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Postmastectomy RT

Loco-regional recurrence after mastectomy in high-risk breast cancer—risk and prognosis. An analysis of patients from the DBCG 82 b&c randomization trials

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Abstract

***Background and purpose*: In the DBCG 82 b&c trials, 3083 patients with stages II and III breast cancer were randomised to receive post-mastectomy radiotherapy (RT) versus no RT in addition to systemic therapy. The study showed a decrease in loco-regional recurrences and an improved survival in patients receiving RT. The aim of the present study was to identify risk factors for loco-regional recurrence (LRR), to evaluate the treatment of LRR and to examine the prognosis after LRR.**

***Patients and methods*: The 18-year probabilities of LRR were calculated for different prognostic factors using the Kaplan-Meier method. The efficacy of different LRR treatments was compared. The 5-year survival and distant metastases (DM) probability after LRR was calculated with regard to initial randomization group, primary tumor and recurrence related variables.**

***Results*: Of the 3083 patients, 535 had a LRR alone as first site of failure. In univariate analyses, large primary tumor size, ductal carcinoma, high malignancy grade, fascia invasion, few removed nodes, many positive nodes and extracapsular invasion were all risk factors for developing LRR. Combined treatment with surgery and RT at the time of LRR increased the persistent loco-regional control. The 5-year probability of subsequent DM was 73% irrespective of initial randomization group. In multivariate analysis, large primary tumor size, many positive nodes, extracapsular invasion, supra/infraclaviculary failures, multiple LRR and a short interval less than 2 years to first LRR were poor prognostic factors for survival.**

***Conclusions*: Twenty-seven percent of LRR patients had no DM 5 years after failure. Initial randomization group did not alter the prognosis after LRR. Combined treatment of the LRR with surgery and RT improved persistent loco-regional control compared with surgery or RT alone.**

Keywords: Breast cancer; Mastectomy; Radiotherapy; Loco-regional failure; Risk factors; Prognosis; Randomized clinical trial

Introduction

Loco-regional recurrence after mastectomy without simultaneous distant metastases (LRR) is a relative common situation, although the frequency varies considerable among published studies due to differences in primary tumor characteristics, surgical and adjuvant treatments and follow-up time [1,2]. The frequency of LRR is especially pronounced among high-risk patients receiving no post-mastectomy radiotherapy (RT) [3]. The criteria for selecting patients for RT are based on the results of studies, which have identified risk factors for LRR among non-irradiated patients. For example increasing T-stage and many involved axillary nodes were risk factors for LRR in studies including patients with T1–T3 tumors, most being axillary node positive and no patients receiving RT [4–6].

Five-year overall survival probabilities after LRR has been reported to be 30–38% [7–11] in published studies including patients with LRR treated from 1948 to 1979, whereas the survival after LRR was higher in studies including patients treated from 1964 to 1992 with 5-year survival probabilities being 42–49% [12–15]. In multivariate analyses, many factors have been found to be prognostic for survival after LRR, such as the initial T-stage and number of positive nodes [14–16], site of LRR, time interval from mastectomy to LRR and achievement of loco-regional control after treatment of the LRR [12,13,15,16].

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The treatment of LRR is often based on institutional preferences, although a curative loco-regional treatment approach consisting of either excision of the LRR, RT or both is commonly recommended [17]. In case of limited surgery only without RT the risk of developing another LRR is very high about 60–70% and likewise, the risk of another LRR is high in patients receiving only RT to small fields with low doses [17]. The combination of radical surgery and loco-regional RT to an appropriate dose results in high frequencies of persistent loco-regional control [18].

The aim of the present study was to explore further the LRR, which appeared among patients randomized in the DBCG 82 b&c trials in order to (1) identify risk factors for LRR; (2) evaluate the importance of treatment of the LRR; and (3) examine the prognosis after LRR.

