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Preliminary results with accelerated partial breast irradiation in high-risk breast cancer patients

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ABSTRACT

PURPOSE: To analyze prognostic factors in adequately staged breast cancer patients who were treated with accelerated partial breast irradiation (APBI).

METHODS AND MATERIALS: Axillary staging was required for invasive carcinomas. Between February 2003 and June 2009, 204 women with early stage breast carcinomas were treated with APBI using multicatheter, MammoSite, or Contura brachytherapy to 34 Gy in 10 fractions bid. Six patient characteristics were examined for prognostic significance: (*1*) N stage, (*2*) estrogen receptor (ER) status, (*3*) histologic subtype, (*4*) margin status, (*5*) age, and (*6*) tumor size. The median followup was 22 months.

RESULTS: There were three failures in the ipsilateral breast (all were elsewhere failures), one relapse in the axilla, and seven relapses at any site. The presence of positive axillary node(s) had a significant adverse effect on ipsilateral breast tumor control ($p = 0.045$) and locoregional control ($p = 0.001$). The presence of an ER (−) tumor had a significant adverse effect on relapse-free survival ($p = 0.04$).

CONCLUSIONS: The patients with positive axillary node(s) were at increased risk for failure elsewhere in the ipsilateral breast or axilla, and the patients with ER (−) tumors were at increased risk for relapse at any site. However, it is unclear whether the pN1 and ER (−) patients would have faired any better if they had received whole breast irradiation rather than APBI. We believe that the patients with positive axillary node(s) or ER (−) tumors should be treated on clinical trials to better define the role of APBI.

Keywords: Prognostic; Factors; Partial; Breast; Irradiation

Introduction

Several prospective randomized trials have addressed the outcome of early stage breast cancer patients treated with lumpectomy ± whole breast irradiation (1−5). In all of these trials, most of the ipsilateral breast recurrences in patients who did not receive radiotherapy occurred near the primary tumor site. In addition, the rate of development of new cancers in the areas of the breast far from the lumpectomy site was similar whether or not whole breast irradiation was delivered. Thus, it would appear that whole breast irradiation primarily exerts its benefit by reducing the risk of recurrence near the primary tumor site.

In a randomized trial involving 258 early stage breast cancer patients, postlumpectomy accelerated partial breast irradiation (APBI) produced 5-year local control, relapse-free survival, and cancer-specific survival rates comparable to those achieved with whole breast irradiation (6). However, pending 10-year results from this and other randomized trials, such as National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/Radiation Therapy Oncology Group (RTOG) 0413, postlumpectomy whole breast irradiation remains the gold standard (7).

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One advantage of APBI over whole breast irradiation is that the radiotherapy is delivered over 1 week rather than 5−7 weeks (8). Another advantage of APBI is that the volumes of heart and lung irradiated to clinically significant levels are lower than with whole breast irradiation (9, 10). In addition, cosmetic results with APBI compare favorably to those with whole breast irradiation (6).

The American Society for Radiation Oncology recently published its Task Force guidelines on the use of APBI outside of a clinical trial (7). The authors of these guidelines noted that there is limited published data on results with APBI in patients who are younger than 50 years and in patients with positive axillary node(s), estrogen receptor (ER) (−) tumors, pure ductal carcinoma *in situ* (DCIS) or invasive lobular carcinoma, close surgical margins (<2 mm), or tumors measuring 21−30 mm. The purpose of this study was to analyze our results with APBI based on these patient characteristics.

Methods and materials

The patient characteristics are presented in Table 1. For a DCIS, no axillary staging procedure was required. Axillary staging was not performed in 10 patients with pure DCIS that measured ⩽10 mm, an ER (+) tumor, and a Scharff-Bloom-Richardson score ⩽6. Axillary staging was performed in the remaining 10 DCIS patients with tumors that measured >10 mm. These tumors were also ER (−) or had a Scharff-Bloom-Richardson score >6. Axillary staging consisted of a sentinel lymph node biopsy alone if all of the sentinel nodes were negative. If a sentinel node was positive, an axillary dissection was performed and at least six nodes removed. For invasive breast carcinomas, an axillary staging procedure was required.

