



## Local recurrence following breast-conserving treatment in women aged 40 years or younger: Trends in risk and the impact on prognosis in a population-based cohort of 1143 patients

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**Abstract Aim:** To evaluate trends in the risk of local recurrences after breast-conserving treatment (BCT) and to examine the impact of local recurrence (LR) on distant relapse-free survival in a large, population-based cohort of women aged  $\leq 40$  years with early-stage breast cancer.

**Methods:** All women ( $n = 1143$ ) aged  $\leq 40$  years with early-stage (pT1-2/cT1-2, N0-2, M0) breast cancer who underwent BCT in the south of the Netherlands between 1988 and 2010 were included. BCT consisted of local excision of the tumour followed by irradiation of the breast.

**Results:** After a median follow-up of 8.5 (0.1–24.6) years, 176 patients had developed an isolated LR. The 5-year LR-rate for the subgroups treated in the periods 1988–1998, 1999–2005 and 2006–2010 were 9.8% (95% confidence interval (CI) 7.1–12.5), 5.9% (95% CI 3.2–8.6) and 3.3% (95% CI 0.6–6.0), respectively ( $p = 0.006$ ). In a multivariate analysis, adjuvant systemic treatment was associated with a reduced risk of LR of almost 60% (hazard ratio (HR) 0.42; 95% CI 0.28–0.60;  $p < 0.0001$ ). Patients who experienced an early isolated LR ( $\leq 5$  years after

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BCT) had a worse distant relapse-free survival compared to patients without an early LR (HR 1.83; 95% CI 1.27–2.64;  $p = 0.001$ ). Late local recurrences did not negatively affect distant relapse-free survival (HR 1.24; 95% CI 0.74–2.08;  $p = 0.407$ ).

**Conclusion:** Local control after BCT improved significantly over time and appeared to be closely related to the increased use and effectiveness of systemic therapy. These recent results underline the safety of BCT for young women with early-stage breast cancer.

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## 1. Introduction

Local recurrence (LR) after prior breast surgery has been linked to an increased risk of distant metastases and death,<sup>1–5</sup> where an early-LR (i.e.  $\leq 5$  years) is associated with a greater risk of developing distant metastases compared to late-occurring LR's.<sup>1–3,5</sup> Young age has always been regarded as an independent prognostic factor for the risk of LR after breast-conserving treatment (BCT). The risk of developing a LR is 2–4 times higher in women younger than 40 years at the time of diagnosis of breast cancer compared to women older than 50 years.<sup>2,3,6–11</sup> Therefore, the risk of developing a LR remains a point of concern in young women treated with BCT.

Multiple studies have shown that the LR-rate after BCT is declining.<sup>12–15</sup> Explanations for this decline are suggested to be multifactorial, including a more careful evaluation of tumour margins, more extensive and accurate use of radiotherapy boost to the tumour bed and more patients receiving (neo)adjuvant systemic therapy.<sup>8,12–14,16,17</sup> The use of new combinations of (neo)adjuvant systemic therapy and the introduction of trastuzumab may have resulted in a further improvement of the local control, especially in young women. Trastuzumab is used in the adjuvant setting in the Netherlands since 2005.<sup>18</sup> Several studies that compared adjuvant chemotherapy with or without trastuzumab in women with surgically removed HER2-positive breast cancer showed that the use of trastuzumab improves LR-free survival.<sup>19–26</sup>

To evaluate the risk of LR after BCT and to determine factors that are of prognostic relevance in consecutive time era's, we studied a large cohort of 1143 patients aged  $\leq 40$  years who received BCT in the period 1988–2010.

## 2. Patients and methods

### 2.1.1. Study population

Patient data were obtained from the population-based Eindhoven Cancer Registry (ECR). This serves a population of approximately 2.4 million inhabitants in the south of the Netherlands and records data on all patients with newly diagnosed cancer since 1955. These data were compared to data provided by the two radiotherapy departments in this region, the Catharina Hospital in

Eindhoven and Institute Verbeeten in Tilburg. Only patients with early-stage (pT1-2/cT1-2, N0-2, M0) breast cancer (TNM/AJCC tumour staging 7th edition) were considered eligible for this study. The ECR identified 1200 patients aged  $\leq 40$  years who were diagnosed with breast cancer and underwent BCT between 1988 and 2010. The medical files from the patients of the two radiotherapy departments were used to extract information with respect to patient, tumour and treatment characteristics as well as to outcome. When recent follow-up information was missing, we contacted the general practitioner. After exclusion of 32 patients with stage III or IV breast cancer, nine patients with non-invasive breast cancer, three patients with synchronous bilateral breast cancer, two patients who underwent mastectomy instead of BCT, 10 patients who presented with a local recurrence or contralateral breast carcinoma instead of a primary breast tumour and one patient who had not received radiotherapy, 1143 patients remained available for the analysis.

### 2.2.2. Treatment

BCT included wide local excision of the tumour and appropriate axillary management followed by irradiation of the whole breast, mostly including a boost to the primary tumour bed. Further details about this cohort have been published before.<sup>13,14</sup> Some major changes in the management of breast cancer in the Netherlands took place during the period covered by our study. The first major change was in 1998, with the publication of the new Dutch guideline<sup>27</sup> according to which lymph node-negative patients with high-risk features, depending on the size, grade and hormone receptor status of their tumour, were advised to receive adjuvant systemic therapy. The second major change was an update of the guideline in 2005, where women with HER2-positive breast cancer were recommended to receive trastuzumab in conjunction with adjuvant chemotherapy. Based on these changes in the guidelines for administering systemic therapy, we decided to divide the study population into three subgroups; 1988–1998, 1999–2005 and 2006–2010.

### 2.3.3. Definition of end-points

The end-points of this study were LR, distant metastasis and death. For each end-point, the time to event

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