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Clinical Investigation: Breast Cancer

Predictors of Local Recurrence Following Accelerated Partial Breast Irradiation: A Pooled Analysis

Chirag Shah, M.D.,* John Ben Wilkinson, M.D.,* Maureen Lyden, M.S.,† Peter Beitsch, M.D.,‡ and Frank A. Vicini, M.D.*

**Department of Radiation Oncology, Beaumont Cancer Institute, Oakland University William Beaumont School of Medicine, Royal Oak, Michigan; †Biostat Inc., Tampa, Florida; and ‡Dallas Breast Center, Dallas, Texas*

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Summary

This study evaluated factors associated with ipsilateral breast tumor recurrence (IBTR) in nearly 2,000 patients undergoing partial breast irradiation. As previously seen, excellent outcomes were noted. The factor most commonly associated with IBTR was estrogen receptor negativity. However, significant differences in characteristics and risk stratifications of the groups led to differences in factors associated with IBTR, suggesting that factors driving IBTR may be dependent on the risk stratification of the patient.

Purpose: To analyze a pooled set of nearly 2,000 patients treated on the American Society of Breast Surgeons (ASBS) Mammosite Registry Trial and at William Beaumont Hospital (WBH) to identify factors associated with local recurrence following accelerated partial breast irradiation (APBI).

Methods and Materials: A total of 1,961 women underwent partial breast irradiation between April 1993 and November 2010 as part of the ASBS Registry Trial or at WBH. Rates of ipsilateral breast tumor recurrence (IBTR), regional recurrence (RR), distant metastases (DM), disease-free survival (DFS), cause-specific survival (CSS), and overall survival (OS) were analyzed for each group and for the pooled cohort. Clinical, pathologic, and treatment-related variables were analyzed including age, tumor stage/size, estrogen receptor status, surgical margins, and lymph node status to determine their association with IBTR.

Results: The two groups weres similar, but WBH patients were more frequently node positive, had positive margins, and were less likely to be within the American Society for Radiation Oncology-unsuitable group. At 5 years, the rates of IBTR, RR, DM, DFS, CSS, and OS for the pooled group of patients were 2.9%, 0.5%, 2.4%, 89.1%, 98.5%, and 91.8%, respectively. The 5-year rate of true recurrence/marginal miss was 0.8%. Univariate analysis of IBTR found that negative estrogen receptor status (odds ratio [OR], 2.83, 95% confidence interval 1.55−5.13, $p = 0.0007$) was the only factor significantly associated with IBTR, while a trend was seen for age less than 50 (OR 1.80, 95% confidence interval 0.90−3.58, $p = 0.10$).

Conclusions: Excellent 5-year outcomes were seen following APBI in over 1,900 patients. Estrogen receptor negativity was the only factor associated with IBTR, while a trend for age less than 50 was noted. Significant differences in factors associated with IBTR were noted between cohorts, suggesting that factors driving IBTR may be predicated based on the risk stratification of the patients being treated.

Keywords: APBI, Breast cancer, Breast conservation therapy, Ipsilateral breast tumor recurrence, Partial breast irradiation

Reprint requests to: Frank A. Vicini, M.D., F.A.C.R., Oakland University William Beaumont School of Medicine, Beaumont Cancer Institute, 3601 W. 13 Mile Rd., William Beaumont Hospital, Royal Oak, MI 48073. Tel: (248) 551-7256; Fax: (248) 551-7845; E-mail: fvicini@pol.net

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Introduction

Breast-conserving therapy (BCT) with whole-breast irradiation (WBI) has been found in numerous trials to provide equivalent outcome to mastectomy alone in terms of both local tumor control and survival. However, despite offering women the ability to preserve their breasts, there are concerns with use of BCT. These relate primarily to the protracted 6- to 7-week courses of radiation therapy (RT) required and to the fact that up to 20% of patients do not receive any form of adjuvant RT (1, 2). One solution for allowing women to undergo BCT that shortens the course of RT while delivering a biologically equivalent dose of RT is accelerated partial breast irradiation (APBI). This technique limits the radiation target to the volume of tissue immediately surrounding the surgical cavity with a variable margin and therefore allows for a hypofractionated treatment regimen which decreases treatment time to one week or less.

