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Outcomes by molecular subtype after accelerated partial breast irradiation using single-entry catheters

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ABSTRACT

PURPOSE: Tumor biology is being recognized as an important indicator of prognosis and risk of locoregional recurrence. Here, we determine actuarial recurrence rates by approximated molecular subtype for women treated with single-entry catheter accelerated partial breast irradiation (sAPBI).

METHODS AND MATERIALS: One thousand four hundred eighty-six women with invasive cancer having known ER, PR, and Her2 status and at least 1-year of followup were treated using MammoSite, Contura, or SAVI sAPBI from 2002 to 2014 at our institution. Actuarial recurrence rates were determined for the following four approximated molecular subtypes using the Kaplan−Meier method: luminal A (n = 1081), luminal B (n = 164), Her2 (n = 123), and triple-negative breast cancer (TNBC; n = 118).

RESULTS: With a median followup time of 3.3 years (range 1−13.6 years), the 5-year in-breast tumor recurrence rate was 2.6% overall, 2.1% for luminal A, 1.5% for luminal B, 4.9% for Her2, and 5.4% for TNBC. Luminal A and B subtypes, as compared with the more aggressive Her2 and TNBC subtypes combined, demonstrated lower 5-year in-breast tumor recurrence (2.1% vs. 5.1%, p = 0.021). The 5-year regional nodal recurrence rate was 1.4% overall, 1.4% for luminal A, 0% for luminal B, 1% for Her2, and 4.2% for TNBC. The 5-year locoregional control is 97.3% for luminal breast cancers and 93.8% for the more aggressive Her2 and TNBC subtypes collectively.

CONCLUSIONS: Luminal cancers demonstrated excellent 5-year locoregional control with sAPBI. Although caution should be used when treating patients with the more aggressive Her2 and TNBC subtypes, these subtypes have demonstrated higher LRR with mastectomy and whole-breast irradiation. Further randomized comparisons are needed to determine the optimal treatment for these higher risk patients.

Keywords: Breast cancer; Brachytherapy; APBI; Molecular subtype

Introduction

Breast cancer is a disease of great biological heterogeneity. This diversity can be represented by genetic profiling or by bio-molecular features of each tumor, such as endocrine receptors and overexpression of the Her2 oncogene. The molecular features of breast cancer are being increasingly recognized as important indicators of prognosis and outcomes (1, 2) and may be better predictors of locoregional recurrence than clinicopathologic features like age, stage, or grade (3−8). Accelerated partial breast irradiation (APBI) is becoming an accepted alternative to whole-breast irradiation (WBI) after breast-conserving surgery (BCS) for the treatment of early-stage breast cancer, due to its shorter treatment time, noninferior local control (9), decreased toxicity, and improved cosmetic outcomes (10). Furthermore, utilization of APBI with commercially available, single-entry, multilumen catheter devices (sAPBI) has increased in recent years owing to their ease of use and

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consistent dosimetric coverage. Proper patient selection is essential to APBI and several expert consensus statements currently exist to guide this process (11−13). Although some guidelines consider estrogen receptor (ER) status, none include progesterone receptor (PR), or Her2 status. To better define the patient population suitable for APBI and to better educate patients on the risks of local recurrence, consideration of molecular subtype data may be necessary.

A recent study by the PROMIS group examined locoregional recurrence by approximated molecular subtype for multicatheter interstitial APBI (mAPBI) (14). Here, we present the in-breast tumor recurrence (IBTR), regional nodal recurrence (RNR), distant recurrence, and disease-free survival (DFS) and overall survival (OS) rates by approximated molecular subtype for patients treated with sAPBI.

