International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

# Pattern of Ipsilateral Breast Tumor Recurrence After Breast-Conserving Therapy

Jan Jobsen, PhD,* Job van der Palen, PhD,[†,‡] Sietske Riemersma, PhD,[§] Harald Heijmans, MD,[||] Francisca Ong, PhD,* and Henk Struikmans, PhD[¶,#]

*Department of Radiation Oncology, Medisch Spectrum Twente, Enschede, The Netherlands; [†]Department of Epidemiology, Medisch Spectrum Twente, Enschede, The Netherlands; [‡]Department of Research Methodology, Measurement, and Data Analysis, Faculty of Behavioral Science, University of Twente, Enschede, The Netherlands; [§]Laboratory for Pathology Oost Nederland, Hengelo, The Netherlands; [||]Department of Surgery, Ziekenhuis Groep Twente, Hengelo, The Netherlands; [¶]Department of Radiation Oncology, Leiden University Medical Centre, Leiden, The Netherlands; and [#]Radiotherapy Centre West, Medical Centre Haaglanden, The Hague, The Netherlands

Received Dec 19, 2013, and in revised form Apr 16, 2014. Accepted for publication Apr 22, 2014.

**Summary**

The rate of ipsilateral breast tumor recurrence (IBTR) in breast cancer after breast-conserving therapy was analyzed. We demonstrate that after 12 years' follow-up, there is an especially high recurrence rate for women ≤40 years old. For women ≤40 years old, the absence of adjuvant systemic therapy and the presence of lymph vascular space invasion (LVSI) are associated with a higher rate of IBTR. For women >40 years old, the presence of LVSI and lobular carcinoma in situ are prognostic factors for IBTR.

**Purpose:** To analyze the incidence and prognostic factors of ipsilateral breast tumor recurrence (IBTR) after breast-conserving therapy (BCT) in a large, population-based, single-center study with long-term follow-up.

**Methods and Materials:** We analyzed 3595 cases in which BCT was performed in 3824 women with stage I or II breast cancer. The incidence of IBTR was analyzed over time and was based on IBTR as first event.

**Results:** The 15-year local relapse-free survival was 90.9%. The hazard estimates for IBTR showed a time course with 2 peaks, the first at approximately 5 years and the second, twice as high, at 12 years. Stratifying subjects by age and margin status showed that, for women ≤40 years old with negative margins, adjuvant systemic therapy led to a 5-fold reduced risk of recurrence compared to none, and the presence of lymph vascular space invasion (LVSI) had a 3-fold increased risk compared to its absence. For women >40 years old, the presence of LVSI (hazard ratio [HR] 2.5) and the presence of lobular carcinoma in situ in the lumpectomy specimen (HR 2.3) were the only 2 risk factors.

**Conclusions:** We demonstrated a pattern in risk of IBTR over time, with 2 peaks, first at approximately 5 years and a second, much higher peak at approximately 12 years, especially for women ≤40 years old. For women ≤40 years old with tumor-free resection margins, we noted that the absence of adjuvant systemic therapy and the presence of LVSI were independent prognostic factors of IBTR. For women >40 years old, the presence of LVSI and the presence of lobular carcinoma in situ were independent risk factors.


Reprint requests to: Jan J. Jobsen, Department of Radiation Oncology, Medisch Spectrum Twente, Haaksbergerstraat 55, 7513 ER Enschede, The Netherlands. Tel: (31) 53 4872750; E-mail: j.jobsen@mst.nl

Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. 89, No. 5, pp. 1006–1014, 2014
0360-3016/$ - see front matter 
http://dx.doi.org/10.1016/j.ijrobp.2014.04.039

## Introduction

For early-stage breast cancer, breast-conserving therapy (BCT) is believed to be the treatment of choice. Treatment has evolved from primary surgery and radiation therapy to a more sophisticated method of surgery followed by radiation therapy and adjuvant systemic therapies like hormone therapy, chemotherapy, and immunotherapy. Breast cancer recurrences are seen both shortly after initial treatment and many years thereafter. Although the risk of ipsilateral breast tumor recurrence (IBTR) exists over many years, changes in recurrence risk over time have hardly received attention. In most studies, the focus has been directed at either recurrence or survival curves depicting the proportion of patients who are recurrence-free after a fixed time interval. In contrast, smoothed hazard curves depict the risk of recurrence at any given time and show how the risk of developing recurrence changes over time. The probability of relapse depends on a variety of prognostic factors (1, 2).