Currently, APBI can be delivered by using multiple techniques including traditional interstitial brachytherapy, balloon-based catheters, intraoperative radiotherapy, or three-dimensional conformal external beam RT (3DCRT). Overall, APBI has been shown not only to be feasible but associated with excellent clinical outcomes with long-term follow-up (3–6). Currently, multiple phase III trials are underway comparing adjuvant WBI with APBI, with one of the largest being the National Surgical Adjuvant Breast and Bowel Project B-39/Radiation Therapy Oncology Group 0413 study (7). Unfortunately, it will be several years before these trials have useful published data to guide treatment decisions. In the interim, APBI is increasingly being used both on- and off-protocol, with limited information to guide clinicians on the most optimal patients for its application (8).

Questions have arisen as to whether the factors that are traditionally associated with ipsilateral breast tumor recurrence (IBTR) in patients undergoing WBI are applicable to those undergoing APBI. While previous series have attempted to address this issue, they are limited by the small population of patients (sample size) and relatively small numbers of IBTRs available to analyze. The purpose of this analysis was to pool data from William Beaumont Hospital (WBH) and the American Society of Breast Surgeons Mammosite Registry Trial in order to create a patient population of nearly 2,000 patients who have received APBI with a median of 5 years of follow-up and analyze factors associated with IBTR in order to compare them with previous APBI series and WBI series.

Methods and Materials

WBH patient population

A total of 521 patients with invasive early-stage breast cancer were treated at WBH with APBI, receiving interstitial brachytherapy, balloon-based brachytherapy, or 3DCRT to the tumor bed as part of their BCT from April 1993 to November 2010. The interstitial population consisted of 221 patients, of whom 158 women were prospectively enrolled in one of three institutional review board-approved APBI protocols. Treatment techniques included a low-dose rate implant which delivered 50 Gy over 96 h at 0.52 Gy/h and a high-dose rate implant that delivered either 32 Gy in 8 fractions twice daily or 34 Gy in 10 fractions twice daily. Balloon-based patients were treated with either the Mammosite radiation therapy system (Hologic, Inc., Bedford, MA) or the Contura Multi-Lumen Balloon (SenoRx, Inc., Aliso Viejo, CA) catheter using a dose fractionation scheme of 34 Gy in 10 fractions twice daily. The 3DCRT patients were treated with 38.5 Gy in 10 fractions. Patients were prospectively entered into an institutional review board-approved database with pertinent patient, pathologic, treatment, and outcome data including follow-up data through May, 2011. This study was approved by our institution's institutional review board (HIC no. 2011-029).

American Society of Breast Surgeons patient population

The American Society of Breast Surgeons (ASBS) Mammosite Registry Trial consisted of 97 institutions treating 1,449 patients with the Mammosite single-lumen applicator between May 4, 2002, and July 30, 2004. Follow-up for the cohort ranged from 1.4 to 90.8 months, as some patients were lost to follow-up following the completion of treatment. A total of 821 patients had follow-up of 5 years or greater. All centers that were provided training in using the Mammosite device were offered participation in the registry trial. Information on enrollment criteria, data collection, and data management has previously been published (5, 6). Of note, patients could be enrolled in the trial at any time during their treatment (before, during, or after treatment), but pretreatment enrollment was encouraged. Since the inception of the trial, two full-service, independent contract research organizations, Synergos, Inc. (The Woodlands, TX) and Biostat International, Inc. (Tampa, FL) have provided data management services as well statistical analyses for the ASBS Registry Trial. Follow-up was complete through April 2011.

Patient characteristics for each set of patients were analyzed including age, tumor size/stage, estrogen receptor status, menopausal status, margin status, lymph node status, tumor grade, and American Society for Radiation Oncology (ASTRO) consensus group (suitable, cautionary, unsuitable). Clinical outcomes that were analyzed include local recurrence (LR), regional recurrence (RR), distant metastases (DM), disease-free survival (DFS), cause-specific survival (CSS), and overall survival (OS). Local recurrence was defined as a recurrence of cancer in the treated breast before or at the same time as a regional or distant failure. Regional recurrence was defined as failure within the regional lymphatics (axillary, supraclavicular, or internal mammary nodes). Distant metastases were determined by a combination of clinical, radiographic, and pathologic factors. Disease-free survival was defined as survival without a LR, RR, or DM. Cause-specific survival was defined as any death that could be attributed to breast cancer, while OS was defined as death secondary to any cause.

Statistical analyses

All time intervals were calculated from the date of RT completion. The rates of LR, RR, DM, DFS, CSS, and OS were determined by the Kaplan-Meier method. A p value of <0.05 was considered statistically significant. Statistical analyses were performed with SAS software (SAS Institute, Cary, NC), and all statistical tests were two-sided.

Results

A total of 1,961 patients and 1,978 breasts were included in this analysis. Patient characteristics were similar between the WBH