Methods and materials

Patient selection and treatment

This study was approved by Western Institutional Review Board. Our database includes 1868 patients with T1-2, N0-1, invasive cancers, who underwent BCS followed by sAPBI at our institution with at least one year of followup from 2002 to 2014. The vast majority of these invasive cancers were ductal or lobular in histology (86% and 8%, respectively), with the remainder being mucinous, papillary, or unknown. Molecular subtype has previously been approximated using Her2 amplification, receptor status, and Ki-67. When Ki-67 results are not readily available, the St. Gallen International Consensus expert panel has allowed for the use of histologic grade as a surrogate marker of proliferation (15). Our data set readily included Her2, receptor status, and grade. Therefore, 1486 women with known ER, PR, Her2 status, histologic grade, and at least one year of followup from treatment completion date were included in this study. The molecular subtypes were then approximated for these patients according to the following criteria: Luminal A (ER-positive, and/or PR-positive, Her2-negative, grade 1−2), luminal B (ER-positive, and/or PR-positive, Her2-negative, grade 3), Her2 (ER-negative, PR-negative, Her2-positive), and triple-negative breast cancer (TNBC; ER-negative, PR-negative, Her2-negative).

All patients underwent high-dose-rate sAPBI following BCS, receiving 32−34 Gy in twice daily fractions of 3.4−4 Gy, separated by at least six hours, for four to five treatment days. The dose was calculated 1 cm from the surface of each device. Multilumen balloon (MammoSite n = 319; Contura n = 743 [both made by Hologic Inc., Marlborough, MA]) or hybrid/strut-adjusted (SAVI applicator n = 424; [Cianna Medical, Aliso, Viejo, CA]) single-entry catheters were used for all patients. Adjuvant systemic therapy included chemotherapy in 18.4% of patients (274/1486), trastuzumab in 64.2% of Her2-enriched patients (79/123) and endocrine therapy in 86% of ER- or PR-positive patients (1144/1335).

Statistical analysis

Patient data from Arizona Center for Cancer Care and Arizona Breast Cancer Specialists was gathered via retrospective chart review. The Kaplan−Meier method was used to calculate IBTR, RNR, distant recurrence, DFS, and OS. The Cox proportional hazards model was used to estimate the risks of IBTR and RNR with respect to the following variables: age, T-stage, N-stage, margin status, grade, chemotherapy, endocrine therapy, and molecular subtype. Lymphovascular space invasion and extensive intraductal were not analyzed, due to the percentage of women with missing data for these variables. Time intervals were calculated from the last date of brachytherapy. The baseline characteristics of our patient subgroups were compared with respect to the analyzed variables using the Mann-Whitney and Kruskal-Wallis tests. Analyses were performed in RStudio, version 2.11.1 (Boston, MA) and XLSTAT, version 2017.1 (New York, NY), and p-values less than 0.05 for two-sided tests were considered statistically significant.

Results

The baseline characteristics of our entire patient cohort are summarized in Table 1. 72.8% (n = 1081) of women had luminal A, 11% (n = 164) luminal B, 8.3% (n = 123) Her2, and 7.9% (n = 118) TNBC. The median followup time is 3.3 years for our entire patient population (range 1−13.6 years), 3.3 years for luminal A, 3.0 years for luminal B, 3.3 years for Her2, and 3.0 years for TNBC. The median age was 64 years, distributed by quartiles as follows: 35−57 years (23.5%), 58−64 years (23.5%), 65−71 years (26.0%), and 72−93 years (26.9%). There was a significant difference in T-stage across the subtype groups, with the luminal B group having a higher proportion of T2 tumors as compared with the luminal A ($p < 0.001$) and Her2 ($p = 0.049$) subgroups. The Her2 and TNBC subgroups also had a significantly higher percentage of T2 tumors as compared with luminal A ($p = 0.008$ and $p < 0.001$, respectively). The N-stage was also significantly different among the subgroups with Her2 having a higher proportion of nodal involvement as compared with luminal A ($p = 0.001$), luminal B ($p = 0.039$), and TNBC ($p = 0.043$). For patients with N1 status, the extent of nodal involvement (N1mi, N1a), if known, is listed in Table 1. The percentage of positive margins across the subgroups was not significantly different, but luminal B and TNBC had a higher percentage of unknown margin status ($p < 0.0001$).

Given the short median followup time of 3.3 years for our entire patient cohort, a separate analysis of recurrence outcomes was performed, excluding patients with less than 36 months of followup. There were 815 patients with at least 36 months of followup, distributed by molecular subtype as follows: luminal A (n = 598), luminal B (n = 82), Her