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Clinical Investigation: Breast Cancer

Prospective Multicenter Trial Evaluating Balloon-Catheter Partial-Breast Irradiation for Ductal Carcinoma in Situ

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Summary

This prospective, multicenter trial evaluated the outcomes of patients with ductal carcinoma in situ (DCIS) treated with accelerated partial-breast irradiation (APBI). A total of 42 breasts were treated with lumpectomy plus APBI. The median follow-up was 5.3 years. The ipsilateral breast tumor recurrence rate was 9.8%, with a 5-year actuarial rate of 11.3%. All recurrences were DCIS and occurred outside the treated area.

Purpose: To determine outcomes of accelerated partial-breast irradiation (APBI) with MammoSite in the treatment of ductal carcinoma in situ (DCIS) after breast-conserving surgery.
Methods and Materials: We conducted a prospective, multicenter trial between 2003 and 2009. Inclusion criteria included age >18 years, core needle biopsy diagnosis of DCIS, and no prior breast cancer history. Patients underwent breast-conserving surgery plus MammoSite placement. Radiation was given twice daily for 5 days for a total of 34 Gy. Patients were evaluated for development of toxicities, cosmetic outcome, and ipsilateral breast tumor recurrence (IBTR).
Results: A total of 41 patients (42 breasts) completed treatment in the study, with a median follow up of 5.3 years. Overall, 28 patients (68.3%) experienced an adverse event. Skin changes and pain were the most common adverse events. Cosmetic outcome at 6 months was judged excellent/good by 100% of physicians and by 96.8% of patients. At 12 months, 86.7% of physicians and 92.3% of patients rated the cosmetic outcome as excellent/good. Overall, 4 patients (9.8%) developed an IBTR (all DCIS), with a 5-year actuarial rate of 11.3%. All IBTRs were outside the treatment field. Among patients with IBTRs, the mean time to recurrence was 3.2 years.
Conclusions: Accelerated partial-breast irradiation using MammoSite seems to provide a safe and cosmetically acceptable outcome; however, the 9.8% IBTR rate with median follow-up of 5.3 years is concerning. Prospective randomized trials are necessary before routine use of APBI for DCIS can be recommended. © 2013 Elsevier Inc.

Introduction

Prospective randomized trials have demonstrated that whole-breast irradiation (WBI) significantly reduces the risk of ipsilateral breast tumor recurrence (IBTR) after breast-conserving surgery (BCS) for ductal carcinoma in situ (DCIS) (1). The rationale for WBI has been recently challenged, however, because most IBTRs occur at the site of the lumpectomy, whereas few occur at remote sites in the breast ("elsewhere" failures) (2-4). Thus, WBI may not be necessary for

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many patients with DCIS. Treatment with WBI is generally administered 5 days per week for a minimum of 6 weeks. Radiation is usually not initiated until at least 3 to 4 weeks after lumpectomy. Thus, the total time from lumpectomy to completion of radiation therapy (RT) is a minimum of 9 weeks. This regime is inconvenient for many women, especially patients with outside employment, elderly patients, and patients living in rural areas.

Accelerated partial-breast irradiation (APBI) targets the lumpectomy cavity and may represent a more attractive alternative to WBI for some patients with DCIS. Accelerated partial-breast irradiation has several potential advantages over WBI, including reduced radiation exposure to normal tissue, shorter treatment time, enhanced use of RT after BCS, and lower mastectomy rates. In 2002, the US Food and Drug Administration approved the use of a single-balloon implantable catheter, MammoSite (Hologic, Bedford, MA), for APBI therapy. The American Society of Breast Surgeons (ASBS) and the American Society of Radiation Oncology (ASTRO) support the use of APBI in select patients with invasive ductal cancer or DCIS; however, they do emphasize caution in treating patients with DCIS (5, 6). Although several studies have reported outcomes of patients with DCIS treated with MammoSite after BCS, data from prospective, randomized clinical trials are not yet available (7-10). Additionally, the largest published series have been registry studies (10). The primary aim of this prospective multicenter study was to determine the IBTR rate after lumpectomy and APBI with MammoSite. The secondary aims were to determine the early and late complication rates and cosmetic outcome after treatment.

