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Clinical Investigation

Pattern of Ipsilateral Breast Tumor Recurrence After Breast-Conserving Therapy

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Summary

The rate of ipsilateral breast tumor recurrence (IBTR) in breast cancer after breast-conserving therapy was analyzed. We demonstrate that after 12 years' follow-up, there is an especially high recurrence rate for women ≤40 years old. For women ≤40 years old, the absence of adjuvant systemic therapy and the presence of lymph vascular space invasion (LVSI) are associated with a higher rate of IBTR. For women >40 years old, the presence of LVSI and lobular carcinoma in situ are prognostic factors for IBTR.

Purpose: To analyze the incidence and prognostic factors of ipsilateral breast tumor recurrence (IBTR) after breast-conserving therapy (BCT) in a large, population-based, single-center study with long-term follow-up.

Methods and Materials: We analyzed 3595 cases in which BCT was performed in 3824 women with stage I or II breast cancer. The incidence of IBTR was analyzed over time and was based on IBTR as first event.

Results: The 15-year local relapse-free survival was 90.9%. The hazard estimates for IBTR showed a time course with 2 peaks, the first at approximately 5 years and the second, twice as high, at 12 years. Stratifying subjects by age and margin status showed that, for women ≤40 years old with negative margins, adjuvant systemic therapy led to a 5-fold reduced risk of recurrence compared to none, and the presence of lymph vascular space invasion (LVSI) had a 3-fold increased risk compared to its absence. For women >40 years old, the presence of LVSI (hazard ratio [HR] 2.5) and the presence of lobular carcinoma in situ in the lumpectomy specimen (HR 2.3) were the only 2 risk factors.

Conclusions: We demonstrated a pattern in risk of IBTR over time, with 2 peaks, first at approximately 5 years and a second, much higher peak at approximately 12 years, especially for women ≤40 years old. For women ≤40 years old with tumor-free resection margins, we noted that the absence of adjuvant systemic therapy and the presence of LVSI were independent prognostic factors of IBTR. For women >40 years old, the presence of LVSI and the presence of lobular carcinoma in situ were independent risk factors.

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Introduction

For early-stage breast cancer, breast-conserving therapy (BCT) is believed to be the treatment of choice. Treatment has evolved from primary surgery and radiation therapy to a more sophisticated method of surgery followed by radiation therapy and adjuvant systemic therapies like hormone therapy, chemotherapy, and immunotherapy. Breast cancer recurrences are seen both shortly after initial treatment and many years thereafter. Although the risk of ipsilateral breast tumor recurrence (IBTR) exists over many years, changes in recurrence risk over time have hardly received attention. In most studies, the focus has been directed at either recurrence or survival curves depicting the proportion of patients who are recurrence-free after a fixed time interval. In contrast, smoothed hazard curves depict the risk of recurrence at any given time and show how the risk of developing recurrence changes over time. The probability of relapse depends on a variety of prognostic factors (1, 2).

This study analyzed all cases of IBTR as a first event and all cases treated with BCT in our region from 1984 through 2010. In this large, population-based, single-center study, we analyzed the incidence and pattern of IBTR after BCT and prognostic factors, with a separate focus on age.

Methods and Materials

This prospective study of a cohort of breast cancer patients was started in 1984 when BCT was introduced in our region. All patients in the Twente-Achterhoek with invasive breast cancer received their irradiation at the Radiotherapy Department of the Medisch Spectrum Twentey. Using the data from 1984 through 2010, we registered a total of 3998 BCT treatments of invasive breast cancer in 3863 women. Patient data, including demographics, histology, staging information, treatment, and outcome were recorded prospectively and were updated regularly.

Histological examination of all cases was done in the Pathology Laboratory Oost Nederland according to standard procedures. For women with a local recurrence, all histology of the primary and the recurrence tissue was reviewed or updated by 1 pathologist. Patients were staged according to the TNM classification system (7th edition, 2009).

