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ORIGINAL ARTICLE

Pattern of relapse after breast conserving therapy, a study of 1519 early breast cancer patients treated in the Central Region of Denmark 2000–2009

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ABSTRACT

Background: The continuous improvements in diagnosing and treatment of breast cancer are reflected in the ever changing pattern of recurrence. The aim of the study was to investigating recurrence pattern and prognostic factors of recurrence in a population-based cohort.

Material and method: In total 1519 consecutive patients treated with breast conserving therapy (BCT) for invasive carcinoma between 2000 and 2009 in the Central Region of Denmark was included. Patients received adjuvant irradiation and systemic treatment according to the guidelines of the Danish Breast Cancer Cooperative Group, including boost for young women and those with a narrow margin.

Results: Median follow-up was 5.3 years (range 0.3–14.4). In total 183 women experienced breast cancer recurrence, 44 ipsilateral breast cancer recurrence, 13 regional recurrences, and 126 distant metastasis (DM). This corresponds to a cumulative risk of DM as first event at five and nine years of 6.5% and 12.6%, respectively. Further 42 women developed breast cancer in the contralateral breast. Disease-free survival (DFS) at five and nine years was 88% and 76%, respectively. Large tumor size (>20 mm), lymph node involvement, and vascular invasion were significantly associated with increased risk of DM. Margin width and age were not associated with risk of DM.

Conclusion: Acceptable recurrence rates and DFS were observed. Patients with large tumors, lymph node involvement, and vascular invasion had an increased risk of DM.

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For early breast cancer the treatment of choice has in recent years been breast conserving therapy (BCT). The method has evolved over the past decades with improvement in screening programs, imaging diagnostics, treatment techniques, and therapy options. As a result an increasing number of patients receive BCT, while the risk of recurrence and mortality is decreasing. Recent reports have revealed 10-year risk of ipsilateral breast tumor recurrence (IBTR) at 4.8% [1] and five-year disease-free survival (DFS) at 85% [2].

In Denmark approximately 4900 women are diagnosed with breast cancer annually. There are national guidelines for all parts of the treatment, and reporting on standardized case report forms to the Danish Breast Cancer Cooperative Group (DBCG) registry is compulsory. Optimal disease control with low recurrence rates is the main objective, highlighting the importance of assessment of quality of treatment.

Several factors are well established as associated with high risk of distant metastasis (DM), including tumor grade, lymph node involvement, and tumor size [3]. The importance of margin width in development of DM is less well established, although recent guidelines recommend a standard margin width of no tumor on ink after BCT [4], as no benefit in local control has been shown with wider free margins [5].

The pattern of recurrence is ever changing with the continuous improvements in diagnosing and treatment of breast cancer. A marked decline in risk of recurrence has been seen over the past decades and the risk of developing an IBTR has never been lower [6]. To be able to predict future challenges a constant evaluation of current data is important.

The present study examined the incidence and pattern of recurrence after BCT in a population-based cohort from the Central Region of Denmark (population 1.3 million), and investigated factors associated with risk of DM.

Method

The study cohort was identified within the population-based registry of the DBCG. All women starting BCT between 1 January 2000 and 31 December 2009 in the Central Region of Denmark were included in the cohort if they were younger than 75 years of age, had no history of prior cancer, and were diagnosed with unilateral, invasive breast cancer. Patients were excluded if they had mastectomy within two months of primary surgery, had incomplete data on margin width, received neo-adjuvant therapy, or had less than three months of follow-up. From the DBCG database we obtained clinical and pathological information about the patient and tumor. Patients were routinely followed up at 3–6 monthly intervals up to five years and annually for further five years. All patient files were reviewed in spring 2014 to ensure complete and updated data on adjuvant therapy and recurrence status. Dates of recurrence, other malignancy, prophylactic

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mastectomy of ipsilateral breast, and death, as well as date of follow-up were recorded. Pathology reports were reviewed in all cases of a second event in the ipsilateral breast to distinguish true recurrences from new primary tumors.

