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Locoregional recurrence after breast-conserving therapy remains an independent prognostic factor even after an event free interval of 10 years in early stage breast cancer

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Abstract ***Introduction:*** Locoregional recurrence (LRR) after breast-conserving therapy is a well-known independent risk factor associated with unfavourable long-term outcome. Controversy exists concerning the prognostic impact of a LRR after a very long event-free interval.
Method: Patients who underwent breast-conserving therapy for early stage breast cancer were pooled from four European Organisation for Research and Treatment of Cancer (EORTC) Breast Group trials. Only LRR as a first event was taken into account. Risk factors such as tumour size, nodal status, young age and chemotherapy were assessed in multivariate Cox regression analysis. LRR was used as a time-dependent variable in the landmark analysis for distant disease-free survival (DFS) and overall survival (OS). Patients were categorised as having at least 0, 5 or 10 years event-free survival.
Results: In total, 7751 early stage breast cancer patients were included with a median follow-up of 10.9 years. Tumour size, nodal status, young age and chemotherapy are strong independent prognostic factors with a significant impact on long-term outcome, but lose their power and significance over time. Including all patients, LRR was the strongest prognostic factor for OS and distant DFS (resp. HR 5.01 and HR 5.31, $p < 0.001$). In the subgroup of patients developing a LRR after at least 5 or 10 years, LRR remained the strongest independent prognostic factor for OS (resp. HR 3.98, HR 4.96, $p \leqslant 0.001$) and distant DFS (HR 4.42, HR 7.57 $p < 0.001$).

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Conclusion: This is the first study which shows LRR after breast-conserving therapy is a very strong, time-independent prognostic factor for long term outcome in early stage breast cancer patients. These findings suggest that a LRR after a long event-free interval seems to be an indicator rather than an instigator of subsequent distant disease.

1. Introduction

Breast cancer in European women is by far the most common form of cancer with an estimated 370,100 new cases per year resulting in approximately 129,900 deaths. It causes 17.4% of all cancer related deaths and is the most frequent cause of cancer death in women.[1] Adequate diagnostics, treatment and follow-up are therefore mandated. Breast-conserving therapy for early stage breast cancer has been a well established therapeutic option for more than 30 years. Although locoregional recurrence (LRR) rates are higher after breast-conserving therapy in comparison with mastectomy, overall survival rates are similar.[2–4]

Mastectomy and breast-conserving therapy have similar long-term outcomes. The event of an isolated locoregional recurrence after breast-conserving therapy has been proven to be an independent prognostic factor associated with unfavourable outcome,[5–7] though controversy still exists concerning the prognostic impact of such a locoregional recurrence after a very long event free interval.[5,8,9] Other significant long term outcome prognostic factors in early stage breast cancer have been identified before. Tumour size, nodal status and grade, tumour markers (cathepsin-D), DNA proliferation markers (Ki-67, S-phase fraction, mitotic index) and lymph vessel invasion all showed a significant association with survival outcome.[10] A more recent review showed tumour size, lymph node status and histological grade are the most important determinants of a breast cancer patients' survival, but their role decreases over time.[11]

The aim of this study was to analyse the independent prognostic value of a locoregional recurrence, as first event after a long event free interval, on long-term outcome in patients who underwent breast-conserving therapy.

2. Methods

2.1. Study population

To study the prognostic values of established clinical-pathological prognostic factors, we pooled the data of four randomised phase III clinical trials conducted by the European Organisation for Research and Treatment of Cancer (EORTC) Breast Cancer Group and the EORTC Radiotherapy Group. These trials consisted of early stage breast cancer patients, included in the period 1980 until 1999, comparing breast conserving therapy (BCT) to modified radical mastectomy and different timing of the same systemic chemotherapy. From these trials we included all patients who underwent breast-conserving therapy, only locoregional recurrences as first event were taken into account.

2.2. Databases

The EORTC trial 10801 (1980–1986, median follow-up 13.4 years) was conducted in order to assess the safety of breast-conserving treatment. Patients were randomised between breast-conserving surgery combined with radiotherapy and modified radical mastectomy. A total of 902 patients were randomised, seven of which developed a LRR after more than 10 years.[3,12]

The EORTC trial 10854 (1986–1991, median follow-up 10.8 years) studied the question whether one course of peri-operative chemotherapy given directly after surgery yields better results in terms of treatment outcome than surgery alone. A total of 2795 patients were included, 16 of which developed a LRR after more than 10 years.[13]

The EORTC trial 10902 (1991–1999, median follow-up 10 years) was set up to compare pre-operative adjuvant chemotherapy with postoperative chemotherapy. A total of 698 patients were randomised, three of which developed a LRR after more than 10 years.[14,15]

The EORTC trial 22881 (1989–1996, median follow-up 10.8 years) studied the value of an extra boost dose of irradiation therapy after primary radical breast-conserving surgery. A total of 5569 patients were randomised, 38 of which developed a LRR after more than 10 years.[16,17]

Data concerning patient age at time of diagnosis, type of surgery, TNM status and administration of chemotherapy were collected for all patients. None of the trials collected data concerning histological grade. One of the trials (EORTC 10801) did not collect data concerning hormone receptor status. Therefore, histological grade, estrogen receptor and progesterone receptor status and the administration of anti-hormone therapy were not included in the analysis.

2.3. Definitions of end points

The goal of this study was to evaluate the independent prognostic impact of locoregional recurrence on long-term outcome as a time dependent variable. Locoregional recurrence was defined as ipsilateral tumour growth in the breast, chest wall or ipsilateral axillary