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Age-dependent outcome in breast cancer

Long-term age-dependent failure pattern after breast-conserving therapy or mastectomy among Danish lymph-node-negative breast cancer patients

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ABSTRACT

Purpose: To describe long-term failure pattern after early-stage breast cancer in relation to local treatment (breast-conserving therapy (BCT) or mastectomy) and age.
Materials and methods: Cohort study with balanced 5-year age groups and prospectively collected data; 813 Danish lymph-node-negative breast cancer patients diagnosed in 1989–98 and treated with mastectomy ($N = 515$) or BCT ($N = 298$) and no adjuvant systemic treatment.
Results: The 20-year local recurrence (LR) risk was 20% after BCT; 8.7% after mastectomy. LR developed in mastectomy patients within the first 10 years; in BCT patients throughout the entire 20-year period. Younger patients' (⩽45 years) 20-year LR risk was generally higher than older patients' (>45 years) (19% vs. 5%, $p < 0.001$).
In younger patients, LR was significantly associated with distant metastasis (DM) (hazard ratio (HR) = 2.7(1.8–4.2)) and 20-year breast-cancer mortality (HR = 2.7(1.7–4.4)). BCT was associated with higher 20-year breast-cancer mortality (HR = 1.5(1.0–2.4)) and higher 20-year all-cause mortality (HR = 1.7(1.2–2.5)) than mastectomy.
In older patients, LR was not associated with DM, and breast-cancer mortality was similar for BCT and mastectomy.
Conclusion: BCT patients with no adjuvant systemic treatment developed LR throughout 20-year period and faced higher LR risk than mastectomy patients. LR was associated with DM among younger patients, and younger BCT patients had higher mortality than younger mastectomy patients.

Breast-conserving therapy (BCT) and mastectomy have been considered equivalent modalities for local treatment of early-stage breast cancer patients since the late 1980s [1–6]. Young age at diagnosis has been a strong predictor for local recurrence (LR), especially after BCT [7–10].

A concern is whether the increased incidence of LR in young patients translates into poor survival. A review of six randomized controlled trials comparing mastectomy and BCT [11] reported similar overall survival (OS) after BCT and mastectomy although the incidence of LR was significantly higher among BCT patients than among mastectomy patients in four of the trials. However, the proportion of young breast cancer patients was low (12–23%). Young breast cancer patients have been studied as a separate group only in a handful of cohort studies [12–17], but these studies use a mixture of different TNM stages, a variety of adjuvant systemic treatments, and a somewhat short follow-up of less than 10 years.

A meta-analysis from EBCTCG evaluating the effect of radiotherapy (RT) after different types of breast cancer surgery [18] indicated that one breast cancer death could be avoided after 15 years for every four LR avoided after 5 years. However, this association has been questioned, and mortality may depend also on tumor characteristics [19] and intrinsic tumor subtypes [20]. It accordingly remains unclear whether an increased LR rate [21] among young breast cancer patients leads to higher mortality [22–23].

We therefore aimed to describe the long-term pattern of failure after early-stage breast cancer as a function of age and local treatment, and to investigate if LR was associated with higher risk of distant metastasis (DM) and mortality.

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Patients and methods

Study population and treatment

The study cohort included 813 lymph-node-negative patients with tumor size <5 cm and no previous cancer. Included were all histological tumor types except invasive ductal carcinoma grade II/III. All patients had given informed consent to be enrolled in the DBCG-89a-protocol [24–25] administered by the Danish Breast Cancer Group (DBCG). Data were collected prospectively. All patients received partial axillary dissection and were advised to receive mastectomy (with no other treatment) or lumpectomy and whole-breast RT of the residual breast (48 Gy in 24 fractions+ boost of 10–16 Gy in 5–8 fractions) [26]. No patients received adjuvant systemic treatment.

The study cohort had a balanced proportion of patients within each 5-year age group. Geographical inclusion criteria were used to secure an unbiased cohort (Sup. Fig. 1): Young patients were included nationwide; old patients from a particular region of Denmark. Patients with known BRCA mutations were excluded ($N = 10$).

Patient follow-up

Patients were followed with clinical examination biannually for 5 years and then annually for up to 10 years. They went off-study in case of any breast cancer event, immigration, or death. Complete 20-year follow-up data (including consecutive registration of all breast cancer events for every patient) were obtained from the Danish Civil Registration System, the National Pathology Register, and general practitioners (GP), and by reviewing the patients' medical records (Sup. Fig. 1).