As it is often difficult, morphologically, to differentiate between a local recurrence and a new primary tumor in the treated breast, all recurrences, invasive carcinoma (IC), and/or ductal carcinoma in situ (DCIS) found in the ipsilateral breast during follow-up were classified as IBTR. For the purposes of this study, the cut-off date for analysis was February 2014.

Treatment

BCT initially consisted of lumpectomy with axillary clearance of disease levels I to III, followed by whole-breast radiation therapy and then followed by a boost aimed at the lumpectomy cavity. After 2001, axillary staging was done primarily by using sentinel lymph node procedures, followed only by complete axillary dissection in cases with proven axillary lymph node metastases or when sentinel node biopsy examination failed. Radiation therapy consisted of 50 Gy in 2-Gy fractions, administered to the whole breast, followed by a boost of 14 Gy to the lumpectomy cavity, regardless of margin status. In 16% slightly altered fractionation schedules for the boost were used. Since 2004, the indication to administer a boost dose has depended on age, lymph node status, and margin status: patients with no lymph node metastases and negative margins and a tumor size of $\leq$1.0 cm who are $>$60 years old or a tumor size of $\leq$2.0 cm and are $>$70 years old have not received a boost. Adjuvant systemic and regional radiation therapy was given according to existing treatment guidelines. Regional radiation therapy was indicated for patients with either 4 or more axillary lymph node metastases or with presence of extra-nodal disease.

In the late 1980s, adjuvant systemic therapy was given for patients with histologically proven axillary lymph node metastasis. From 1992 on, all premenopausal patients with histologically proven axillary lymph node metastasis have received chemotherapy. For postmenopausal patients, adjuvant hormone therapy was given in cases of tumor-positive axillary lymph nodes. Since 1999, the indications for adjuvant systemic therapy have depended not only on lymph node status but also on MAI, histological grade, and tumor size. Premenopausal women receive chemotherapy and hormone therapy when the estrogen receptor status is positive.

In late 2004, treatment with trastuzumab in combination with adjuvant chemotherapy was introduced in our region for HER 2-neu-positive cases.

Statistical methods

Time to recurrence and length of follow-up were calculated from the date of the lumpectomy. To test between-group differences for categorical data χ^2 tests were used, and local recurrences were analyzed in relation to the number of BCT treatments given. For all survival analyses, patients were censored if they had not experienced an event (local recurrence, distant metastasis) at the date of last follow-up or at the date of death. Local recurrence-free survival (LRFS) is defined as survival time without local recurrent disease.

The Cox proportional hazards model was used to test the independent effect after adjusting for known prognostic factors, and hazard ratios (HR) estimated with 95% confidence limits are presented.

For comparison of recurrence distributions, the log-rank test was used. Univariate variables related to the outcomes of interest ($P<.05$) were entered in the multivariate analyses. To visualize the risk of recurrence over time, HR values are plotted. Wilcoxon rank sum and McNemar tests

Table 1 Patient and tumor characteristics of 3963 cased of BCT in 3828 women at primary diagnosis according to status local control*

Characteristic	No local recurrences (n=3779) (%)	Local recurrences (n=184) (%)	*P* value†
Age (y)			
≤40	201 (5.2)	31 (16.8)	<.001
41-50	793 (20.9)	51 (27.7)	
>50	2785 (73.9)	102 (55.4)	
Family history			
Positive	922 (24.3)	41 (22.3)	NS
Negative	2843 (75.3)	142 (77.2)	
Unknown	14 (0.4)	1 (0.5)	
Histology			
Ductal carcinoma	3065 (81.3)	135 (73.4)	
Lobular carcinoma	385 (10.1)	28 (15.2)	
Medullar carcinoma	49 (1.3)	5 (2.7)	NS
Tubular carcinoma	190 (5.0)	10 (5.4)	
Other	90 (2.3)	6 (3.3)	
Malignancy grade			
1	874 (23.1)	41 (22.3)	
2	1450 (38.4)	80 (43.5)	NS
3	808 (21.4)	55 (29.9)	
Unknown	647 (17.1)	8 (4.4)	
Lymph vascular space invasion			
Positive	332 (8.8)	31 (16.8)	
Negative	3425 (90.6)	152 (82.6)	<.001
Unknown	22 (0.6)	1 (0.6)	
Presence of CIS			
DCIS	1013 (26.8)	49 (26.6)	
LCIS	204 (5.4)	20 (10.9)	.006
None	2562 (67.8)	115 (62.5)	
Mitotic activity index			
Low (<13 in 2 mm^2)	1921 (50.8)	120 (65.2)	
High (>12 in 2 mm^2)	899 (23.7)	49 (26.6)	NS
Unknown	959 (25.5)	15 (8.2)	
Hormone receptor			
ERPR positive	2427 (64.2)	129 (70.1)	
ERPR negative	516 (13.7)	27 (14.7)	NS
ER positive and PR negative	514 (13.6)	17 (9.2)	
ER negative and PR positive	73 (1.9)	6 (3.3)	
Unknown	249 (6.6)	5 (2.7)	
HER 2 status			
Positive	113 (3.0)	6 (3.3)	
Negative	1310 (35.1)	137 (74.5)	NS
Unknown	2325 (61.9)	41 (22.3)	
Re-excision			
Yes	265 (7.0)	13 (7.1)	
None	3497 (92.5)	168 (91.3)	NS
Unknown	17 (0.5)	3 (1.6)	
Margin status			
Negative	3343 (88.4)	148 (80.4)	
Positive IC	259 (6.9)	19 (10.3)	.008
Positive DCIS	137 (3.7)	13 (7.2)	
Positive IC + DCIS	40 (1.1)	4 (2.2)	
Tumor size			
pT1	2894 (76.4)	136 (73.9)	
pT2	875 (23.3)	48 (26.1)	NS
Other	10 (0.3)	0	
Lymph node status			

(*continued on next page*)

Table 1 (*continued*)

Characteristic	No local recurrences (n = 3779) (%)	Local recurrences (n = 184) (%)	*P* value†
pN0	2702 (71.4)	142 (77.2)	
pN+	996 (26.4)	42 (22.8)	NS
Unknown	81 (2.2)	0	

Abbreviations: BCT = breast-conserving therapy; DCIS = ductal carcinoma in situ; ER = estrogen receptor; IC = invasive carcinoma; LCIS = lobular carcinoma in situ; NS = not significant; PR = progesterone receptor.

* Of 217 instances of ipsilateral breast tumor recurrence, 184 occurred within 15 years.

† *P* values were calculated based on the known components of the variables.

were used for differences in time until IBTR and for within-patient differences in histological tumor characteristics between primary tumors and IBTR, respectively.

In order to analyze the above-mentioned changes in recurrence risk over time, we divided this cohort into 4 periods (1984-1991, 1992-1998, 1999-2003, and 2004-2010) according to treatment changes in 1992, 1999, and 2004.

Age and margin status were regarded as independent variables, both with major prognostic impact on local recurrence, whereas the age of 40 is generally accepted as a turning point in the risk of recurrence (3). For this reason, a separate analysis was performed of women ≤40 years old and >40 years old, both with negative margins. Analyses were performed using Stata, version 12.1 software (Stata Corp, College Station, TX).

Results

During the study period of 27 years, 6.3% (252 of 3998) IBTR cases were recorded, of which 245 had recurrence of IC and 7 with only DCIS. Of those, 14 patients showed recurrence after distant metastatic disease, and 21 instances of IBTR were observed simultaneously with distant metastases, leaving 217 cases of IBTR (5.5%). The follow-up ranged from 3 to 353 months, a median of 105 months. Analyses were carried out until the maximum follow-up period of 15 years because many patients were lost to follow-up afterward. Of the 217 case of IBTR registered as the first event, 184 occurred within 15 years, with 3963 BCTs and were used in these analyses. The median time to IBTR was 86 months.

