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CLINICAL INVESTIGATION **Breast**

INTRAOPERATIVE RADIOTHERAPY AS A BOOST DURING BREAST-CONSERVING SURGERY USING LOW-KILOVOLTAGE X-RAYS: THE FIRST 5 YEARS OF EXPERIENCE WITH A NOVEL APPROACH

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Purpose: Intraoperative radiotherapy (IORT) during breast-conserving surgery (BCS) has been recently introduced using different devices. We report the first 5 years of a single-center experience after introduction of a novel approach to deliver IORT as a tumor bed boost during BCS for breast cancer.
Methods and Materials: A total of 155 breast cancers in 154 women (median age, 63 years; range, 30–83 years; T1/T2 = 100/55; N0/N+ = 108/47) were treated between February 2002 and December 2007 at the University Medical Center Mannheim, in whom IORT as tumor bed boost was applied using 50-kV X-rays (20 Gy) followed by 46–50 Gy whole-breast external-beam radiotherapy (EBRT). Chemotherapy, if indicated, was given before EBRT. The median interval between BCS plus IORT and EBRT was 40 days. Median follow-up was 34 months (maximum 80 months, 1 patient lost to follow-up). Overall survival and local relapse-free survival were calculated at 5 years using the Kaplan-Meier method. Seventy-nine patients were evaluated at 3-year follow-up for late toxicity according to the Late Effects in Normal Tissues–Subjective, Objective, Management, and Analytic system.
Results: Ten patients died, 2 had in-breast relapse, and 8 developed distant metastases (5-year overall survival = 87.0%; 5-year local relapse-free survival = 98.5%). Grade 3 fibroses of the tumor bed were detected in 5% of the patients after 3 years. Skin toxicity was mild (telangiectases and hyperpigmentations in approximately 6% each).
Conclusions: Intraoperative radiotherapy as a tumor bed boost during BCS for breast cancer using low-kilovoltage X-rays followed by EBRT yields low recurrence and toxicity rates. © 2010 Elsevier Inc.

Breast cancer, Intraoperative radiotherapy, Boost, Local recurrence, Late toxicity.

INTRODUCTION

Breast-conserving surgery (BCS) followed by external-beam whole-breast radiotherapy (EBRT) has become the standard of care in early breast cancer (1, 2). Adjuvant EBRT after BCS significantly reduces the risk for in-breast tumor recurrence (IBTR) and improves overall survival (3) over BCS alone. Additional radiation dose to the tumor bed (i.e., a boost) leads to a further reduction of local recurrences (4–7). However, there is a considerable risk for geographic miss and increased side effects when the tumor bed boost is given with EBRT (5, 6, 8).

Recently, the concept of intraoperative radiotherapy (IORT) during BCS has been introduced using linear accelerators, brachytherapy, or dedicated, mobile IORT devices generating fast electrons or low-energy X-rays (9–19). Here, we report the outcome of the first 5 years after introduction of a novel approach to deliver IORT as a tumor bed boost during BCS for breast cancer, followed by EBRT.

METHODS AND MATERIALS

A total of 249 breast cancers (cases) were treated with IORT in 247 patients between February 2002 and December 2007 at the University Medical Center Mannheim, University of Heidelberg, Germany. Forty of these patients were included in the prospective TARGIT trial (9, 10), 18 patients received IORT alone for breast cancer in a previously irradiated breast, and 35 patients received no EBRT after BCS plus IORT owing to the presence of distant metastases, severe comorbidity, or patient refusal and were therefore excluded from the present analysis.

This analysis includes 155 breast cancers in 154 women (median age, 63 years; range, 30–83 years; T1/T2 = 100/55; N0/N1/N2/N3 = 108/34/11/2) in whom IORT as tumor bed boost was applied, followed by EBRT.

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Intraoperative radiotherapy was given as previously reported (11, 20–23). In short, after wide excision of the breast cancer, a single dose of 20 Gy was given (mean ± SD, 19.7 ± 1.5 Gy). The first 8 cases received 14.7–17.6 Gy during dose finding, but later only 2 cases received <20 Gy owing to treatment interruptions secondary to machine failure (6 Gy and 18 Gy, respectively). Radiation dose was prescribed to the applicator surface and delivered using 50-kV X-rays with the INTRABEAM miniature X-ray generator (Carl Zeiss Surgical, Oberkochen, Germany; Fig. 1). The median applicator size was 4.5 cm (range, 2.5–5.0 cm), resulting in treatment durations of 7.5–51.1 min (median, 36.6 min). Axillary clearance was performed when the sentinel node was positive.

External-beam radiotherapy to the breast was initiated after completion of wound healing and/or chemotherapy, with a median interval between IORT and EBRT of 40 days (range, 13–226 days). Using CT-based three-dimensional treatment planning (Brilliance CT Big Bore [Philips, Cleveland, OH]; Oncentra MasterPlan [Nucletron, Veenendaal, The Netherlands]) a dose of 46 Gy in 2-Gy fractions was prescribed using standard tangential treatment portals (6 MV; Synergy; Elekta, Crawley, United Kingdom). A dose of 50 Gy was given to the breast and the supra/infraclavicular fossa when there was an indication for inclusion of the supra/infraclavicular lymph nodes (n = 26).

During treatment planning the breast volume and—when present—the tumor bed seroma were contoured slice by slice on the planning CT for volumetric analysis in 148 cases (including 77 patients with 3-year follow-up).