IBTR was defined as invasive recurrence in the ipsilateral breast. Regional recurrence (RR) was defined as recurrence in the ipsilateral axilla, supra- and infraclavicular nodes, or internal mammary nodes. The primary endpoint DM was defined as recurrence beyond local and regional disease. Contralateral invasive breast tumors were recorded as new primary cancers and not recurrences. Death was recorded regardless of cause.

The surgical, pathological, and oncological treatment was standardized in the national DBCG guidelines and described in details elsewhere [7,8]. Macroscopic evaluation of the margin was done on the excised specimen in a fresh state. If sufficient, the specimen was fixated in formalin. Application of ink for orientation was used and serial slicing at intervals of 2–4 mm was applied after the fixation. Representative sections of all margins and the tumor were chosen and paraffin embedded. The tumor histology, grade, immunohistochemical profile, and margins were then examined under microscope. The margin was microscopically measured at smallest distance from invasive tumor or ductal carcinoma in situ (DCIS) to the resection margin. A positive margin was defined as invasive carcinoma or DCIS on ink. A free margin was defined as no tumor on ink. Re-excisions were recommended in case of insufficient margin, at that time less than 5 mm microscopic. If a patient underwent re-excision the final margin after this procedure was recorded.

BCT consisted of lumpectomy with axillary clearance of level I–II, followed by adjuvant breast radiotherapy. Routine use of sentinel node biopsy was implemented in 2002 [9]. Adjuvant therapy consisted of systemic treatment, radiotherapy, and boost irradiation. The standard radiotherapy was 48 Gy in 24 fractions increasing to 50 Gy in 25 fractions from January 2009 [8]. An additional boost dose of 10 Gy in 5 fractions was given to the tumor bed to patients <50 years of age and to women ≥ 50 years of age on individual indication in case of narrow margin. In 2009 guidelines for boost treatment were changed, recommending 16 Gy in 8 fractions for women <41 years or margin <2 mm, and 10 Gy in 5 fractions for women aged 41–49 years. Regional radiotherapy was given to patients with one or more macrometastasis. Patients with tumor ≤ 2 cm, non-ductal or ductal carcinoma NST grade I, ER positive, and no lymph node involvement did not receive any adjuvant systemic therapy. All other patients were offered chemotherapy, endocrine therapy, trastuzumab, or a combination depending on risk factors. From 2002 onwards all patients ≤ 35 years of age received adjuvant systemic therapy, as did all patients with HER2 positive tumor from 2007. Nationwide screening was implemented in 2008 offering mammography to women age 50–69 every other year.

The study was approved by The Danish Data Protection Agency and consent was given by the Regional Science Ethical Committee.

Statistical analyses

Time to recurrence and length of follow-up were calculated from the day of primary surgery. A competing risk approach was used to calculate the cumulative incidence of DM. Competing risk factors were IBTR, RR, new primary breast cancer, other malignancy, and death. DFS was defined as survival time without breast cancer recurrence. Both unadjusted and adjusted hazard rates were calculated using Cox proportional hazards regression. Results are presented with 95% confidence intervals (95% CI), and p-values <0.05 were considered statistical significant. Stata version 12 was used for analyses.

Results

A total of 1519 women received BCT for unilateral early breast cancer in the Central Region of Denmark between 2000 and 2009.

Patient and treatment characteristics are presented in Table 1. Median age at time of surgery was 58.3 years (range 27.3–74.8). All patients received adjuvant radiotherapy, most as 48 Gy in 24 fractions [900 patients (59%)], 50 Gy in 25 fractions [536 patients (35%)], or 40 Gy in 15 fractions [74 patients (5%)]. Boost was received by 447 (29%). Of these, 344 (77%) received boost due to age <50 years. Chemotherapy was received by 616 (41%), endocrine treatment by 912 (60%), and 110 (7%) were treated with trastuzumab. Twenty-four percent did not receive any adjuvant systemic treatment. There was a good correlation between treatment recommendations and actual treatment given. While all received adjuvant radiotherapy, nine patients (0.6%) did not follow a standard radiotherapy program. Boost was not received by five (0.3%) women below 50 years of age as recommended. The standard adjuvant systemic treatment protocol was followed for 1367 (90%) of the patients (including at least one year of prescribed endocrine therapy). An additional 61 (4%) received more systemic treatment than guidelines suggested, and further 30 (2%) were allocated to both chemotherapy and endocrine treatment but only received one or the other. Any discrepancy between offered and received systemic therapy was mainly due to deselection of endocrine therapy ($n = 35$, 2%).