Primary endpoints and statistical analysis

Endpoints considered included LR defined as tumor growth (excluding ductal carcinoma *in situ*) in the ipsilateral chest wall, breast, or overlying skin; regional recurrence (RR) defined as tumor growth in ipsilateral axillary or infraclavicular lymph nodes; contralateral breast cancer (CC) defined as tumor growth in the contralateral breast; and distant metastasis (DM) defined as tumor growth in all other regions. LR developed simultaneous (within a month) with RR or CC was registered as RR or CC, respectively. LR/RR/CC occurring more than a month after DM was not taken into account.

Cumulative incidence curves for LR, RR, and DM were calculated using a competing risk model. Time-to-event was defined as the interval between the date of surgery and the occurrence of the event of interest. In the absence of LR or RR, the observation time was censored at the earliest of the following competing events: other breast cancer events, other malignant disease, or death. In the absence of DM, the observation time was censored at the earliest of either other malignant disease or death. Follow-up was continued until return date of the letter from the GP, reading date of the electronic medical records, or death. Overall survival was described by Kaplan–Meier plots, counted from the date of surgery to the date death; and patients were censored from follow-up at 1 March 2016. For breast-cancer mortality, other causes of death were recorded as competing events, and a cummulative incidence curve were calculated. Crude hazard ratios (HR) were computed for all end-points using Cox proportional hazards regression. If the assumption of proportional hazard could not be accomplished, a risk difference was calculated using the pseudo-value approach. Cox multivariate regression analyses were performed separately for younger and older patients using DM, breast cancer mortality, and all-cause mortality, adjusting for local treatment, tumor size and histological type. Assumptions of proportional hazards were tested graphically using –ln(–ln(survival) vs. –ln(analysis time) plots and by testing zero slopes of scaled Schoenfeld residuals. Groups were compared using the chi-square test. Level of significance was 5%, and all estimated *P* values were two-sided. All statistical tests were performed using STATA version 12.1 (StataCorp, College Station, Texas, USA).

Definition of age: Failure pattern for each 5-year age group was listed (Sup. Table 1). Among patients developing LR, a distinct difference was observed between the age groups 41–45 and 46–50. Overall, patients $\leqslant$45 years (=younger) had a much higher frequency of DM than patients >45 years (=older). Based on this difference, age was dichotomized using 45 years as the cut-point.

Results

Distribution of clinical–pathological parameters

The study population's clinical–pathological parameters are shown in Table 1. BCT was performed in 37% ($N = 298$), mastectomy in 63% ($N = 515$). Overall, BCT patients were younger ($p < 0.001$) and had a much lower proportion of large tumors (21–50 mm) ($p < 0.001$) than mastectomy patients.

Failure patterns

Failure patterns as a function of local treatment and age appear in Table 2 and Sup. Fig. 1. The frequency of LR was higher among BCT patients than among mastectomy patients, regardless of age: younger (28% vs. 14%, $p < 0.001$) and older (10% vs. 3% $p < 0.001$). The risk of developing DM simultaneously with LR or later was high among younger patients – about 1 DM for every 2 LR: BCT (47 LR:19 DM) and mastectomy (40 LR:21 DM). In contrast, among older patients developing LR, only 1 developed DM; BCT (11:0) and mastectomy (6:1).

Local failure

The median follow-up was 17.2 years (range 0.5–24.6). Overall, after 20 years of follow-up, the cumulative incidence proportion (CIP) of LR was 13% (11–15) (Fig. 1A); within the first 7 years, it was 7.0% (5.2–8.57) (Fig. 1A, Sup. Table 2).

After BCT, the 20-year CIP of LR was 20% (15–25); and patients developed LR throughout the 20-year period, regardless of age. The 20-year CIP of LR was higher among younger than among older patients; risk difference (RD) = 18% (9.0–27) (Fig. 1B). Younger patients had a higher CIP of both early LR (0–7 years) and late LR (>7–20 years) (Sup. Table 2).

After mastectomy, the 20-year CIP of LR was 8.7% (6.3–11.2); and it was significantly higher among younger than older patients; RD = 11% (7.0–16) (Fig. 1B). Younger patients developed LR within the first 10 years after surgery (except for 3 events recorded after), and the frequency of LR was highest within the first 5 years. Older patients developed LR within the first 5 years after surgery.

BCT patients had a significantly higher 20-year CIP of LR than mastectomy patients; RD = 11% (6.1–17) (Fig. 1A). The 7-year CIP of LR was not significantly different between BCT and mastectomy patients (Sup. Table 2), but BCT patient had a higher CIP of late LR (>7–20 year); RD = 13% (7.9–19).

The results were consistent if simultaneous events of LR and RR/CC were included in the 20-year CIP of LR: Mastectomy (younger: 16% vs. older 3.8%) and BCT (younger: 30% vs. older 10%).