Methods and Materials

Study design

We conducted a prospective, multicenter clinical trial from 2003 to 2009 at five institutions: University of Minnesota (Minneapolis, MN), Indiana University (Bloomington, IN), Vantage Oncology (Manhattan Beach, CA), Center for Advanced Breast Care (Arlington Heights, IL), and Surgical Specialists of Minnesota (Minneapolis, MN).

Institutional review board approval was obtained from each of the 5 participating centers. The study was in compliance with the University of Minnesota Data and Safety Monitoring plan, and regular meetings were required between the study's principal investigator and the XXXX Clinical Trials Office and the Data and Safety Monitoring Council.

Patient selection

Patients aged $\geq$18 years with a diagnosis of DCIS confirmed by core needle biopsy, who had unicentric disease $\leq$3 cm in size by mammogram, and who had an estimated life expectancy of >5 years were eligible for inclusion in this study. Patients with a prior history of cancer, those who were pregnant or breastfeeding, or had a relative contraindication to radiation (ie, collagen vascular disease) were excluded from the study. After surgical resection and pathologic review, patients were excluded from the study if invasive breast cancer was detected.

Treatment plan

All patients underwent standard lumpectomy. Acceptable negative margins were defined according to the National Surgical Adjuvant Breast Project (NSABP) B-17 guidelines as no ink on tumor (11). If positive margins were detected at the time of final pathologic review, the margins were resected. The MammoSite catheter was implanted either at the time of lumpectomy or within 4 weeks of the initial surgery. A minimum distance of $\geq$5 mm from the surface of the balloon to the skin was required to minimize the risk of skin necrosis. The balloon was filled with saline solution to facilitate conformation of the balloon to the lumpectomy cavity. Postoperative mammograms were not prescribed by the protocol.

Radiation therapy was delivered via high-dose-rate brachytherapy in 10 fractions of 3.4 Gy twice daily for a prescribed depth of 1 cm for a total dose of 34 Gy. Treatment was begun between 2 and 5 days after implant. All treatments were done using commercially available high-dose-rate and ^{192}Ir radioactive sources. Before the initiation of RT, a CT scan was obtained to ensure an adequate distance from the balloon to the skin and conformance of the balloon to the lumpectomy cavity. Patients also received standard orthogonal x-rays each day before treatment. After the last treatment the catheter was removed.

Patients with disease that was estrogen receptor positive were offered adjuvant endocrine treatment at the discretion of the treating physician.

Data collection

Patients were followed by the treating surgeons, radiation oncologists, nurses, and research coordinators at each center at specific time intervals after completion of APBI: 3 weeks, 6 months, 12 months, and then annually. The IBTRs were considered true local recurrences if they occurred at the treatment site and elsewhere recurrences if they recurred outside the treatment site.

Outcomes

The primary outcome of recurrence was assessed by physical examination at each follow-up and by mammography at 6 months and then yearly. The secondary outcome of complications was assessed at 3 weeks, 6 months, and yearly. An early complication was one that was present within 6 months after completion of RT; any complication occurring after 6 months was defined as a late complication. Complications were defined as erythema, drainage, pain, hematoma, skin necrosis, nonhealing wounds, and cellulitis. These were graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) Acute Radiation Morbidity Scoring Criteria (12). Cosmetic outcomes were assessed by the surgeon or radiation oncologist at 6 and 12 months using EORTC criteria (13). Ratings were based on the evaluation of breast size and shape, skin tone, nipple shape and location, appearance of surgical scar, and overall cosmetic results. Patients were also asked to rate the cosmetic outcome as excellent, good, fair, or poor.

Statistical analysis

We prospectively collected information on patient demographics, tumor characteristics, radiation and operative therapy, and postoperative outcomes. Each site had a designated study coordinator who was responsible for data collection. The information was then sent to the study coordinator at the University of Minnesota and routinely reviewed by the Principal Investigator. Descriptive