Median follow-up was 5.3 years (range 0.3–14.4). Time to first recurrence (IBTR, RR, or DM) was 3.7 years (range 0.3–12.2). In total 183 patients (12%) experienced recurrence as first event, 44 IBTR, 13 RR (eight simultaneous with IBTR), and 126 DM (11 simultaneous with IBTR and/or RR). Further 42 patients (3%) developed a new primary breast cancer in the contralateral breast. Off the 44 IBTRs 13 were by the pathologists deemed to be new primary tumors. DM as first event was in 41 patients (33%) of cases bone metastasis only. Liver, lung, and brain were the most common localizations of soft tissue metastasis (Table 2). Time to DM was shortest for those with bone metastasis alone, followed by liver and lung metastasis. Of those having a loco-regional recurrence first, 29% had a second recurrence (two loco-regional, 14 DM). Median time to this second event was 1.5 year (range 0.6–7.6). DM secondary to loco-regional recurrence was in three patients bone metastasis alone, 11 had soft tissue metastasis. Forty-nine women (3%) developed other malignant disease, most commonly lung or colorectal cancer ($n = 16$). During follow-up 138 (9%) women died, 83% after recurrence or other malignancy.

Table 1. Characteristics and unadjusted and adjusted risk of DM as first event.

	N	%	Event	Unadjusted			Adjusted[b]		
	1519		126	HR	95% CI	p-Value	HR	95% CI	p-Value
Boost						0.19			0.08
Boost	447	29	40	0.78	0.53–1.13		0.64	0.41–1.05	
No boost	1072	71	86	1			1		
Adjuvant systemic therapy						0.002			0.94
Adjuvant systemic therapy	1145	76	112	1			1		
No adjuvant systemic therapy	371	24	12	2.54	1.40–4.63		1.03	0.52–2.02	
Unknown	3		2						
Final margin						0.80			
0 mm	6	<1	1	1.22	0.17–8.75				
>0–1 mm	33	2	3	1.20	0.44–3.36				
2–4 mm	88	6	9	1.41	0.71–2.78				
≥5 mm	1392	92	113	1					
Grade						<0.001			0.14
I–II[a]	1012	69	69	1			1		
III	332	23	48	2.06	1.43–2.99		1.50	1.01–2.24	
Special subtypes, not graded	128	9	5	0.71	0.28–1.75		0.68	0.27–1.69	
Unknown	47		4						
Tumor size						<0.001			<0.001
≤20 mm	1096	72	61	1			1		
>20 mm	421	28	65	2.84	2.01–4.03		2.37	1.62–3.46	
Unknown	2								
Lymph node status						<0.001			<0.001
Negative	934	61	46	1			1		
Positive	585	39	80	2.62	1.82–3.76		2.00	1.33–3.02	
Vascular invasion						<0.001			0.01
No	1324	88	95	1			1		
Yes	174	12	31	2.65	1.76–3.97		1.74	1.12–2.69	
Unknown	21								
ER status						0.14			
Negative	236	16	28	1					
Positive	1251	84	96	0.72	0.48–1.10				
Unknown	32		2						
Localization						0.21			
Medio-central	483	34	43	1					
Lateral	918	66	66	0.78	0.53–1.14				
Unknown	118		17						
Re-excision						0.28			
No	1341	88	113	1					
Yes	178	12	13	0.74	0.42–1.31				
Re-excision and residual						0.51			
No re-excision	1341	88	113	1					
Re-excision, no residual	129	8	10	0.79	0.42–1.52				
Re-excision, residual	49	3	3	0.60	0.19–1.88				
Age						0.83			0.73
<45	167	11	17	0.96	0.53–1.76		1.03	0.48–2.18	
45–64	1012	67	81	0.88	0.57–1.36		0.87	0.56–1.35	
65–74	340	22	28	1			1		
DCIS outside tumor						0.78			
No	1305	89	108	1					
Yes	156	11	14	1.08	0.62–1.89				
Unknown	58		4						
Histology						0.33			
Ductal carcinoma NST[a]	1287	85	114	1					
Lobular	96	6	7	0.81	0.38–1.74				
Special subtypes	128	8	5	0.55	0.22–1.35				
Unknown	8								

[a]Including tubular carcinoma, n = 29; [b]adjusted for age, boost, adjuvant therapy, grade, tumor size, lymph node status, vascular invasion.

