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Locoregional recurrence by molecular subtype after multicatheter interstitial accelerated partial breast irradiation: Results from the Pooled Registry Of Multicatheter Interstitial Sites research group

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ABSTRACT

PURPOSE: To determine in breast tumor recurrence (IBTR) and regional nodal recurrence (RNR) rates for women treated with multicatheter interstitial accelerated partial breast irradiation.

METHODS AND MATERIALS: Data from five institutions were collected for patients treated from 1992 to 2013. We report outcomes of 582 breast cancers with ≥1 year of followup. Molecular subtype approximation was performed using estrogen receptor, progesterone receptor, Her2, and grade. The Kaplan−Meier method was used to calculate overall survival, IBTR, RNR, and distant recurrence rates. Univariate and multivariate Cox proportional hazard models were performed to estimate risks of IBTR and RNR.

RESULTS: With a median followup time of 5.4 years, the 5-year IBTR rate was 4.7% overall, 3.5% for Luminal A, 4.1% for Luminal B, 5.2% for Luminal Her2, 13.3% for Her2, and 11.3% for triple-negative breast cancer. Positive surgical margins and high grade were associated with increased risk for IBTR, as was Her2 subtype in comparison with Luminal A subtype. Other individual subtypes comparisons did not show a significant difference. Analysis of Luminal A vs. all other subtypes demonstrated lower IBTR risk for Luminal A (5-year IBTR 3.5% vs. 7.3%, $p = 0.02$). The 5-year RNR rate was 2.1% overall, 0.3% for Luminal A, 4.6% for Luminal B, 2.6% for Luminal Her2, 34.5% for Her2, and 2.3% for triple-negative breast cancer. RNR risk was higher for women with Her2 compared to the other four subtypes and for Luminal B compared to Luminal A subtype.

CONCLUSIONS: Molecular subtype influences IBTR and RNR rates in women treated with multicatheter interstitial accelerated partial breast irradiation.

Keywords: Breast cancer; Brachytherapy; Multicatheter; Molecular subtype

Introduction

Randomized trials have shown that radiation therapy improves local control, with a small benefit in breast cancer−specific survival, in women who have undergone breast-conserving surgery (BCS) for early-stage breast cancer (1). Accelerated partial breast irradiation (APBI) is an appealing alternative to whole breast irradiation (WBI), given the short duration of therapy (i.e., 1 week or less) and reduced radiation exposure to healthy adjacent tissues (2), such as the surrounding uninvolved breast, axilla, heart, and lungs. One randomized controlled trial has shown that

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multicatheter APBI (mAPBI) produces superior long-term cosmetic outcomes, as compared with WBI (3). A prospective, single institution study of mAPBI has shown no detriment to quality of life through 2 years of followup (4). For some women, such as those with cosmetic breast augmentation, limiting radiation dose to tissues outside the tumor bed may be particularly important in achieving optimal long-term toxicity results (5). Recently, a landmark Phase 3 trial conducted by GEC-ESTRO has been published, showing noninferior local control, disease-free survival, and overall survival (OS) achieved with mAPBI vs. WBI in women with low-risk breast cancer and ductal carcinoma *in situ* (6).

To properly counsel women on the pros and cons of APBI, it is important to understand the risks for local recurrence with this technique, as compared with WBI. Expert consensus groups have developed guidelines for patient selection off-protocol (7–9). These guidelines are based upon limited data concerning molecular subtypes of breast cancer. The ASTRO 2009 consensus guidelines recommend consideration of estrogen receptor (ER) status, but do not consider progesterone receptor (PR), Her2, or grade. Other consensus guidelines do not consider molecular subtype.

The Pooled Registry Of Multicatheter Interstitial Sites database was formed by compiling data from five institutions with experience treating women with mAPBI. Here, we present the in breast tumor recurrence (IBTR) and regional nodal recurrence (RNR) rates of this patient cohort, according to clinically approximated molecular subtype.

Methods and materials

Patient selection and treatment

This study was approved by the institutional review boards of all five participating institutions. From our total data set of 1372 cases, we first identified 821 women with 830 invasive ductal breast cancers who underwent BCS followed by mAPBI from 1992 to 2013 and had at least 1 year of followup data after completion of mAPBI. Published series use variable methods of grouping women into approximated molecular subtypes on the basis of readily available clinical information, with some using receptor status only (10) and others including Ki-67 (11) or grade (12) as an acceptable surrogate measure of proliferation (13). Given that our data set included hormone receptor and Her2 status, as well as grade but not Ki-67, we chose to include receptor status and grade in our analysis (Table 1). Our final study cohort, therefore, consists of 577 women with 582 invasive ductal breast cancer cases with data for ER, PR, Her2, and histologic grade (Table 2).

All patients underwent BCS followed by mAPBI using either high-dose-rate (n = 573; 98.5%) or low-dose-rate (n = 9, 1.5%) technique. Patients treated with high-dose-rate mAPBI generally received 32–34 Gy in 8–10 twice daily fractions, whereas low-dose-rate patients received 50 Gy. Insertion technique was variable and included intraoperative, freehand, ultrasound-guided, prone mammogram-guided, and supine CT-guided catheter placement. Patients treated in early years were planned using two-dimensional techniques, whereas patients treated in more recent years had CT-based treatment planning. Some participating institutions have previously published details concerning their mAPBI techniques (14–16).

Table 1
Molecular subtype approximation

Subtype	Definition
Luminal A	ER+ or PR+, Her2−, Grades 1–2
Luminal B	ER+ or PR+, Her2−, Grade 3
Luminal Her2	ER+ or PR+, Her2+
Her2	ER− and PR−, Her2+
TNBC	ER−, PR−, Her2−

ER = estrogen receptor; PR = progesterone receptor; TNBC = triple-negative breast cancer.

Adjuvant systemic treatment included chemotherapy in 23.0% of patients (134/582) and trastuzumab in 29.0% (18/62) of women with Her2 amplified breast cancers. Prescription of endocrine therapy was documented for 79.8% (414/519) of women with Luminal A, Luminal B, or Luminal Her2 breast cancers.

Statistical analysis

Patient data from all five institutions were obtained via retrospective chart review, compiled and analyzed. All IBTR, RNR, and distant recurrences were included in our analysis, regardless of any prior or simultaneous events. All time intervals were calculated from the date of completion of brachytherapy. The Kaplan–Meier method was used to calculate OS, IBTR, RNR, and distant recurrence rates. Univariate and multivariate Cox proportional hazard modeling was performed to estimate the risks of IBTR using the following variables: molecular subtype, age, grade, tumor size, N-stage, margin status, endocrine therapy, chemotherapy, and year of treatment. Lymphovascular space invasion and extensive intraductal component were not analyzed, due to the percentage of women with missing data for these variables. The Wilcoxon rank-sum test was used to compare the baseline characteristics of our patient subgroups with respect to analyzed variables. Pairwise contrast analysis was performed to further elucidate potentially meaningful differences. All analyses were performed with SAS, version 9.4 (SAS Institute, Cary, NC), and p-Values less than 0.05 for two-sided tests were considered statistically significant.

Results

As shown in Table 2, 71.3% (n = 415) of women had Luminal A, 9.8% (n = 57) Luminal B, 8.1% (n = 47)