This study analyzed all cases of IBTR as a first event and all cases treated with BCT in our region from 1984 through 2010. In this large, population-based, single-center study, we analyzed the incidence and pattern of IBTR after BCT and prognostic factors, with a separate focus on age.

## Methods and Materials

This prospective study of a cohort of breast cancer patients was started in 1984 when BCT was introduced in our region. All patients in the Twente-Achterhoek with invasive breast cancer received their irradiation at the Radiotherapy Department of the Medisch Spectrum Twentey. Using the data from 1984 through 2010, we registered a total of 3998 BCT treatments of invasive breast cancer in 3863 women. Patient data, including demographics, histology, staging information, treatment, and outcome were recorded prospectively and were updated regularly.

Histological examination of all cases was done in the Pathology Laboratory Oost Nederland according to standard procedures. For women with a local recurrence, all histology of the primary and the recurrence tissue was reviewed or updated by 1 pathologist. Patients were staged according to the TNM classification system (7th edition, 2009).

As it is often difficult, morphologically, to differentiate between a local recurrence and a new primary tumor in the treated breast, all recurrences, invasive carcinoma (IC), and/or ductal carcinoma in situ (DCIS) found in the ipsilateral breast during follow-up were classified as IBTR. For the purposes of this study, the cut-off date for analysis was February 2014.

### Treatment

BCT initially consisted of lumpectomy with axillary clearance of disease levels I to III, followed by whole-breast radiation therapy and then followed by a boost aimed at the lumpectomy cavity. After 2001, axillary staging was done primarily by using sentinel lymph node procedures, followed only by complete axillary dissection in cases with proven axillary lymph node metastases or when sentinel node biopsy examination failed. Radiation therapy consisted of 50 Gy in 2-Gy fractions, administered to the whole breast, followed by a boost of 14 Gy to the lumpectomy cavity, regardless of margin status. In 16% slightly altered fractionation schedules for the boost were used. Since 2004, the indication to administer a boost dose has depended on age, lymph node status, and margin status: patients with no lymph node metastases and negative margins and a tumor size of $\leq$1.0 cm who are $>$60 years old or a tumor size of $\leq$2.0 cm and are $>$70 years old have not received a boost. Adjuvant systemic and regional radiation therapy was given according to existing treatment guidelines. Regional radiation therapy was indicated for patients with either 4 or more axillary lymph node metastases or with presence of extra-nodal disease.

In the late 1980s, adjuvant systemic therapy was given for patients with histologically proven axillary lymph node metastasis. From 1992 on, all premenopausal patients with histologically proven axillary lymph node metastasis have received chemotherapy. For postmenopausal patients, adjuvant hormone therapy was given in cases of tumor-positive axillary lymph nodes. Since 1999, the indications for adjuvant systemic therapy have depended not only on lymph node status but also on MAI, histological grade, and tumor size. Premenopausal women receive chemotherapy and hormone therapy when the estrogen receptor status is positive.

In late 2004, treatment with trastuzumab in combination with adjuvant chemotherapy was introduced in our region for HER 2-neu-positive cases.

### Statistical methods

Time to recurrence and length of follow-up were calculated from the date of the lumpectomy. To test between-group differences for categorical data $\chi^2$ tests were used, and local recurrences were analyzed in relation to the number of BCT treatments given. For all survival analyses, patients were censored if they had not experienced an event (local recurrence, distant metastasis) at the date of last follow-up or at the date of death. Local recurrence-free survival (LRFS) is defined as survival time without local recurrent disease.

The Cox proportional hazards model was used to test the independent effect after adjusting for known prognostic factors, and hazard ratios (HR) estimated with 95% confidence limits are presented.

For comparison of recurrence distributions, the log-rank test was used. Univariate variables related to the outcomes of interest ($P<.05$) were entered in the multivariate analyses. To visualize the risk of recurrence over time, HR values are plotted. Wilcoxon rank sum and McNemar tests