Cumulative risk of DM as first event with or without concurrent loco-regional recurrence at five and nine years was 6.5% and 12.6%, respectively (Figure 1). Cumulative risk of IBTR and/or RR not concurrent with DM was 2.4% and 5.7% at five and nine years, respectively. Cumulative risk of contralateral breast cancer was 2.0% and 4.0% at five and nine years, respectively. Cumulative risk of DM irrespective of any previous loco-regional recurrence was at five and nine years 6.9% and 13.8%, respectively. DFS at five and nine years were 88% and 76%, respectively.

Hazard estimates for DM over nine years showed a different pattern for ER positive and ER negative tumors (Figure 2) with DM in ER negative tumors peaking within two years and decreasing hereafter, while DM in ER positive tumors were slower to present but continued to develop during the entire follow-up. Compared to overall mean time to DM, patients with ER negative tumors, grade III, lymph node involvement, and vascular invasion presented prior to average (Figure 3).

In unadjusted analysis adjuvant therapy, high grade, large tumor size, lymph node involvement, and vascular invasion were associated with risk of DM (Table 1). Margin width was not associated with risk of DM, nor was re-excision or residual disease at re-excision. When adjusting for boost, adjuvant therapy, age, grade, tumor size, lymph node involvement,

Table 2. Overview of localization of distant metastasis as first event and time to event.

	N (%)	Median time to event, years (range)
Localization	126	
Bone	41 (33)	3.0 (0.3–12.2)
Lung &pleura[a]	37 (29)	4.6 (0.9–9.3)
Liver[b]	33 (26)	3.3 (0.6–9.6)
CNS[c]	4 (3)	–
Other	11 (8)	4.2 (1.1–8.8)

[a]8 lung/pleura alone, 14 concurrent with bone metastasis, 15 with concurrent metastasis in liver or more widespread; [b]12 liver alone, 15 concurrent with bone metastasis, 6 more widespread; [c]3 CNS alone, 1 concurrent with bone metastasis.

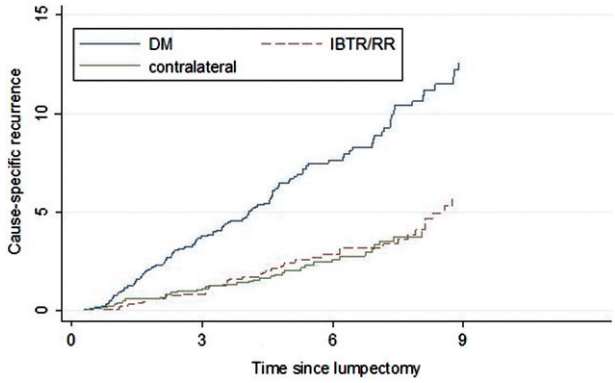

Figure 1. Cumulative risk of DM, IBTR/RR, and contralateral breast cancer as first event.

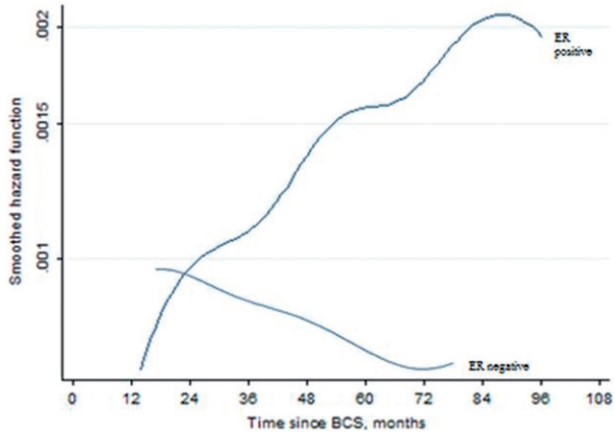

Figure 2. Hazard estimates for distant metastasis by ER status over 9 years.

