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Clinical Investigation: Breast Cancer

Impact of Lymph Node Status on Clinical Outcomes After Accelerated Partial Breast Irradiation

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Summary

When comparing node-negative patients with node-positive patients receiving receiving accelerated partial breast irradiation, no differences in local recurrence or axillary failure were noted. Higher rates of supraclavicular failure and distant metastases were noted in the node-positive patients; however, these node-positive patients had a limited nodal burden and therefore, were unlikely to have received regional nodal irradiation had they received whole breast irradiation. This data supports the continued accrual of node-positive patients to Phase III trials.

Purpose: To compare outcomes after accelerated partial breast irradiation (APBI) between node-negative and node-positive patients.

Methods and Materials: A total of 534 patients with early-stage breast cancer received APBI including 39 node-positive (N+) cases. Clinical, pathologic, and treatment-related factors were compared between node-negative (N−) and N+ cohorts. Local recurrence (LR), regional recurrence (RR), axillary failure (AF), distant metastases (DM), disease-free survival (DFS), cause-specific survival (CSS), and overall survival (OS) were analyzed.

Results: N+ patients were younger ($p = 0.04$), had larger tumors ($p < 0.001$), and were more likely to receive chemotherapy ($p < 0.001$). Mean follow-up was 7.8 years for N+ patients and 6.3 years for N− patients ($p = 0.06$). No differences were seen in 5-year actuarial rates of LR (2.2% vs. 2.6%, $p = 0.86$), AF (0% vs. 0%, $p = 0.69$), DFS (90.0% vs. 88.0%, $p = 0.79$), or OS (91.0 vs. 84.0%, $p = 0.65$) between the two groups, whereas higher rates of RR (0% vs. 6.1%, $p < 0.001$) and DM (2.2% vs. 8.9%, $p = 0.005$) were noted in N+ patients. A trend for improved CSS ($p = 0.06$), was seen in N− patients. Age, tumor size, receptor status, T-stage, chemotherapy, APBI technique, and nodal status ($p = 0.86$) were not associated with LR, while a trend for an association with LR was noted with close/positive margins, ($p = 0.07$), and failure to receive adjuvant hormonal therapy ($p = 0.06$).

Conclusions: No differences were seen in the rates of LR or AF between N− and N+ patients after APBI. These results support the continued enrollment of node-positive patients in Phase III trials evaluating the efficacy of APBI including the National Surgical Adjuvant Breast and Bowel Project-B39/Radiation Therapy Oncology Group 0413.

Keywords: Partial breast irradiation, Node positive, Breast cancer, Breast conservation therapy, APBI

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Introduction

Node positive (N+) breast cancer represents 25−35% of newly diagnosed cases and is typically associated with worse clinical outcomes than those observed with node-negative (N−) disease (1−3). Patients with nodal metastases more frequently develop regional nodal failure and distant metastases. Typically, adjuvant whole-breast irradiation (WBI) with or without regional nodal irradiation after breast-conserving surgery represents the standard of care in these patients (4).

Accelerated partial breast irradiation (APBI) is a recent therapeutic alternative to WBI, providing a biologically equivalent dose to the lumpectomy cavity with limited dose to the remaining breast and axilla. Initial outcomes with APBI have been excellent and comparable to those observed with WBI when selected, early-stage breast cancer patients are treated using this technique (5−9). Because of limited data on outcomes after APBI in N+ breast cancer patients and to the belief that the omission of WBI eliminates potential micrometastatic disease within the axilla in these patients, APBI is generally not offerred to these women. In fact, the American Society for Therapeutic Radiology and Oncology (ASTRO) consensus panel guidelines on the use of APBI off protocol places N+ disease in the "unsuitable" category, whereas the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology guidelines list pN1mic and pN1a as intermediate risk (10, 11).

As noted previously, there are only a few series that have addressed N+ disease treated with APBI. A recent study from Tufts University found that 2 of 3 patients with nodal metastases developed an ipsilateral breast tumor recurrence (IBTR) after APBI (12). Further, two trials from the United Kingdom have found higher rates of locoregional recurrence with older partial breast techniques (13, 14). However, other retrospective analyses have shown no difference in the rates of axillary failure (AF) or regional nodal failures (RNF) in patients receiving APBI compared with WBI. Fortunately, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/Radiation Therapy Oncology Group (RTOG) 0413 Phase III trial, randomizing patients to either WBI or APBI is currently enrolling higher risk patients, including those with one to three positive lymph nodes. Mature data from this trial will help to address the efficacy of APBI in these high-risk patients; however, these results will not be available for several years.

The purpose of the present study was to examine clinical outcomes in patients with N+ early-stage breast cancer patients treated with APBI and to compare the rates of IBTR and AF with N− patients receiving APBI.

Methods and Materials

A total of 534 patients with invasive early-stage breast cancer were treated at William Beaumont Hospital with APBI as part of their breast-conserving therapy between April 1993 and November 2010. Patients were treated with either interstitial brachytherapy, balloon-based brachytherapy (either single lumen or multichannel), or three-dimensional conformal radiation therapy to the tumor bed. The interstitial population consisted of 221 patients, of whom 158 women were prospectively enrolled on one of three institutional review board−approved APBI protocols. Our techniques for each type of APBI along with our inclusion and exclusion criteria have been previously published (15−18). Treatment techniques included a low-dose rate implant that 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. Three-dimensional conformal radiation therapy patients were treated predominantly with 38.5 Gy in 10 fractions as described in previous publications (5). Patients were prospectively entered into an institutional review board−approved database with pertinent patient, surgical/pathologic, treatment, and outcome data including follow-up data through March 2011.

Patients were stratified by nodal status. Node-positive patients included N1mi and N1 patients. Patients with N0i+ ($n = 6$), follow-up <0.1 years ($n = 12$), and patients with missing treatment information ($n = 6$) were excluded from this analysis. Patient characteristics for each group were analyzed including age, tumor size, receptor status, margin status, adjuvant hormonal therapy, adjuvant chemotherapy, and follow-up. The number of positive nodes, size of nodal metastases, and percentage of nodes were analyzed in the N+ cohort. Clinical outcomes analyzed include local recurrence (LR) (ipsilateral breast tumor recurrence), AF, 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. RR was defined as failure within the regional lymphatics (axillary, supraclavicular, or internal mammary nodes), whereas AF were defined as failures limited to the axilla. Distant metastases were determined by a combination of clinical, radiographic, and pathologic factors. DFS was defined as survival without a LR, RR, or DM, whereas CSS was defined as any death that could be attributed to breast cancer. OS was defined as death secondary to any cause. Univariate analysis was performed in order to analyze the impact of patient, pathologic (including nodal status), and treatment on LR and AF.

Statistical analyses

All time intervals were calculated from the date of radiation therapy completion. The rates of LR, RR, AF, DM, DFS, CSS, and OS were determined using the Kaplan-Meier method, whereas the statistical significance of differences between the N+ and N− patients were calculated using the log−rank test. The association of categorical variables by nodal status was performed using Pearson's chi-square test. The differences between two sample means of continuous variables were analyzed using Student's unpaired t-test. A p value of ≤ 0.05 was considered statistically significant. Statistical analyses were performed using SYSTAT version 11 (SYSTAT Software, Chicago, IL) and all statistical tests were two-sided.

Results

Table 1 lists clinical, pathologic and treatment related characteristics for the N− and N+ cohorts of patients. N+ patients were younger than N− patients (61.5 vs. 65.3 years of age, $p = 0.04$)