Table 1
Patient characteristics.

	All		Mastectomy						BCT					
			All		Younger		Older		All		Younger		Older	
Total	813		515	63%	278	34%	237	29%	298	37%	175	22%	123	15%
Tumor characteristic														
Tumor size														
⩽10 mm	245	30%	132	26%	77	28%	55	23%	113	38%	60	34%	53	43%
11–20 mm	361	44%	218	42%	116	42%	102	43%	143	48%	85	48%	58	47%
21–50 mm	179	22%	145	28%	73	26%	72	31%	34	11%	22	13%	12	10%
Unknown, but <50 mm	28	4%	20	4%	12	4%	8	3%	8	3%	8	5%	0	–
Histological diagnose														
Invasive ductal carcinoma	558	69%	345	67%	195	70%	150	63%	213	72%	122	70%	91	74%
Invasive lobular carcinoma	134	16%	98	19%	45	16%	53	23%	36	12%	21	12%	15	12%
Other carcinomas	121	15%	72	14%	38	14%	34	14%	49	16%	32	18%	17	14%

Treatment: breast conserving therapy (BCT) vs. mastectomy.
Age: younger (⩽45 year) vs. older (>45).

Table 2
Failure pattern as a function of local treatment and age.

			Mastectomy						BCT					
			All		Younger		Older		All		Younger		Older	
All	813		515	63%	278	34%	237	29%	298	37%	175	22%	123	15%
No recurrence	525	65%	340	66%	172	62%	168	71%	185	62%	92	53%	93	75%
LR total	104	13%	46	9.0%	40	14%	6	2.5%	58	19%	47	27%	11	8.9%
LR	63	7.8%	24	4.7%	19	6.8%	5	2.1%	39	13%	28	16%	11	8.9%
LR later DM	34	4.2%	17	3.3%	16	5.8%	1	0.4%	17	5.7%	17	9.7%	0	
Sim LR-DM	7	0.9%	5	1.0%	5	1.8%	0		2	0.7%	2	1.1%	0	
RR total	25	3.0%	13	2.6%	8	2.9%	5	2.0%	12	4.0%	11	6.3%	1	0.8%
RR*	10(3)	1.2%	7(3)	1.4%	6(3)	2.2%	1	0.4%	3	1.0%	3	1.7%	0	
RR* later DM	9(5)	1.1%	4(3)	0.8%	2(1)	0.7%	2(2)	0.8%	5(2)	1.7%	5(2)	2.9%	0	
Sim RR*-DM	6	0.7%	2	0.4%	0		2	0.8%	4	1.3%	3	1.7%	1	0.8%
CC total	69	8.6%	52	10%	25	9.0%	27	11%	17	5.7%	10	5.7%	7	5.7%
CC*	56(1)	6.9%	41	8.0%	19	6.8%	22	9.3%	15(1)	5.0%	8(1)	4.6%	7	5.7%
CC*later DM	11(1)	1.4%	9	1.7%	5	1.8%	4	1.7%	2(1)	0.7%	2(1)	1.1%	0	
Sim CC*-DM	2(1)	0.3%	2(1)	0.4%	1(1)	0.4%	1	0.4%	0		0		0	
DM as 1 event	90	11%	64	12%	33	12%	31	13%	26	8.7%	15	8.6%	11	8.9%
DM total	159	20%	103	20%	62	22%	41	17%	56	19%	44	25%	12	10%

Patients with a breast cancer event were defined with one of the following: LR, LR later DM, simLR-DM, RR*, RR*, simRR*-DM, CC*, CC*later DM, simCC*-DM as 1 event and DM total.
Sim = simultaneous events diagnosed within the same month.
* = includes simLR-RR/simLR–CC, (number of simultaneous event).

Regional failure

Overall, the 20-year CIP of RR was 3.3% (2.0–4.6), and there was no significant difference between BCT and mastectomy patients; HR = 1.4(0.7–3.5) (Fig. 1C). The 20-year CIP of RR within the BCT group was higher among younger than among older patients; RD = 5.8% (1.7–9.9) (Fig. 1D).

Distant metastasis

Overall, the 20-year CIP of DM was 20% (17–23), and no difference was observed between BCT and mastectomy patients; HR = 0.9(0.7–1.3) (Fig. 1E).

Within the BCT group, the 20-year CIP of DM was higher among younger patients than older patients; RD = 17% (8.0–26), but there was no significant difference observed between the age groups within the mastectomy group (Fig. 1F).

Among younger patients, no significant difference in DM was seen between local treatments; RD = 4.6% (−4.1–13); however, older mastectomy patients had a higher 20-year CIP of DM; RD = 8.3% (0.8–18) (Fig. 1F).