The median follow-up for women ≤40 years old was 119 months and 104 months for women >40-years old. Tumor and patient characteristics at primary diagnosis according to the presence of IBTR are shown in Table 1. Significantly more young women developed IBTR. Also, women with IBTR showed significantly higher presence of lymph vascular space invasion (LVSI). Table 2 shows the treatment characteristics.

Local relapse-free survival and pattern

The LRFS rate for all women was 98.2% at 5 years, 95.3% at 10 years, and 90.9% at 15 years. In multivariate Cox regression analysis, the following variables were significant: women ≤40 years old (HR 3.0, 95% CI 2.0-4.5) compared to older women, presence of LVSI (HR 2.1; CI 1.4-3.1), presence of lobular carcinoma in situ (LCIS; HR 2.2; CI 1.3-3.5), presence of a positive resection margin for IC and DCIS with HRs of 1.7 and 2.0, respectively.

Figure 1 shows the hazard estimates (HE) for the IBRT rate over 15 years with a double peak, a first peak of 0.0009 after 48 months and a second one of 0.0017 after 142 months. We examined the impact of various variables on the slope of the curve. We found that the late high peak was limited to women ≤40 years old ($P<.001$) and those who did not receive adjuvant systemic therapy ($P=.114$).

We analyzed the group of patients with IBTR and focused on the histological differences between primary and IBTR (Table 3). We observed significant differences

Table 2 Treatment characteristics of 3963 cases of BCT in 3828 women at primary diagnosis according to status local control*

Characteristics	No local recurrence (n = 3779) (%)	Local recurrence (n = 184) (%)	*P* value†
Adjuvant systemic therapy			
None	2232 (58.9)	130 (70.6)	
Chemotherapy	347 (9.2)	20 (10.9)	.002
Hormone therapy	757 (20.1)	23 (12.5)	
Both	443 (11.8)	11 (6.0)	
Radiation therapy			
Breast only	3194 (84.6)	151 (82.1)	NS
Breast + regional	585 (15.4)	33 (17.9)	
Radiation therapy breast			
Boost	3502 (92.6)	177 (96.8)	NS
No boost	277 (7.4)	7 (3.8)	
Radiation therapy dose boost			
2.5/15.0 Gy	202 (92.8)	15 (7.2)	
2.0/14.0 Gy	3153 (95.2)	161 (4.8)	.022
2.66/13.3 Gy	87 (100)	0	
Other	60 (98.4)	1 (1.6)	
None	277 (97.5)	7 (2.5)	

Abbreviation: BCT = breast-conserving therapy.

* Of 217 instances of ipsilateral breast tumor recurrence, 184 occurred within 15 years.

† *P* values were calculated based on the known components of the variables.

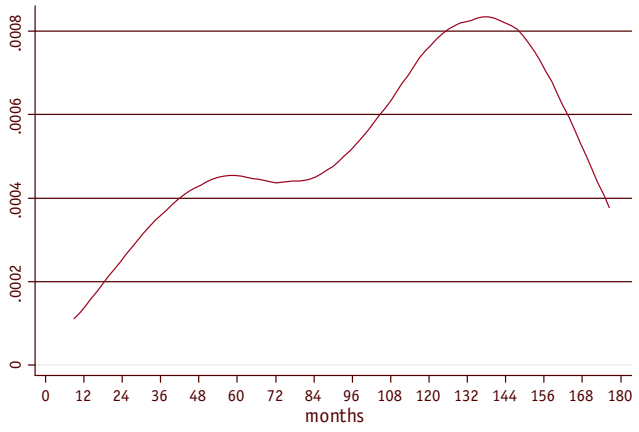

Fig. 1. Hazard estimates for IBTR over 15 years in 3963 case of BCT. BCT = breast-conserving therapy; IBRT = ipsilateral breast tumor recurrence.

between the primary tumor and recurrent diseases only for HER 2 neu status.