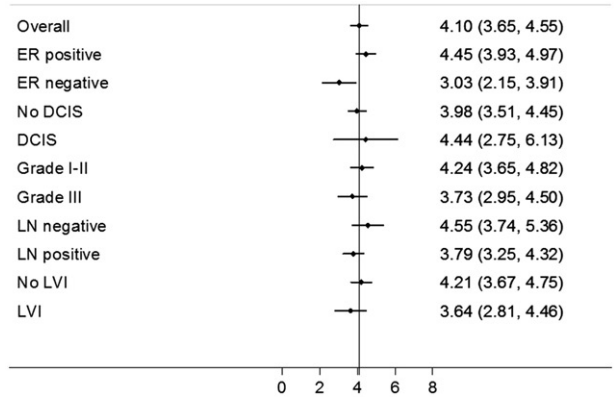

Figure 3. Mean time, year (95% CI) to DM for selected tumor variables compared to overall mean.

and vascular invasion an increased risk of DM was seen for patients having large tumors (>20 mm), lymph node involvement, or vascular invasion, while receiving a boost reduced the risk of DM with borderline significance.

In a subgroup analysis of 261 patients meeting the inclusion criteria of the ongoing DBCG PBI protocol (http://clinicaltrials.gov/show/NCT00892814, including ≥60 years of age, non-lobular tumor, grade I–II, tumor size ≤20 mm, ER positive, HER2 negative, margin width ≥2 mm, and no lymph node involvement) with a median follow-up of 4.3 years 24 first events were found. Two IBTR, three RR, nine DM, and seven contralateral breast tumors – equivalent to a five-year cumulative risk of 2.7% for IBTR/RR, 2.7% for DM, 3.7% for contralateral breast cancer, and a two-year risk of 0.8% for new primary. HER2 status was unknown for 95 of the patients included in the analysis.

Similarly in a subgroup analysis of 516 meeting the inclusion criteria of IMPORT-LOW (http://clinicaltrials.gov/show/NCT00814567, including ≥50 years of age, non-lobular tumor, grade I–III, tumor size ≤30 mm, ER positive, HER2 negative, margin width ≥2 mm and no lymph node involvement) a total of 58 first events were found (9 IBTR, 3 RR, 25 DM, 15 contralateral breast cancers, six new primary cancers in ipsilateral breast). The cumulative risk of recurrence at 5 year was 1.5% for IBTR/RR, 3.8% for DM, 3.2% for contralateral breast cancer, and the 2 year risk for new primary 0.6%. A total of 214 patients with unknown HER2 status were included in the analysis.

Discussion

In a population-based regional setting, representing 23% of the Danish population, the five-year actuarial risk of DM and DFS were 6.5% and 88%, respectively, for 1519 consecutive patients treated with BCT for invasive carcinoma. Patients with large tumor size, lymph node involvement, and vascular invasion had an increased risk of DM. Margin width was not associated with risk of DM.

At five years after surgery, the cumulative risk of DM in the present study was 6.5% and 12.6% at nine years. This is comparable to or lower than other recent reports [10,11]. A five-year DFS at 88%, decreasing to 76% at nine years were also in line with recent reports [10,11]. Several studies have investigated the pattern of recurrence. Although definitions of recurrence varied, and some studies include all breast cancer patients regardless of surgical modality, several suggest a pattern of recurrence after breast cancer with more than one peak [11,12] which could represent a difference in time to recurrence depending on tumor characteristics. We found that median time to DM for patients with ER negative tumors were shorter than for those having ER positive tumors (3.0 years vs. 4.5 years), and that for patients with ER negative tumors the majority of DM events would develop within three years, while the risk of developing DM for patients with ER positive tumor would persist. At the time five years of endocrine treatment was recommended, guidelines have since been changed and 10 years of endocrine therapy are currently recommended [13]. In addition, the high risk criteria for

offering endocrine therapy have been modified, so that tumors 11 mm or more are now high risk, in contrast to previous 21 mm or more. We acknowledge that selection for, and type of adjuvant systemic therapy changed over the time of the study, and that the majority of patients in the present study preceded routine HER2 testing and treatment with trastuzumab. Likewise centralization of the breast cancer treatment could have influenced and improved the outcome.