Survival

The median follow-up on vital status was 19.6 years (range 0.5–26.1). The 20-year breast-cancer mortality and 20-year overall survival were similar in BCT and mastectomy patients, 16% vs. 18% (HR = 1.0(0.7–1.4)) and 71% vs. 68% (HR = 1.0(0.8–1.2)), respectively (Fig. 2A/B). Among younger patients, the 20-year breast-cancer mortality was similar for BCT and mastectomy patients, 22% vs. 18%, 1.3(0.9–2.0); but the 20-year overall survival was poorer after BCT, 72% vs. 80% (HR = 0.7(0.5.0–1.0), (Fig. 2C/D). Among older patients, the breast-cancer mortality was similar as well (BCT: 8.9% vs. mastectomy: 20%, HR = 0.6(0.3–1.1), but BCT patients had a significantly better 20-year overall survival (71% vs. 54%, HR = 1.9(1.0–3.5)) (Fig. 2E/F).

Causes of death are shown in Table 3. Among younger patients, only 2 died from heart disease and both had received BCT. Compared with mastectomy patients, BCT patients had a higher frequency of "second primary cancer" ($p = 0.007$), most of which were associated with the lung (6/8). Among older patients, the frequency of different death causes was not significantly different between the treatment groups, and in both groups only few patients died from heart disease.