Analyses stratified by age, ≤40-years old >, for women with negative margins only

The IBTR rates for 233 women ≤40 years old at 5, 10, and 15 years were 4.9%, 10.2%, and 19.3%, respectively. For 3730 women >40-years old, these rates were 1.4%, 3.8%, and 7.6%, respectively.

Table 4 shows the independent significant risk factors after multivariate Cox regression analyses. Figure 2 shows the HE for IBTR over 15 years according to age with a peak of 0.0123 after 132 months for women ≤40 years old. For women >40 years old, the peak of 0.0011 appeared after 136 months and was ~10 times smaller (log rank $P<.001$). Both curves do not show a clear first peak at approximately 60 months.

Time periods for women with negative margins only

Because of the long time span of 27 years, we divided this cohort in 4 periods. The median follow-up for the subsequent periods lasted 196.5, 177.5, 129, and 65 months, respectively. Table 5 shows the characteristics for the 4 periods of those variables are significant in multivariate analyses for LRFS, including hormone status, malignancy grading, and whether a boost was given. All were different for the periods. The 5-year LRFS rates for the 4 periods were 97.0%, 98.6%, 98.6%, and 98.4% and 93.4%, 96.5%, 96.3, and 94.2% for the 10-year period, respectively. No significance was shown, although the test for trend was significant for the 5-year ($P=.028$) but not for the 10-year ($P=.0698$) period.

Figure 3 shows the HE for the 4 periods; only the third period showed a late peak after approximately 146 months, although it is not significant. This late peak of the third period was not influenced by the category of age ≤40-years old, presence of LVSI, boost dose, or margin status. Only the peak was not seen in women treated with adjuvant systemic therapy and also in women with estrogen receptor- and progesterone receptor-negative tumor status of the primary. Both variables did not show significance even when stratified for the time periods.

Table 3 Pathological characteristics of the primary versus those in recurrent tumors in 184 women with breast cancer treated with BCT

Characteristic	Recurrence (n=184) (%)	Primary (n=184) (%)	*P* value*
Histology			
Ductal carcinoma	118 (64.1)	135 (73.4)	
Lobular carcinoma	33 (17.9)	28 (15.2)	
Medullar carcinoma	0	5 (2.7)	†
Tubular carcinoma	1 (0.5)	10 (5.4)	
Rest	6 (3.3)	6 (3.3)	
Unknown	26 (14.1)		
Malignancy grade			
1	21 (11.4)	41 (22.3)	
2	80 (43.5)	80 (43.5)	.067
3	55 (29.9)	55 (29.9)	
Unknown	28 (15.2)	8 (4.6)	
Oestrogen receptor			
Positive	119 (64.7)	147 (79.9)	
Negative	28 (15.2)	33 (17.9)	.523
Unknown	37 (20.1)	4 (2.2)	
Progesterone receptor			
Positive	110 (59.8)	135 (73.4)	
Negative	37 (20.1)	44 (23.9)	.608
Unknown	37 (20.1)	5 (2.7)	
HER 2neu status			
Positive	17 (9.2)	6 (3.3)	
Negative	122 (66.3)	137 (74.5)	.013
Unknown	45 (24.5)	41 (22.3)	

Abbreviation: BCT = breast-conserving therapy.

* *P* values were calculated using the McNemar test based on the known components of the variables and for patients for whom the variables were known for both the primary tumor and the recurrent tumor.

† Could not be calculated because no medullar carcinoma was observed in the recurrent tumors.

Discussion

In this study of early stage breast cancer patients treated with BCT, we observed different patterns of relapse over a 15-year follow-up period, with a high peak at 12 years after treatment.

At 10 years after treatment, the cumulative risk for IBTR in our population was 4.8% and 9.1% at 15 years, which seems better than that in reports in the literature (4-7). Because of the long time span of 27 years of this study, we were able to investigate the influence of time on IBTR

Table 4 HR for the significant variables in the multivariate Cox regression analyses of local failure in BCT for breast cancer according to age and with negative margins

	Stratified by age		Stratified by age + negative margins	
Variable	≤40 years old HR (95% CI)	>40 years old HR (95% CI)	≤40 years old HR (95% CI)	>40 years old HR (95% CI)
Lymph vascular space invasion				
Negative	1	1	1	1
Positive	2.4 (0.9-6.0)	2.1 (1.4-3.4)	3.1 (1.1-8.4)	2.4 (1.5-4.0)
Margin Status				
Negative	1			
Positive IC	5.0 (1.3-18.7)			
Positive DCIS				
Positive IC + DCIS				
Presence of CIS				
None		1		1
LCIS		2.2 (1.3-3.7)		2.4 (1.4-4.0)
DCIS				
Adjuvant systemic therapy				
None	1		1	
Yes	0.4 (0.2-0.8)		0.3 (0.1-0.7)	

Abbreviations: CI = confidence interval; CIS = carcinoma in situ; DCIS = ductal carcinoma in situ; HR = hazard ratio; IC = invasive carcinoma; LCIS = lobular carcinoma in situ.

by dividing the cohort in 4 time periods, according to treatment changes. The results suggested a slight improvement (but not significant) over the first 5 to 10 years. In both LRFS rate and HE, we noticed less IBTR in the first years, whereas after 15 years, the opposite occurred, with higher HE for the third period. Because of the short follow-up of the fourth period, we were not able to demonstrate the late effect of this period. Over this period of the 27-year period, this finding was unexpected because we might expect a trend in improvement of the treatment results because (*1*) introduction of breast cancer screening resulted in diagnosing more smaller sized tumors; (*2*) the extension of the indications for adjuvant systemic therapy resulted in more patients being treated with adjuvant systemic therapy; (*3*) use of the markers in the lumpectomy area enabled more precise radiation therapy; and (*4*) and the development in radiation therapy from radiology simulation to computed tomography simulation allowed us to contour the surgical lumpectomy cavity as well as visualize normal structures. All this obviously did not result in a significant decrease in the IBTR rate in our series. For women older than 40 years, this might be due to the low relapse rate, and for the younger women, we have to take the small number into account. Other investigators did observe a decrease in local recurrence rates over time (6, 8, 9).

A separate analysis of the impact of the time period on LRFS was done for different variables. No significance was noted, but the late peak of the third period disappeared with adjuvant systemic therapy and with negative hormone status of the primary. We could not confirm the findings of another Dutch study demonstrating an improvement for young women (10).

In a study of 6135 unilateral breast cancer patients, including 847 BCT treatments, Yu et al (11) showed a recurrence pattern with a peak near 5 to 6 years. Another study with 1901 BCT treatments showed peaks at 2 and 4 years after surgery (12).

Demicheli et al (13), in a study of growth traits of tumor foci that eventually resulted in IBTR, compared patients who underwent lumpectomy/quadrantectomy with those who underwent quadrantectomy plus radiation therapy. The radiation therapy patients demonstrated a delay in the early risk peak compared to the cases treated with only surgery. This peak at approximately 48 months was explained by the killing effect of radiation therapy on residual tumor cells, resulting not only in a reduction of IBTR but also in some delay. The first peak in our study might be explained by the last argument, but the second, higher peak reflects a late enhancement of tumor cells in the breast. Our first peak at 48 months is comparable with that in the literature data, but as far as we know this is the first time a second peak at approximately 142 months has been shown. The latter occurrence might be due to the fact that most studies were smaller and analyzed recurrences until 10 years. We analyzed the impact of various variables on the slope of the curve. A statistical difference was noted only for women >40 years old compared to those ≤40 years old.