Patients and methods

Study population and treatment

The DBCG 82 b&c trials have previously been described in details [19,20]. In brief, between 1982 and 1990, 3083 high-risk breast cancer patients were randomized to $\pm$RT in addition to systemic therapy after total mastectomy and partial axillary dissection. Of the 1538 patients randomized to RT, 1341 patients (87%) had megavoltage RT to the chest wall and regional lymph nodes including the axillary, supra/infraclaviculary and ipsilateral internal mammary nodes with the prescribed dose of 48–50 Gy in 22–25 fractions, four or five fractions per week, 120 patients (8%) had orthovoltage RT (36 Gy/20 fx, 5 fx/week) and 77 patients (5%) never began or completed RT [21]. The adjuvant systemic therapy consisted of nine cycles of CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, fluorouracil 600 mg/m^{2}l) to the pre-menopausal patients randomized to no RT and eight cycles of CMF to the pre-menopausal patients randomized to RT [19]. The post-menopausal patients had tamoxifen 30 mg daily for 1 year [20].

In the DBCG 82 b&c studies, no guidelines were available for the treatment of patients with subsequent LRR which thus was carried out according to institutional preferences.

Follow-up, endpoints and statistical analysis

Long-term follow-up information in all patients except those with DM as first breast cancer event was collected from medical records, death certificates, general practitioners and the National Patient Registry. Follow-up was continued until death, emigration, or last date of contact with hospital or general practitioners. Nine patients were lost for follow-up because of emigration, otherwise the follow-up was complete.

A LRR was defined as (1) any reappearance of cancer in the ipsilateral chest wall or skin or soft tissue overlaying the ipsilateral chest wall, axilla or supra/infraclaviculary region; or 2) cancer spread to the ipsilateral axillary nodes or 3) ipsilateral supra/infraclaviculary nodes. If a DM occurred within 1 month of the LRR the patient was not included in this analysis. Staging procedures at the time of LRR included clinical examination, chest X-ray, bone scan and optionally bone X-ray and laboratory tests in order to screen for DM. Liver ultrasonography was done only in the case of abnormal liver enzymes or clinical symptoms. Two percent of the LRR was not cytologically or histologically proven.

Risk factors for developing LRR were only evaluated for the 1545 patients randomized to no RT, since the LRR among patients randomized to RT were rare.

For evaluating the treatment of the LRR, we defined complete remission as disappearance of all visible tumor tissue at the site of LRR and persistent loco-regional control was defined as no further LRR in the follow-up period among the patients with complete remission of the first LRR.

For evaluating prognosis after LRR, the endpoints were overall survival, second LRR (LRR2) and DM. LRR2 was defined as an ipsilateral chest wall and/or axillary and/or supra/infraclaviculary failure irrespective of DM status. No distinction was made regarding LRR2 as a re-recurrence at the same site or if this was another location. DM was defined as any appearance of breast cancer outside the ipsilateral loco-regional area. Histopathological or cytological confirmation of DM was not routinely performed and often the diagnosis was based on clinical findings or diagnostic imaging.

We estimated the probability of LRR, survival after LRR, subsequent LRR2 and subsequent DM by the Kaplan–Meier method. Using the Kaplan–Meier method for estimating other events than survival has previously been shown to be a problem due to the non-independence between these different events [22]. Therefore, also frequencies of LRR were presented.

When calculating probability of LRR, censuring was done in the case of DM, contralateral breast cancer (CBC), death or the date of last contact. Survival time after LRR was calculated from the date of LRR to death or evaluation date for survival. The time to subsequent LRR2 was calculated from the date of first LRR to second LRR, death or last date of contact. The time to subsequent DM was calculated from the date of LRR to DM, or censuring (CBC, death, last date of contact).

The log-rank test was used for comparison between the subgroups of patients. Test for trend was performed. Univariate significant variables with P values less than 0.10 were included in a Cox regression model using the enter method. The assumption of proportional hazard was tested and accepted for all variables. The Level of significance was chosen as 5% and all P values were two-tailed.

The treatment effect was evaluated in accordance with the intention to treat principle. The patients were included in their randomization group, irrespective of whether they completed the planned treatment or not.

The evaluation date for recurrences and survival was November 15, 2004, which resulted in a median potential follow-up time after mastectomy of 18 years (range 15–22).

Calculations were done using SPSS version 11.5 for Windows.

Results

A total of 535 patients had a LRR as first site of failure (chest wall: $N=259$, axilla: $N=153$, supra/infraclaviculary: