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Original article

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 ⩽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%).

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