In our analyses of prognostic factors, young age, presence of LVSI and LCIS, and positive margins for IC and/or DCIS were shown to be independent, significant risk factors for IBTR. Age was the strongest risk factor. Among the other 3 factors, margin status was the one that could be influenced by treatment through re-excision (14). We suggest that negative margin should be made a prerequisite for completing BCT. Separate analyses were done with

Table 5 Pathological and treatment characteristics according to the 4 time periods

Characteristic	1984-1991 (n=484) (%)	1992-1998 (n=1014) (%)	1999-2003 (n=975)	2004-2010 (n=1490)	*P* value*
Age (y)					
≤40	53 (11.0)	70 (6.9)	60 (6.1)	50 (3.4)	
41-50	140 (28.9)	240 (23.7)	187 (19.2)	280 (18.8)	<.001
>50	291 (60.1)	704 (69.4)	728 (74.7)	1160 (77.8)	
Malignancy grade					
1	36 (7.4)	158 (15.6)	238 (24.4)	483 (32.4)	
2	57 (11.8)	314 (31.0)	511 (52.4)	645 (43.3)	<.001
3	97 (20.0)	192 (18.9)	224 (23.0)	351 (23.6)	
Unknown	294 (60.7)	350 (34.5)	2 (0.2)	11 (0.7)	
Lymph vascular space invasion					
Positive	41 (8.4)	116 (11.4)	71 (7.3)	136 (9.1)	
Negative	431 (89.1)	894 (88.2)	901 (92.4)	1349 (90.5)	.014
Unknown	12 (2.5)	4 (0.4)	3 (0.3)	5 (0.3)	
Presence of CIS					
DCIS	122 (25.2)	241 (23.8)	215 (22.1)	483 (32.4)	
LCIS	17 (3.5)	60 (5.9)	83 (8.5)	63 (4.2)	<.001
None	345 (71.3)	713 (70.3)	677 (69.4)	944 (63.4)	
Hormone receptor					
ERPR-positive	269 (55.6)	544 (53.6)	687 (67.4)	1086 (72.9)	
ERPR-negative	55 (11.4)	164 (16.2)	127 (13.0)	167 (13.2)	<.001
ER positive and PR negative	64 (13.2)	116 (11.4)	160 (16.4)	191 (12.8)	
ER negative and PR positive	11 (2.3)	37 (3.6)	23 (2.4)	8 (0.5)	
Unknown	85 (17.6)	153 (15.1)	8 (0.8)	8 (0.5)	
Margin Status					
Negative	427 (88.2)	860 (84.8)	852 (87.4)	1353 (90.8)	
Positive IC	34 (7.0)	87 (8.6)	67 (6.9)	89 (6.0)	<.001
Positive DCIS	13 (2.3)	50 (4.9)	44 (4.5)	43 (2.9)	
Positive IC + DCIS	10 (2.1)	17 (1.7)	12 (1.2)	5 (0.3)	
Adjuvant systemic therapy					
None	384 (79.3)	723 (71.3)	488 (50.1)	764 (51.3)	
Chemotherapy	41 (8.5)	94 (9.3)	92 (9.4)	140 (9.4)	<.001
Hormone therapy	58 (12.0)	167 (16.5)	236 (24.2)	322 (21.6)	
Both	1 (0.2)	30 (3.0)	159 (16.3)	264 (17.7)	
Breast radiation therapy					
Boost	483 (99.8)	1011 (99.7)	968 (99.3)	1217 (81.7)	
No boost	1 (0.2)	3 (0.3)	7 (0.7)	273 (18.3)	<.001

Abbreviations: DCIS = ductal carcinoma in situ; ER = estrogen receptor; IC = invasive carcinoma; LCIS = lobular carcinoma in situ; PR = progesterone receptor.

* *P* values were calculated based on the known components of the variables.

negative margins for women ≤40 years old, and we showed that the late high peak in the recurrence pattern seemed to occur mainly in women ≤40 years old. For women ≤40 years old adjuvant systemic therapy (HR 0.3) and presence of LVSI (HR 3.1) were independent risk factors.

High-grade malignancy and positive lymph nodes are often mentioned as risk factors for LF (15, 16). Even in univariate analyses, we were not able to confirm this.

