Original Study

Outcomes According to Breast Cancer Subtype in Patients Treated With Accelerated Partial Breast Irradiation

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Abstract

Using molecular and immunohistochemical-based testing for gene and protein expression patterns, the most commonly studied breast cancer variants are the luminal A, luminal B, HER2, and basal subtypes. Previous reports on outcomes for the breast cancer subtypes have focused on patients treated with traditional breast-conserving therapy with whole-breast irradiation. In this analysis, we observed 5-year local control rates in 278 women after treatment with accelerated partial breast irradiation, which is excellent for luminal, HER2, and basal phenotypes of early-stage breast cancer.

Background: The purpose of the study was to determine outcomes for patients treated with accelerated partial breast irradiation (APBI) on the basis of breast cancer subtype (BCST). **Patients and Methods:** Our single-institution, institutional review board-approved APBI database was queried for patients who had complete testing results for the estrogen (ER), progesterone (PR), and HER2/*neu* receptors to determine outcomes for each BCST. Women were assigned as luminal A (LA), luminal B (LB), HER2, and basal BCST using their ER, PR, and HER2/*neu* receptor status. Degree of ER expression supplemented the receptor-based luminal BCST assignment. Two hundred seventy-eight patients had results for all 3 receptors (LA = 164 [59%], LB = 81 [29%], HER2 = 5 [2%], basal = 28 [10%]), which were submitted for analysis (ipsilateral breast tumor recurrence [IBTR], regional nodal failure, distant metastasis [DM], disease-free survival [DFS], cause-specific survival [CSS], and overall survival [OS]). **Results:** Median follow-up was 5.4 years (range, 0.1-12.4 years). Basal and HER2 subtype patients had higher histologic grades (Grade 3 = 75% vs. 10% LA/LB; $P < .001$), larger tumors (13.0 mm basal vs. 10.7 mm LA/LB; $P = .059$), and were more likely to receive chemotherapy (68% vs. 15% LA/LB; $P < .001$). Margin and nodal status were similar among BCSTs. At 5 years, IBTR rates were similar (1.8%, 2.9%, 0%, and 4.8%) for LA, LB, HER2, and basal subtypes, respectively ($P = .62$). DM was only seen in LA (2.9%) and LB (1.3%) ($P = .83$). DFS (95%-100%), CSS (97%-100%), and OS (80%-100%) were not statistically different ($P = .97, .87, .46$, respectively). **Conclusion:** Five-year local control rates after breast-conserving surgery, APBI, and appropriate systemic therapy are excellent for luminal, HER2, and basal phenotypes of early-stage breast cancer; however, further study of receptor subtype effect on risk stratification in early-stage breast cancer is needed.

Clinical Breast Cancer, Vol. ■, No. ■, ■-■ © 2016 Published by Elsevier Inc.
Keywords: APBI, Brachytherapy, Breast cancer subtype, Radiotherapy, Triple negative

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Submitted: Apr 6, 2016; Revised: Jul 3, 2016; Accepted: Jul 20, 2016

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1526-8209/$ - see frontmatter © 2016 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.clbc.2016.07.010

Introduction

Breast cancer has been reported to be a heterogeneous disease that can be classified into very distinct subgroups on the basis of molecular subtyping. Studies have shown that the disease can be divided into luminal, HER2, or basal-like subtypes on the basis of expression of particular groups or clusters of similar or coexpressed genes.[1,2] It is thought that these molecular subtypes arise from different progenitor cells[3] and have been shown to have disparate clinical outcomes[4,5]; particularly the HER2 and basal subtypes.[6,7] The original definition of each breast cancer subtype (BCST) was predicated on microarray-based genetic profiling[1]; however, the genetic expression of each subtype have now been linked with particular patterns of estrogen (ER), progesterone (PR), and human epidermal receptor 2 (HER2/*neu*) receptor staining.[8-10]

