] reported an IBTR rate of 6% after a follow-up of

Table 6 Course of disease after IBTR

Nr.	Interval to IBTR (months)	Therapy	Interval from 1st to 2nd recurrence (months)	Therapy	Alive	Year of death
1	18	Lumpectomy + AD	125 (IBTR)	Mastectomy	X	
2	20	Mastectomy	24 (Scar)	Tumorectomy + RT	X	
3	49	Mastectomy			X	
4	4*	Mastectomy				1999
5	97	Mastectomy + AHT				2006
6	9*	Mastectomy + AHT				2005
7	72	Mastectomy + AHT			X	
8	73	Tumorectomy	40 (Bones and Pleura)		X	
9	26	Mastectomy			X	
10	152	Mastectomy			X	
11	6	No therapy				1996
12	110	Tumorectomy + HT			X	
13	20	Mastectomy + NCT + ACT + NRT				2002
14	57	Lumpectomy			X	

*, additional distant metastases; AD, axillary dissection; NCT, neoadjuvant chemotherapy; ACT, adjuvant chemotherapy; AHT, adjuvant hormone therapy; DM, distant metastases; NRT, neoadjuvant radiotherapy

130.8 months but they included patients only with free margins in their study. Compared to our study, the higher median follow up periods and the time period where the patients were treated, may have caused the higher reported IBTR rates in these three studies.

One publication is closer to our study setting and may display a better comparison: The work of Elder et al. [29], who also observed a similar period of time, found a IBTR rate of 4.9% with a follow up time of 48 months.

Probably due to the limited number of patients in our study, we could not demonstrate a statistically significant association of IBTR with poorer overall survival, as has been demonstrated by Fortin et al. [30].

One of the most important factors influencing the risk for IBTR is the pathologic margin status after BCT [31]. Positive surgical margins seem to be relevant predictors for systemic recurrence as well [32]. In our study we could confirm that R1 resection was a statistically significant predictor of IBTR. Of note, the resection margin in the cases with IBTR was rather wider than in cases without IBTR. This demonstrates, that adequate excision of the tumor was accomplished and that the margins chosen, had probably no impact on IBTR in our patients.

Although no clear guidelines concerning re-resection of breast tissue have been determined, common practice aims today at achieving microscopically free margins of more than 1 mm [6].

More controversial than the R-status is the influence of concomitant LCIS around the invasive tumor. As opposed to Abner et al. [33] who have shown no significant difference between patients with concomitant LCIS in the tumor bed and without, we could elucidate that presence of LCIS has a significant influence on IBTR. Therefore, LCIS when present with invasive breast cancer should carefully be controlled during follow up. In addition, the impact of other adjuvant modalities such as hormonal therapy in the management of LCIS should be discussed as suggested by Fisher et al. [16]. This theory is also confirmed by the work of Jolly et al. [34], whose conclusion is, that LCIS may have significant premalignant potential and progress to an invasive IBTR at the site of index lesion.

Although several studies in the past have shown young age as a significant risk factor for IBTR [11] we could only show a trend towards this direction. We assume that the smaller number of cases in the present study, compared to Elkhuizen's [11], might be a relevant reason for that.

In conclusion, with an observed IBTR rate of 4% our results lay within the frequency range of IBTR in published data. Moreover, we could implement that the impact of concomitant LCIS and R1-margins are independent predictors for IBTR.

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