Approval for APBI was obtained from the Western Institutional Review Board and the informed consent was obtained from all the patients. The patients with a positive margin per NSABP criteria or multicentric disease were not eligible for APBI. From February 2003 to June 2009, we treated 204 patients with early stage carcinomas of the breast at least 1 mm from the inked edge of the lumpectomy specimen with high-dose-rate ^{192}Ir multicatheter (Alpha-Omega Services Inc., Bellflower, CA), MammoSite (Hologic Inc., Bedford, MA), or Contura (SenoRx Inc., Aliso Viejo, CA) brachytherapy. Up until September 2007, we typically treated patients with nonspherical lumpectomy cavities or lumpectomy cavities that were only 3−4 mm from the skin with multicatheter brachytherapy. Since December 2007, we have treated almost all of our APBI patients with Contura brachytherapy on clinical trials (11).

With multicatheter brachytherapy, the planning target volume for plan evaluation (PTV_EVAL) was defined as the breast tissue volume bounded by the uniform expansion of the lumpectomy cavity in all dimensions by 15 mm. With MammoSite or Contura brachytherapy, PTV_EVAL was defined as the breast tissue volume bounded by uniform expansion of the balloon radius in all dimensions by 10 mm less than the balloon volume. For all the three brachytherapy techniques, PTV_EVAL was limited to 5 mm from the skin surface and by the posterior breast tissue extent. Chest wall and pectoralis muscles were excluded. Dose−volume histogram analysis of target coverage confirmed that ⩾90% of the prescribed dose covered ⩾90% of PTV_EVAL.

Surgeons placed the MammoSite and Contura catheters using a closed-cavity technique between 0 and 68 days (median, 27 days) postlumpectomy. With regard to homogeneity of the radiation dose within the breast, the volumes of tissue receiving 150% (V_{150}) and 200% (V_{200}) of the prescribed dose were limited to ⩽50 and ⩽10 cc, respectively (12, 13). High-dose-rate brachytherapy was delivered to a total dose of 34 Gy in 10 fractions bid separated by 6 h daily over 5−7 days.

During brachytherapy, we prophylactically treated patients with an oral antibiotic, such as cephalexin (Keflex) or azithromycin (Zithromax).

An ipsilateral breast tumor recurrence refers to any recurrence in the treated breast before or at the time of regional failure or metastasis. As suggested by Recht *et al.* (14), an ipsilateral breast tumor recurrence was further subclassified as a true recurrence/marginal miss if it was located within or immediately adjacent to the primary tumor site or as an elsewhere failure if it was located several centimeters from the primary site. Locoregional control refers to the absence of carcinoma in the ipsilateral breast and axilla.

We define acute toxicity as toxicity occurring within 90 days of the first day of brachytherapy (15). The median followup was 22 months.

We used a two-sided Pearson chi-square test (16), Kaplan−Meier analysis (17), and a log-rank test (18) to analyze the data. Based on the small number of events, we did not perform multivariate Cox regression (19). If the p value is less than 0.05, there is a significant difference between groups.

Results

There were three failures in the ipsilateral breast (all were elsewhere failures), one relapse in the axilla, seven relapses at any site, and three deaths. The patient characteristics for the seven relapses at any site are presented in Table 2. Univariate log-rank test p values for patient characteristics are presented in Table 3. Only the presence of positive axillary node(s) had a significant adverse effect on ipsilateral breast tumor control ($p = 0.045$) and locoregional control ($p = 0.001$). Only the presence of an ER (−) tumor had a significant adverse effect on relapse-free survival ($p = 0.04$). No patient characteristic had prognostic significance for overall survival.