Most receptor-based subtype classifications define the 4 groups of patients: ER-positive (ER^+) and/or $PR^+/HER2^-$ for luminal A (LA), ER^+ and/or $PR^+/HER2^+$ for luminal B (LB), ER^- and $PR^-/HER2^+$, for HER2, and ER^-, PR^-, and $HER2^-$ for basal or triple-negative BCSTs.[8,9] Inclusion of additional immunohistochemical (IHC) stains (ie, cytokeratin (CK) 5/6, epidermal growth factor receptor (EGFR), Ki-67, p53) has been shown to improve the accuracy of BCST group assignment (especially in the basal group).[11] It is generally held, however, that there are inherent inaccuracies in assigning a BCST only using traditional receptor-based IHC methods because discrepancies exists between the percentage of breast tumors assigned to each subtype using the gold standard, microarray genetic analysis, and results reported using IHC receptor testing alone.[12] Of particular interest, a heterogeneous group of ER^+ breast cancers with decreased degree of ER and PR expression has been described using cluster analysis.[13] This subtype is best identified as the LB subtype, but is not entirely captured using strict receptor-based subtype grouping because it does not take the degree of receptor expression into account. We present clinical outcomes of early-stage breast cancer patients treated with accelerated partial breast irradiation (APBI) grouped according to BCST using a receptor-based system that further accounts for the degree of ER expression (ERE).

Patients and Methods

Study Participants and Treatment Method

We studied our entire experience of early-stage breast cancer patients who received APBI at our institution between October 1998 and October 2010. Methods of APBI delivery included interstitial brachytherapy (15.5%, n = 43), applicator-based brachytherapy (39.8%, n = 111), and 3-D conformal external beam radiation (3D-CRT; 44.6%, n = 124). All systemic therapy, if administered, was at the discretion of the patient's medical oncologist and was delivered after APBI was complete. All patients with ER^+ tumors had a consultation with a medical oncologist regarding endocrine therapy. Trastuzumab had not yet received approval from the US Food and Drug Administration for use in early-stage breast cancer during most of the time patients in this analysis were treated. Rates of systemic therapy use are reported in the results section of this report. After obtaining institutional review board approval for this analysis, a query was performed of our APBI database to identify patients who received receptor status testing.

Breast Cancer Subtype Assignment

Women were assigned a BCST on the basis of results of testing for ER, PR, and HER2 receptors. Our institution's criteria for positive and negative receptor status has been reported previously.[14] Patients who did not have test results for all 3 receptors were excluded (n = 109). A total of 278 patients who had testing results for all 3 receptors were identified. One hundred fifty patients (54%) were treated as part of a prospective national or institutional clinical trial and 128 patients (46%) were treated as standard of care and followed as part of our APBI database. These patients were each assigned to a BCST and submitted for analysis. Receptor status and degree of ERE were used to approximate BCST as follows: ER^+ and/or PR^+, $HER2^-$, and ERE $\geq$60% = LA (n = 164 patients; 59%); ER^+ and/or PR^+ and $HER2^+$, or strong ER^+ and PR^-, or ER^+ with ERE <60% = LB (n = 81 patients; 29%); ER^-, PR^- and $HER2^+$ = HER2 (n = 5; 2%); and ER^-, PR^- and $HER2^-$ = basal (n = 28; 10%). Sixty percent ERE was selected internally as a natural cutoff point within our patient cohort to distinguish between highly estrogen-expressing LA patients and the more modest ERE patients with LB histology.

Outcome Measures

Patients were followed every 3 to 4 months for the first 2 years by a radiation oncologist, breast surgeon, or medical oncologist and then every 6 months thereafter. Mammograms are obtained 6 months after completion of radiotherapy and then annually thereafter with additional imaging studies ordered at the discretion of the radiologist or ordering physician. Clinical outcomes evaluated included ipsilateral breast tumor recurrence (IBTR), regional nodal failure (RNF), distant metastasis (DM), overall survival (OS), disease-free survival (DFS), and cause-specific survival (CSS).

Statistical Analysis

The estimated likelihood for IBTR, RNF, DM, OS, DFS, and CSS were calculated using the Kaplan–Meier method. Microsoft Excel (Microsoft Office 2013 version, Microsoft Corp, Redmond, WA) was used to calculate data counts, mean, median, and ranges for patient characteristics. Statistical significance of toxicity levels compared with radiation dose and clinical outcomes were established using linear regression, a Pearson χ^2 test, and 2-sample *t* tests. $P < .05$ was considered significant. Statistical analyses were performed using SYSTAT 13 (Systat Software, Inc, Chicago, IL), and all statistical tests were 2-sided.

Results

Clinical and Treatment-Related Characteristics

Patient characteristics are summarized in Table 1. Median follow-up was 5.4 years for all patients (range, 0.1-12.4 years) with median follow-up for each subtype of 4.5 years (LA), 6.4 years (LB), 5.6 years (HER2), and 3.5 years (basal). Mean tumor sizes were 10.5 mm (LA), 11.1 mm (LB), 11.6 mm (HER2), and 13.0 mm (basal; $P = .41$). Patients with the basal subtype had a trend toward