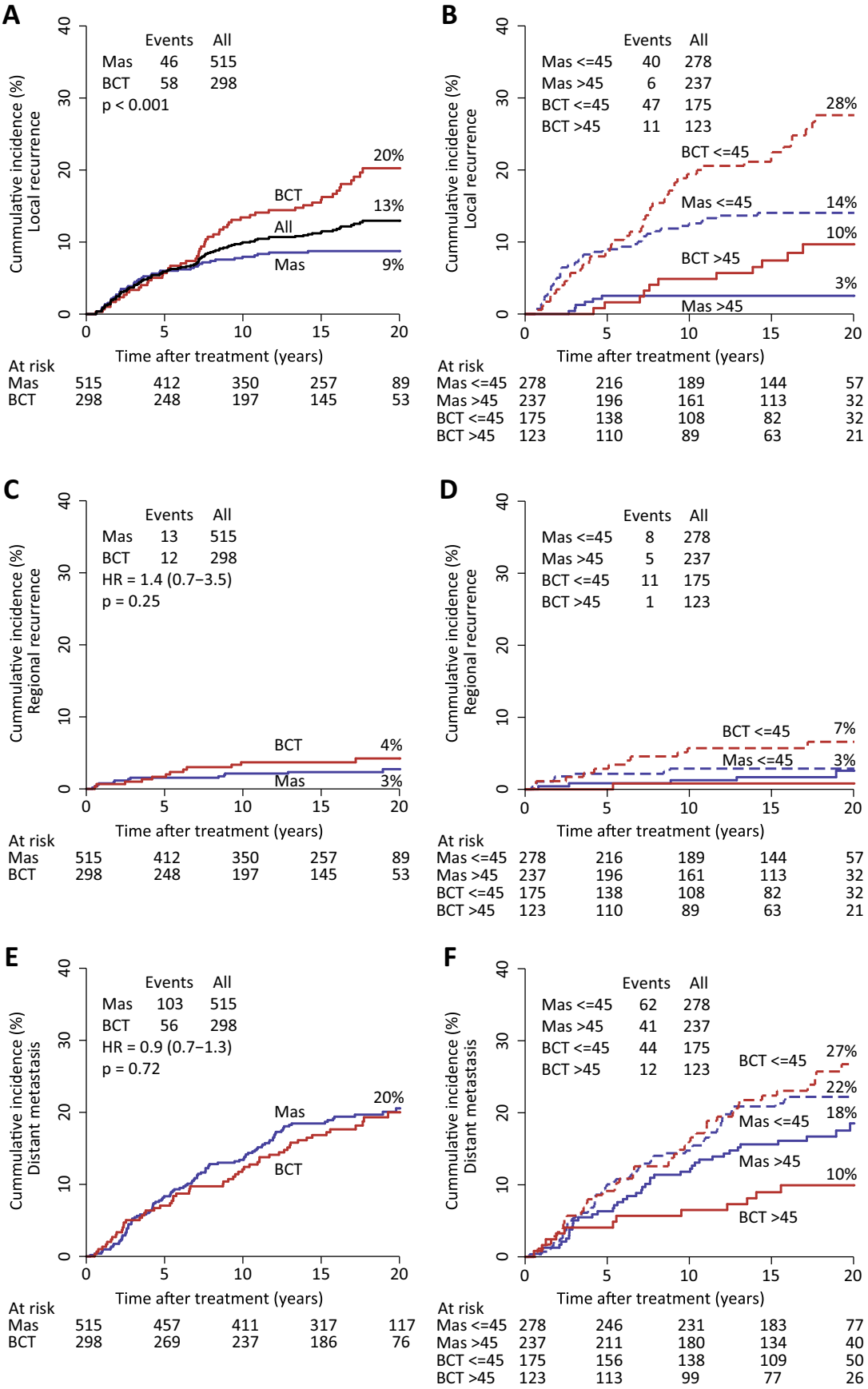

Fig. 1. 20-Year cumulative incidence of local recurrence (A, B), RR (C, D) and DM (E, F) as a function of BCT (red) and mastectomy (blue). (D–F) The same plot; with one exception the cohort was subdivided into a younger (⩽45) and older (>45) group.

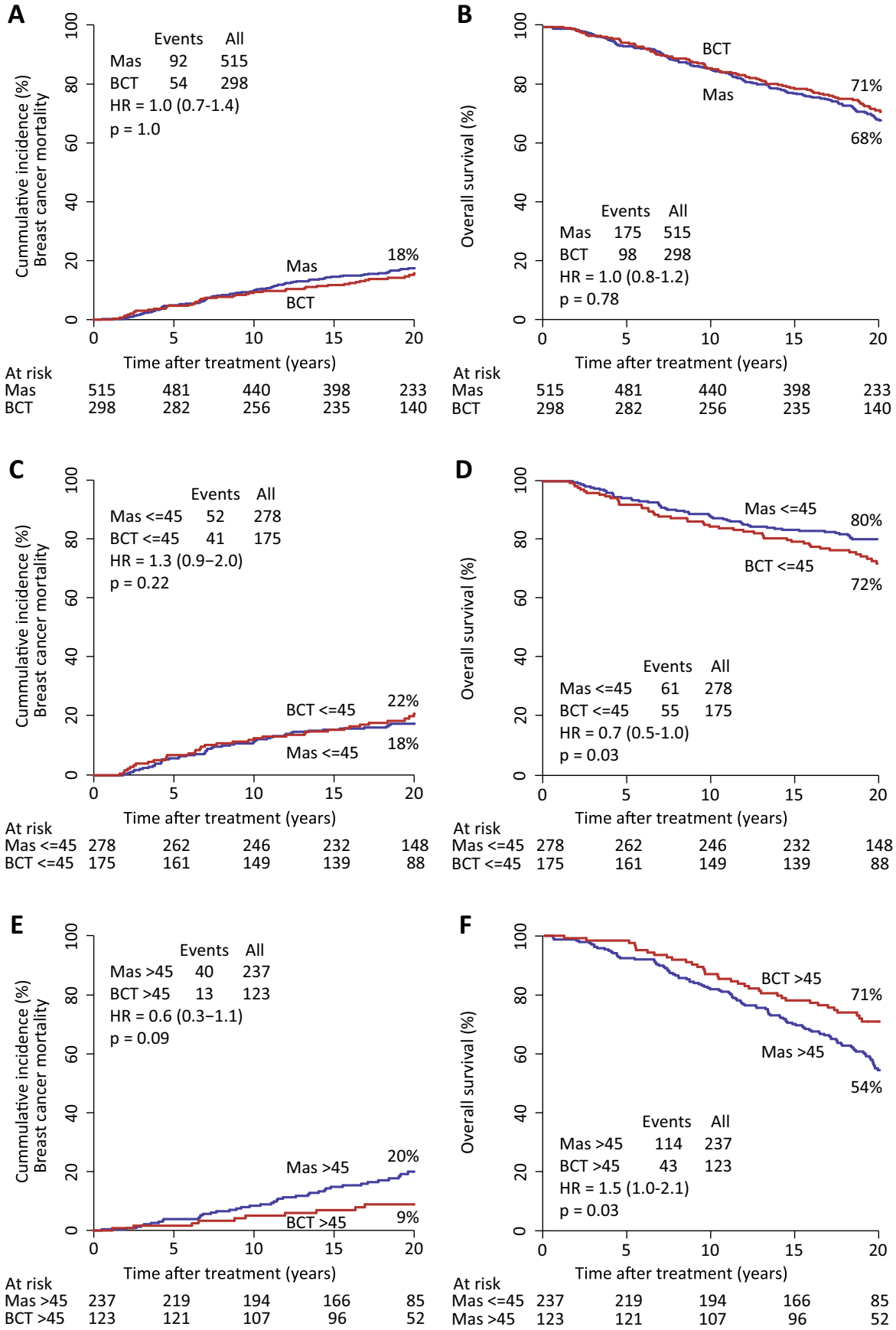

Fig. 2. Breast-cancer mortality (A, C and E) and overall survival (B, D and F) after 20 years of follow-up, comparison of BCT (red) and mastectomy (blue). (A and B) All patients. (C and D) Younger patients (⩽45). (E and F) older patients (>45).