In subgroup analysis of patients meeting the inclusion criteria of the DBCG PBI protocol and the IMPORT-LOW trial we found low risk of all recurrent events. As both trials investigate the safety in terms of recurrence in using partial breast irradiation for selected patients it is reassuring to find low risk of local and distant events in both subgroups.

As expected, predictors of DM included large tumor size (>20 mm), lymph node involvement, and vascular invasion [11,14]. We did not find an increased risk of DM associated with young age (<50 years), as previously described in some studies [15,16]. However, in those studies the high risk of DM was primarily seen in patients ≤35 years. We were not able to investigate these very young women separately, due to small number of patients in this group (n = 28). The lack of long-term follow-up and the small number of young women in this study may explain why no association between age and DM is seen. The prognostic relevance of tumor grade is well established [14] and confirmed by our results. The importance of margin status for development of DM has been described in a number of studies with diverse results. Voogd et al. [15] reported a higher risk of DM in patients with a positive margin, defined as tumor on ink, as did Jobsen et al. [17]. However, in the latter study this association was only found among women ≤40 years of age. A number of studies with similar margin definitions did not find any association between margin width and risk of DM [18,19]. We had only six patients with a final positive margin, and a limited total number of patients with margins <5 mm (n = 121), however, our results do not suggest an increased risk of DM with narrow but free margins compared to wider in patients.

A high percentage of women received adjuvant therapy according to guidelines. The guidelines were followed for 90% of the patients with further 6% receiving adjuvant systemic therapy that diverged from standard regimes. An additional 2% initiated endocrine therapy but discontinued within first year, the reason most commonly being adverse effects. The reduction in recurrence and mortality achieved with chemotherapy and endocrine treatment are well established [20], emphasizing the importance of high patient adherence. We are well aware that a higher number of patients may have discontinued their endocrine therapy, as the treatment is self-administered. Our results are based on the file-recorded information the patients have given at the follow-up visits. As treatment in Denmark is provided free of cost regardless of insurance status, financial issues should not be a factor. Discontinuation rates of 7–10% per year have been reported [21]. Hershman et al. [22] reports in a study with 4.5 years of follow-up that only 49% of the patients complete their endocrine therapy.

The use of boost in Denmark is restricted to patients younger than 50 years of age or patients with a narrow margin. In the present study adjuvant boost was received by 97% of patients younger than 50 years of age or with margin width <2 mm, correlating to only 11 patients not receiving the recommended treatment. In spite of a relatively low number of patients receiving boost (29%), we did observe DFS in line with recent studies, and have previously published result reporting corresponding low risks of IBTR [23]. In the recent ASTRO guidelines [4], it is not recommended to base the use of boost on the margin width. However, in the meta-analysis by Houssami et al. [5] 96% of the patients received boost, and although only 29% of all patients in the current study received boost, 96% of those with margins <2 mm did. It seems that very little can be concluded on the impact of boost on narrow margins. While the benefit of boost on IBTR has been clearly shown in randomized trials [24], this must be weighed against the morbidity associated with increased irradiation dose [25]. The morbidity following irradiation in modern day treatment is currently being investigated in the DBCG HYPO trial (http://clinicaltrials.gov/show/NCT00909818).

Strengths of the study include consecutive patients with complete follow-up and detailed information on patient characteristics and outcome. However, limited follow-up and small number of events restricted analyses, and we were not able to investigate in details the long-term course of events. The study is also limited by lack of information on genomic subtyping.

In conclusion, the risk of distant recurrences after BCT in early breast cancer is low within a period of nine years. Narrow free margin width compared to wider free margins was not associated with higher risk of DM, suggesting that with current treatment modalities, the recommendation of 'no tumor on ink', as sufficient margin width in BCT, is adequate for control of DM. Further studies with larger cohorts and longer follow-up are needed to in details explore the pattern of recurrence after BCT.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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