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Impact of margin status on outcomes following accelerated partial breast irradiation using single-lumen balloon-based brachytherapy

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ABSTRACT

PURPOSE: To examine the impact of margin status on clinical outcomes for patients enrolled in the American Society of Breast Surgeons (ASBrS) MammoSite® Registry Trial.

METHODS AND MATERIALS: One thousand four hundred forty-nine cases of early-stage breast cancer underwent breast-conserving therapy with a single-lumen balloon-based applicator used to deliver adjuvant accelerated partial breast irradiation (34 Gy in 10, bid fractions). One thousand two hundred fifty-five cases (87%) had invasive breast cancer (median size = 10 mm) and 194 cases (13%) had ductal carcinoma in situ (DCIS; median size = 8 mm).

RESULTS: Patients were stratified by margin status into negative ($n = 1326$), close (<2mm; $n = 110$), and positive ($n = 13$) margins. One hundred twenty-three cases (8.5%) had close or positive margins. Overall, no statistical difference in the 6-year rate of ipsilateral breast tumor recurrence (IBTR) was noted for close margins compared with that of margin-negative patients (8.7% vs. 4.1%, $p = 0.10$) or for positive margins compared with that of margin-negative patients (14.3% vs. 4.1%, $p = 0.41$). In patients with DCIS, there was a statistically significant increase in IBTR with close margins (17.6% vs. 4.2%, $p = 0.004$) and when close and positive margins were pooled (15.7% vs. 4.2%, $p = 0.01$ with a nonsignificant reduction in disease-free survival for DCIS patients with close margins (82.4% vs. 90.8%, $p = 0.12$). The increase in IBTR for close and close/positive patients was secondary to statistically significant increases in elsewhere failures rather than true recurrences/marginal misses.

CONCLUSION: Nonsignificant increases in the rates of IBTR were noted with close and positive margins for invasive cancer with further data required to validate these findings.

Keywords: Breast-conserving therapy; Brachytherapy; Partial breast irradiation; MammoSite; Breast cancer; Surgical margins

Introduction

Accelerated partial breast irradiation (APBI) represents an adjuvant radiation therapy (RT) technique that allows the delivery of a biologically equivalent dose to the lumpectomy cavity compared with whole breast irradiation (WBI) delivering 50 Gy while shortening the overall RT course to 1 week or less. At this time, APBI can be delivered using multiple techniques including interstitial catheters, balloon or strut-based single-entry devices, intraoperative applicators, or external beam RT. With several series reporting more than 5 years of follow-up, APBI has been shown to be

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associated with clinical outcomes comparable with traditional WBI (1). Furthermore, when using the interstitial technique, 12-year data from a randomized trial along with 12-year retrospective data have been published, demonstrating that APBI has equivalent outcomes to WBI (2, 3).

In women undergoing breast-conserving therapy (BCT), rates of close/positive margins have been found to be up to 30% in some studies (4, 5). Furthermore, some series have suggested that close/positive margins may increase rates of local recurrence; for example, data from Harvard University found a significant difference between rates of local recurrence (27% vs. 7%) in patients with positive margins receiving WBI as part of their BCT, whereas another analysis evaluating focally positive margins did not (6, 7). At present, limited data exist on outcomes in women with close/positive margins undergoing APBI and the rates of ipsilateral breast tumor recurrence (IBTR) as compared with women with negative margins undergoing APBI. Currently, the American Society for Radiation Oncology (ASTRO) Consensus Panel guidelines list close margins (<2 mm) in the cautionary risk group and positive margins in the unsuitable risk group based predominantly on a paucity of prospective data for these patients (8). Therefore, the purpose of this analysis was to use the American Society of Breast Surgeons (ASBrS) MammoSite (Hologic, Inc., Bedford, MA) Registry Trial to examine the impact of margin status on clinical outcomes in patients receiving APBI.

Methods and materials

The ASBrS MammoSite Registry Trial evaluated patients receiving intracavitary brachytherapy as adjuvant RT via the MammoSite single-lumen Radiation Therapy system (RTS) catheter and consisted of 97 institutions treating a total of 1449 cases of early-stage breast cancer between May 4, 2002 and July 30, 2004. The goals and objectives of the registry trial were to provide a forum to prospectively, objectively, and systematically document data on the use and efficacy of the applicator. Information on enrollment criteria, data collection, treatment techniques, follow-up protocols, and data management has previously been published (9–11). In summary, patients received a total dose of 34 Gy, given as 3.4-Gy fractions, twice daily for 10 total fractions to a point 1.0 cm from the surface of the balloon over 5–7 days using a remote high-dose-rate afterloader. After the treatment, patients were followed-up either by their radiation oncologist and/or surgeon and the data collected included: cosmetic evaluation, use of adjuvant therapy, imaging assessment, recurrence and treatment of recurrence, survival status, and toxicities.

Over the course of the trial and in follow-up, two full-service, independent contract research organizations, Synergos, Inc. (The Woodlands, TX) and Biostat International (BSI), Inc. (Tampa, FL) have provided data management services as well as statistical analyses for the ASBrS Registry Trial. As mentioned in greater detail in previous publications, all paper records were verified to be entered into the database accurately, site verification of recurrence information was obtained and a reexamination of adverse event records for terminology and missing descriptive information such as grading and timing of onset was completed (9–11). Definitions of recurrence and toxicity categories, and follow-up visit windows, were provided by the ASBrS and its independent scientific advisory committee to BSI. Management and analysis of the data at BSI occurs only through in-depth discussions between statisticians at BSI and the ASBrS.

For the purposes of this analysis, negative margins were defined as greater than or equal to 2 mm between all inked margins and the tumor. Close margins were defined as less than 2 mm of space to an inked margin, and positive margins were defined as ''tumor on ink'' (focal or otherwise). No central pathology was performed and margin classifications were based on reporting from the treating institution. An IBTR was defined as the reappearance of breast cancer in the treated breast before development of a distant metastasis and was required to be confirmed pathologically (12). A true recurrence/marginal miss (TR/MM) was defined as a recurrence of the treated cancer within or immediately adjacent to the primary tumor site. An elsewhere failure (EF) was defined as an IBTR several centimeters from the primary site. Investigators were also asked to classify regional failures as axillary, supraclavicular, or internal mammary in location. Overall survival in this study reflected all deaths, cancer related or otherwise, whereas cause-specific survival was based on deaths attributed only to breast cancer. For this analysis, follow-up was complete by December 2011.

Statistical methods

All time intervals were calculated from the date of MammoSite RT system explantation. Differences in clinical, pathologic, and treatment-related variables among negative-margin and close-margin, positive-margin, and close/positive-margin patients were performed via the pairwise Wilcoxon rank sum test and pairwise χ^2 tests. Differences in clinical outcomes were analyzed using the log-rank test. Kaplan–Meier tests were used to calculate clinical outcomes. Univariate analysis of IBTR was performed for negative-margin and close/positive-margin patients; within each group, the analysis was repeated for invasive and ductal carcinoma in situ (DCIS) cases separately. All tests were two sided and declared statistically significant if the p-value was less than or equal to 0.05. Version 8.0 or higher of the SAS (Cary, NC) statistical software package was used to provide all statistical analyses.

Results

A total of 1440 patients with 1449 treated breasts were analyzed including 1326 (91.5%) with negative margins, 110 (7.6%) with close margins, and 13 (0.9%) with positive