Table 3
Causes of death.

	All		Mastectomy						BCT					
			All		Young		Old		All		Young		Old	
Total	813		515	66%	278	34%	237	29%	298	34%	175	22%	123	15%
Alive	540	66%	340	66%	217	78%	123	52%	200	67%	120	69%	80	65%
All-cause death	273	34%	175	34%	61	22%	114	48%	98	33%	55	31%	43	35%
Causes of death														
Breast cancer	146	18%	92	18%	52	19%	40	17%	54	18%	41	23%	13	11%
Heart disease	19	2%	10	2%	0	.	10	4%	9	3%	2	1%	7	6%
Second primary cancer	36	4%	21	4%	2	1%	19	8%	15	5%	8	5%	7	6%
Other causes	69	9%	51	10%	6	2%	45	19%	18	6%	3	2%	15	12%
Unknown	3	0.4%	1	0.2%	1	0.4%	0	.	2	0.7%	1	0.6%	1	0.8%

Table 4
Multivariate analysis for younger (upper part) and older patients: DM, breast-cancer mortality and all-cause mortality.

	Distant metastasis				Breast-cancer mortality				All-cause mortality			
			Model includes LR, RR, CC				Model includes LR, RR, CC				Model includes LR, RR, CC	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Younger patient, ⩽45												
BCT vs. Mas	1.4	(0.9–2.0)	1.1	(0.7–1.7)	**1.5**	**(1.0–2.4)**	1.2	(0.8–1.9)	**1.7**	**(1.2–2.5)**	**1.4**	**(1.0–2.1)**
LR vs. no LR	–	–	**2.7**	**(1.8–4.2)**	–	–	**2.7**	**(1.7–4.4)**	–	–	**2.1**	**(1.3–3.2)**
RR vs. no RR	–	–	**2.5**	**(1.0–5.8)**	–	–	**3.2**	**(1.3–7.6)**	–	–	**2.2**	**(1.0–5.3)**
CC vs. no CC	–	–	1.4	(0.6–3.1)	–	–	1.8	(0.8–4.0)	–	–	1.5	(0.8–3.0)
Tumor size												
11–20 vs. ⩽10 mm	**2.8**	**(1.6–5.0)**	**2.5**	**(1.5–4.7)**	**3.0**	**(1.6–5.7)**	**2.9**	**(1.5–5.5)**	**2.0**	**(1.2–3.2)**	**1.9**	**(1.2–3.2)**
>20 vs. ⩽10 mm	**4.1**	**(2.2–7.8)**	**3.5**	**(1.9–6.7)**	**4.5**	**(2.2–9.0)**	**3.9**	**(1.9–7.9)**	**2.5**	**(1.4–4.5)**	**2.3**	**(1.3–4.2)**
Histologic type												
Lobular vs. ductal	1.5	(0.9–2.5)	1.5	(0.9–2.5)	**1.8**	**(1.1–3.2)**	**1.9**	**(1.1–3.1)**	**1.7**	**(1.0–2.7)**	**1.7**	**(1.0–2.8)**
Other vs. ductal	0.8	(0.4–1.5)	0.9	(0.5–1.6)	0.9	(0.5–1.6)	1.0	(0.5–1.8)	1.0	(0.6–1.7)	1.1	(0.6–1.9)
Older patients, >45												
BCT vs. Mas	0.6	(0.3–1.1)	0.6	(0.3–1.2)	0.6	(0.3–1.1)	0.6	(0.3–1.2)	0.7	(0.5–1.1)	0.8	(0.5–1.1)
LR vs. no LR	–	–	0.4	(0.1 –3.1)	–	–	0.4	(0.1–2.9)	–	–	0.7	(0.3 –1.6)
RR vs. no RR	–	–	3.2	(0.8–14)	–	–	3.7	(0.9–16)	–	–	1.8	(0.4–7.6)
CC vs. no CC	–	–	0.7	(0.2–1.9)	–	–	0.7	(0.2–1.9)	–	–	1.0	(0.6–1.7)
Tumor size												
11–20 vs. ⩽10 mm	**2.4**	**(1.1–5.4)**	**2.3**	**(1.0–5.1)**	**2.4**	**(1.1–5.2)**	**2.2**	**(1.0–5.0)**	1.3	(0.9–1.9)	1.3	(0.8–1.9)
>20 vs. ⩽10 mm	**2.5**	**(1.0–6.1)**	**2.5**	**(1.0–6.1)**	**2.6**	**(1.1–6.3)**	**2.6**	**(1.1–6.4)**	**1.5**	**(1.0–2.4)**	1.5	(1.0–2.4)
Histologic type												
Lobular vs. ductal	0.7	(0.3–1.4)	0.7	(0.3–1.5)	0.7	(0.3–1.5)	0.7	(0.3–1.6)	1.3	(0.9–1.9)	1.3	(0.9–1.9)
Other vs. ductal	0.8	(0.3–1.7)	0.8	(0.3–1.8)	0.8	(0.3–1.8)	0.8	(0.3–1.8)	0.8	(0.5–1.3)	0.8	(0.5–1.3)