One of the prognostic factors for local recurrences in women >40 years old was the presence of LCIS (HR 2.3). In our study of only 5.5% of the cases, LCIS was found in association with invasive carcinoma. This might not be a realistic score, because during the latest years of this study, the presence of LCIS was not routinely documented. In the literature, the presence of LCIS ranges from 5% to 12% (17-19). Few studies investigated the impact of the presence of LCIS in BCT. Two studies also demonstrated an increased risk for LF with the presence of LCIS (18, 19). Two other studies did not see a relationship to LF (17, 20). Considering those studies, long follow-up might be necessary to see an effect on LF.

During the study period, the radiation therapy regimen was changed slightly. Since 2004, a highly favorable group did not receive a boost anymore. This seems not to have had a negative effect on local control, although numbers were small and follow-up was (relatively) short.

When we examined IBTR as an endpoint in this study, we were aware that probably not all recurrences were true local recurrences and, particularly, not all late

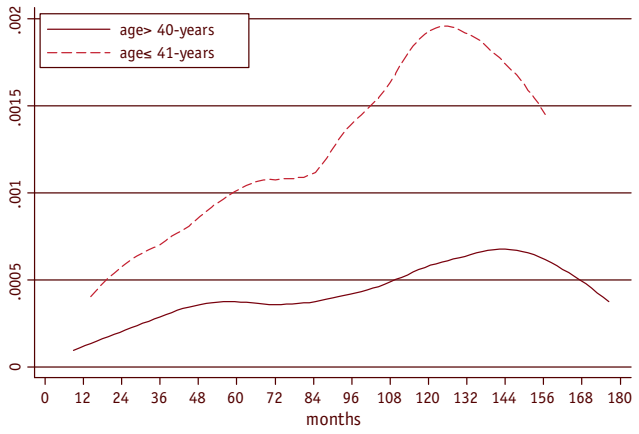

Fig. 2. Hazard estimates for IBTR over 15 years in 3489 cases of BCT with negative margins according to age category. BCT = breast-conserving therapy; IBRT = ipsilateral breast tumor recurrence.

recurrences. Finally, we looked for differences in histology between the primary and IBTR cases, and the time until the appearance of the IBTR was also taken into account. However, no clear distinction was found. Only for HER 2neu positivity was significance shown. Unfortunately for more than 20% of women, the HER 2neu status was unknown.

Conclusions

Despite our excellent IBTR rates at 5, 10, and 15 years of follow-up, we also demonstrated that even after 12 years, we observed a considerably high recurrence rate, especially for women ≤40 years old. The pattern of recurrence did not change during the study period. Our study demonstrated for women ≤40 years old that the absence of adjuvant systemic therapy and the presence of LVSI are independently associated with a higher rate of IBTR after BCT with negative

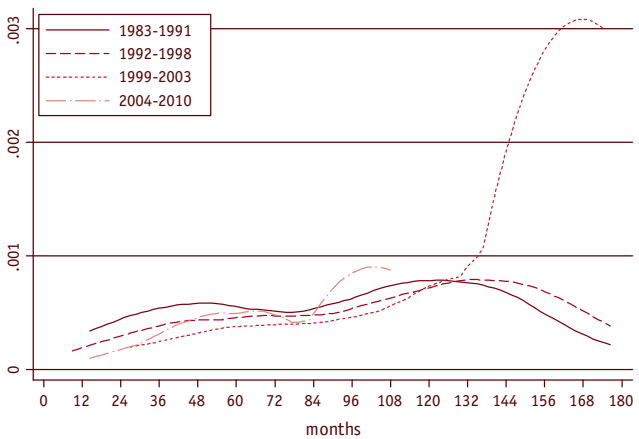

Fig. 3. Hazard estimates for IBTR over 15 years in 3489 cases of BCT with negative margins according to 4 time periods. BCT = breast-conserving therapy; IBRT = ipsilateral breast tumor recurrence.

margins. For women >40 years old, the presence of LVSI and of LCIS are independently associated with a higher rate of IBTR after BCT and negative margins. We could not show an improvement of the treatment efficacy in time.

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