Systemic therapy was given according to the St. Gallen consensus recommendations. Chemotherapy (n = 46; 4 patients, 6× cyclophosphamide, methotrexate and 5-fluorouracil; 7 patients, 4–6× epirubicin and cyclophosphamide [EC]; 14 patients, 3–6 × 5-fluorouracil, epirubicin, and cyclophosphamide [FEC]; 10 patients, 4 × EC plus 4× docetaxel; 5 patients, 3 × FEC plus 3× paclitaxel /docetaxel; 3 patients, 3–6× docetaxel, doxorubicin, and cyclophosphamide; 3 patients other) was routinely given before EBRT. One hundred twenty-nine cases received endocrine therapy (61 patients tamoxifen [TAM]; 13 patients TAM plus luteinizing hormone–releasing hormone; 18 patients TAM → aromatase inhibitor; 37 patients aromatase inhibitor), which was started 8–14 days after surgery or after completion of chemotherapy.

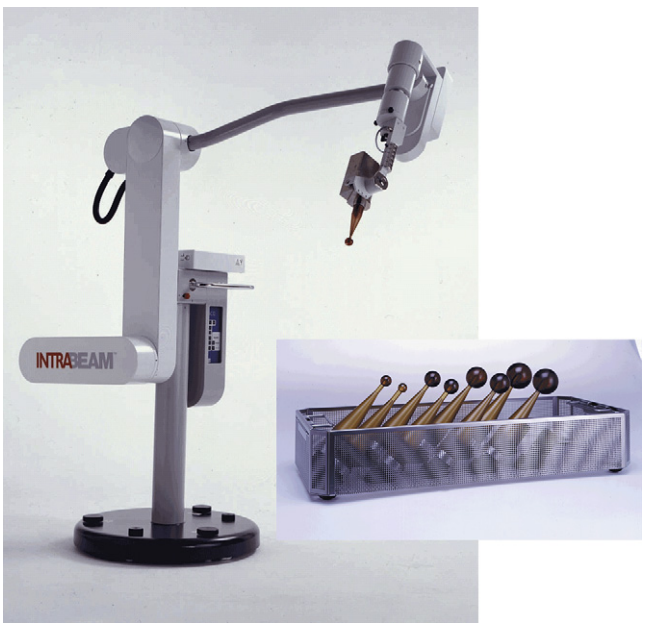

Fig. 1. The INTRABEAM system for intraoperative radiotherapy of breast cancer consists of a 50-kV X-ray generator mounted on a flexible floor stand and a set of applicators ranging from 1.5 to 5 cm in diameter.

Patients were recalled every 6–12 months for follow-up visits. Clinical late toxicity at 3 years was scored by the treating radiation oncologists (F.W., U.K.T.) according to the modified Late Effects in Normal Tissues–Subjective, Objective, Management, and Analytic (LENT-SOMA) scoring system, as previously reported (22, 24), in all 79 cases having a follow-up time of 3 years with an intact breast (range, 30–39 months). Date of evaluation was December 2008. One mastectomy was performed because of diffuse, severe fibrosis 12 months after EBRT. This patient was scored as fibrosis Grade 3, but no further LENT-SOMA grading could be performed.

Median follow-up of the surviving patients was 34 months (maximum, 80 months; 1 patient lost to follow-up). Overall survival and local (in-breast) relapse-free survival were calculated at 5 years. All survival and follow-up times were calculated from the day of IORT. Data are reported as mean ± SD, median (range), and frequencies. For statistical analysis the Student's t test, the Mann-Whitney U test, the χ^2 test, and the Spearman rank correlation coefficient were used. A two-sided p value of <0.05 was considered statistically significant. Survival times were calculated using the Kaplan-Meier method. All data were analyzed with SPSS 16.0.2 for Windows (SPSS, Chicago, IL).

RESULTS

Survival and local control

There were a total of 10 deaths, eight distant metastases, and two in-breast recurrences, resulting in an overall survival rate at 5 years of 87.0% and local (in-breast) relapse-free survival rate of 98.5% (Fig. 2).

One of these recurrences was observed in a patient with massive lymphangio-invasion at initial diagnosis and represented as a diffuse recurrence in the whole breast 10 months after IORT. The second recurrence occurred 3 cm distant from the initial tumor bed in a patient who initially refused re-excision although recommended because of ductal

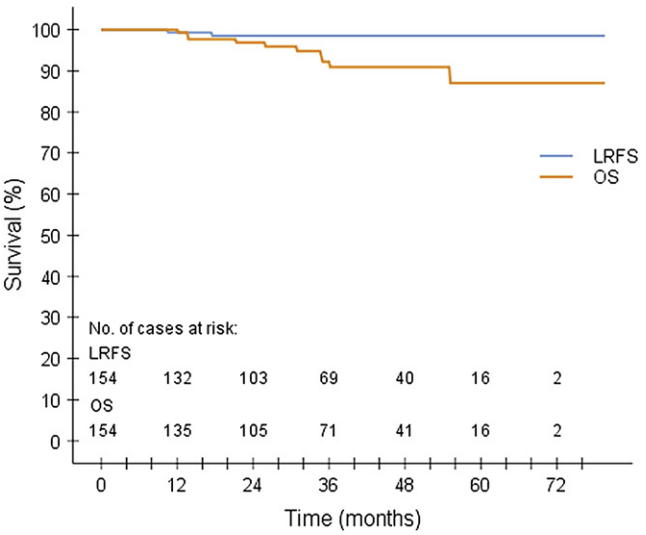

Fig. 2. Overall survival (OS) and local (in-breast) recurrence-free survival (LRFS) after breast-conserving surgery and intraoperative radiotherapy followed by external-beam radiotherapy.