For each endpoint, an analysis was performed with and without including local recurrence (LR), regional recurrence (RR), and contralateral cancer (CC). Hazard ratios in bold if $p < 0.05$.

In the adjusted analysis (Table 4), tumor size was significantly associated with each endpoint irrespective of age and treatment. Among younger patients, invasive lobular cancer had a worse prognosis than invasive ductal carcinoma, whereas histological type had no impact among older patients. Within the younger group, those who developed LR had a higher risk of DM (HR: = 2.7(1.8–4.2)) and a higher risk of 20-year breast cancer mortality (HR = 2.7(1.7–4.4)). Compared with mastectomy patients, BCT patients had a higher 20-year breast cancer mortality (HR = 1.5 (1.0–2.4)) and 20-year all-cause mortality (HR = 1.7(1.2–2.5)). However, among older patients, LR was not associated with DM (HR = 0.4(0.1–3.1)); and BCT patients' 20-year breast-cancer mortality was not significantly different from that of mastectomy patients (HR = 0.6(0.3–1.1)).

As demonstrated in the adjusted analysis, tumor size was associated with DM and survival, and Table 1 showed a significantly lower proportion of large tumors in the BCT group. A subanalysis was therefore performed within the young group, restricted to tumors below 2 cm (Sup. Fig. 2). After 20 years, younger BCT patients had a higher breast-cancer mortality than younger mastectomy patients, 20% vs. 13% (HR = 1.7(1.0–2.9)).

Discussion

This cohort study with complete long-term follow-up data showed that BCT patients developed LR throughout the 20-year period and had a higher risk of LR than mastectomy patients.

Younger patients' LR was linked to DM (HR = 2.7(1.7–4.4)), and younger BCT patients had an increased adjusted breast-cancer mortality (HR = 1.5(1.0–2.4)) and all-cause mortality (HR = 1.7 (1.2–2.5)) than mastectomy patients. In contrast, older patients' LR was not linked to DM, and older BCT patients had similar adjusted breast-cancer mortality than mastectomy patients. Only few patients died of heart disease, and their death was not associated with BCT.

Similar levels of survival after BCT and mastectomy are reported in several randomized trials including mainly post-menopausal

patients [1–6]. Recently, several large cohort studies described a better survival after BCT [27–31]. These findings confirm our results among older patients. In contrast, the survival difference between younger BCT and mastectomy patients observed in the present study was found neither in a meta-analysis [32] of six studies comprising 22,598 young patients below the age of 40 years, nor in a cohort study that was not included in the meta-analysis [17]. These inconsistencies may arise because these studies included mastectomy patients with significantly worse prognostic markers (e.g., lymph-node-positive tumors, large tumors, and higher histological grade) and because they used different systemic treatments in the two groups and had a shorter follow-up (i.e., most had follow-up shorter than 10 years). The importance of long follow-up is demonstrated in one of the studies [14] which reported a significantly lower incidence of DM after BCT among young patients during the first 7 years after surgery and a significantly higher incidence of DM from 7 to 15 years after surgery. A similar, non-significant reversal of survival risk was reported by Mahmood et al. [15].

Long-term follow-up is also necessary to demonstrate a difference in LR after BCT and mastectomy. In a study of 1451 young breast cancer patients [14], young mastectomy patients developed LR only within the first 6 years (6%), whereas BCT patients experienced LR throughout the whole 15-year period. Adjuvant systemic therapy following BCT reduced the 15-year LR risk form 33% to 16%. Similar results were reported in another cohort study of 1874 young patients [5], where the 15-year LR risk was 36% after BCT and 12% after mastectomy. In contrast, among 965 young patients most of whom also received systemic treatment, Cao et al. found no difference in the 15-year LR risk between BCT and mastectomy patients, (14% vs. 15%) [17].

The nature of the observed late LR after BCT is unclear. A few studies have tried to explore whether it is a 'true recurrence' or a new primary tumor in the residual breast [33–35]. In a subset of patients from the EORTC boost trial [36], Vrieling found that primary tumors with the presence of ductal carcinoma *in situ* had a higher incidence of LR more than 10 years after primary surgery [37], indicating that late LR may be new primary tumors.

In our study, LR was significantly associated with an increased risk of DM among younger patients, and a potential higher proportion of insufficient pathologically free margin in the young group could not explain the finding [38] Within the BCT group, for every 2 LR among younger patients, 1 developed DM. Among older patients, this ratio was 11:0. The EBCTCG meta-analysis, which evaluated the effect of RT after breast conserving surgery, suggested that RT reduced "any first recurrence" by about 1/2 and reduced breast-cancer mortality by about 1/6. [18]. The association between LR and premature death is heterogeneous [19–20,39], and patients with a good prognosis (e.g., small tumor, grade I, luminal A subtype) had the smallest absolute 5-year LR risk reduction after RT, but the highest 15-year mortality reduction compared with those whose tumor characteristics were less favorable. The present study demonstrated that age affects the association between LR and DM as well; hence, this association was found only among the younger patients. No association between LR and survival was found in the EORTC boost trial [36] and the randomized trials comparing BCT with mastectomy [1–6]. We speculate that this may be so because these studies included mainly postmenopausal women; furthermore, 1/5 of the patients had less favorable tumor characteristics (lymph-node positive). In both subgroups (age older than 45 years and lymph-node positive patients), the association between LR and DM was less outspoken or non-existent.

Our analysis was not based on data from a randomized clinical trial wherefore selection bias and confounding may exist, leading to divergent results as demonstrated when SEER observational data were compared with randomized data [40]. However, a study evaluating the implementation of BCT as a routine procedure in Denmark (DBCG 89-program) displayed an equal failure pattern and improved survival in comparison with women from the clinical randomized DBCG 82 tm protocol evaluating BCT vs. mastectomy [41]. The procedure for data collecting used in this study, was also used in the present study.

Our study has several strengths, including the large cohort (comprising all young lymph-node-negative patients in Denmark within a 10 year-period who received local treatment only), complete registration of incident breast cancer, and complete follow-up data on mortality and LRs within 20 years. Selection bias due to non-response or loss to follow-up is therefore an unlikely explanation for our findings. Information on breast cancer and all-cause mortality had high validity [42–43], which minimized the potential risk of information bias.

The patients were guided to receive BCT or mastectomy based on information provided by the surgeons. As expected, patients having mastectomy had larger tumors than those who underwent BCT. Inversely, tumor-related prognostic factors, like histological type, grade, and ER-status, did not contribute to the choice of surgical procedure as these factors were assessed postoperatively. Thus, one would assume that the mastectomy group would have higher mortality as large tumor size is a strong prognostic marker for survival [44]. Yet, we found that younger BCT patients had higher breast-cancer mortality after 20 years, and their overall survival was poor. Particularly surprising was the higher incidence of lung cancer after BCT. Unfortunately, information on smoking status was not available and we can therefore only speculate as to the cause of this excess incidence. However, the possibility of radiation-induced second lung cancer cannot be ruled out [45].

Almost all of the patients in our study would have received adjuvant anti-hormonal therapy, chemotherapy, and/or Trastuzumab if they had been treated according to present-day guidelines. This evidently affects the generalizability of our findings to today's clinical practice. Systemic treatment reduces LR [14,22,46–47] and may improve survival, especially in young patients who undergo BCT [12]. However, LR rates have decreased over the past decades, and a 10-year LR risk at 2–3% has been published [48–50]; however, long-term data from this period are lacking. The low 5–10-year LR rate seen today would likely reduce the observed survival difference between young patient receiving BCT and mastectomy in the present study.

Nevertheless, it is noteworthy that two-thirds of the study population had no recurrence after 20 years even if they received no adjuvant systemic treatment.

Conclusion

Patients treated with BCT and no adjuvant systemic treatment developed LR throughout the whole 20-year period, and they had an increased risk of LR. Among younger patients ($\leqslant$45 years of age), LR was associated with DM, and younger BCT patients had an increased breast-cancer and all-cause mortality compared with mastectomy patients. In contrast, older patients (>45 years of age) receiving BCT did not have an increased mortality. When future treatment guidelines for young lymph-node-negative patients are to be updated, the possibility of a negative impact of BCT on survival in this cohort should be taken into account.

Conflict of interest statement

The authors declare no relevant potential conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2016.05.006.

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