Table 1
Patient characteristics

	Multicatheter brachytherapy ($n = 111$)	MammoSite brachytherapy ($n = 59$)	Contura brachytherapy ($n = 34$)
Followup, mo, median (range)	25 (1−60)	35 (1−74)	5 (1−19)
Age, y			
18−49	21% (7)	14% (16)	25% (15)
50−59	32% (11)	32% (36)	17% (10)
>59	47% (16)	53% (59)	58% (34)
Race			
African American	3% (1)	0% (0)	2% (1)
Asian	15% (5)	2% (2)	2% (1)
Hispanic	6% (2)	12% (13)	15% (9)
White	73% (25)	83% (93)	79% (47)
Other	3% (1)	3% (3)	2% (1)
Margins (mm)			
1	29% (10)	30% (33)	12% (7)
>1	71% (24)	70% (78)	88% (52)
Tumor size (mm)			
1−20	85% (29)	91% (101)	85% (50)
21−30	15% (5)	9% (10)	15% (9)
Pathologic T stage			
Tis	3% (1)	4% (4)	25% (15)
Tmic	0% (0)	0% (0)	0% (0)
T1a	15% (5)	8% (9)	5% (3)
T1b	20% (7)	35% (39)	25% (15)
T1c	47% (16)	45% (50)	33% (19)
T2	15% (5)	8% (9)	12% (7)
Pathologic N stage			
NX	3% (1)	3% (3)	10% (6)
N0	73% (25)	89% (99)	88% (52)
N1mi	6% (2)	1% (1)	0% (0)
N1a	18% (6)	7% (8)	2% (1)
Histology			
Ductal carcinoma *in situ*	12% (4)	18% (20)	25% (15)
Infiltrating ductal carcinoma	82% (28)	76% (84)	66% (39)
Infiltrating lobular carcinoma	3% (1)	3% (4)	0% (0)
Colloid carcinoma	3% (1)	1% (1)	3% (2)
Tubular carcinoma	0% (0)	2% (2)	6% (3)
ER			
Positive	77% (26)	86% (96)	88% (52)
Negative	23% (8)	14% (15)	12% (7)
PR			
Positive	70% (24)	79% (88)	75% (44)
Negative	30% (10)	21% (23)	25% (15)
HER-2/neu			
Positive	18% (6)	24% (27)	21% (12)
Negative	82% (28)	76% (84)	79% (47)
Scharff-Bloom-Richardson grade			
3	5% (2)	3% (3)	5% (3)
4	5% (2)	7% (7)	9% (5)
5	18% (6)	23% (25)	5% (3)
6	24% (8)	37% (40)	43% (25)
7	18% (6)	10% (11)	23% (14)
8	12% (4)	7% (7)	5% (3)
9	18% (6)	7% (7)	10% (6)

ER = estrogen receptor; HER-2/neu = human epidermal growth factor receptor 2; is = *in situ*; mi = micrometastasis; mic = microinvasion; N = node; PR = progesterone receptor; T = tumor.

Table 2
Characteristics of patients who did or did not relapse at any site

	Patients who relapsed at any site ($n = 7$)	Patients who did not relapse at any site ($n = 197$)
Followup, mo, median (range)	43 (19–63)	22 (1–74)
Age, y		
18–49	0% (0)	19% (38)
50–59	57% (4)	27% (53)
>59	43% (3)	54% (106)
Race		
African American	0% (0)	1% (2)
Asian	0% (0)	4% (8)
Hispanic	0% (0)	12% (24)
White	86% (6)	81% (159)
Other	14% (1)	2% (4)
Margins (mm)		
1	29% (2)	24% (48)
>1	71% (5)	76% (149)
Tumor size (mm)		
1–20	100% (7)	88% (173)
21–30	0% (0)	12% (24)
Pathologic T stage		
Tis	0% (0)	10% (20)
Tmic	0% (0)	0% (0)
T1a	0% (0)	9% (17)
T1b	43% (3)	29% (58)
T1c	57% (4)	41% (81)
T2	0% (0)	11% (21)
Pathologic N stage		
NX	0% (0)	5% (10)
N0	71% (5)	87% (171)
N1mi	0% (0)	1% (3)
N1a	29% (2)	7% (13)
Histology		
Ductal carcinoma *in situ*	14% (1)	21% (38)
Infiltrating ductal carcinoma	72% (5)	74% (146)
Infiltrating lobular carcinoma	0% (0)	2% (5)
Colloid carcinoma	14% (1)	1% (3)
Tubular carcinoma	0% (0)	2% (5)
ER		
Positive	57% (4)	86% (170)
Negative	43% (3)	14% (27)
PR		
Positive	57% (4)	80% (158)
Negative	43% (3)	20% (39)
HER-2/neu		
Positive	28% (2)	39% (77)
Negative	72% (5)	61% (120)
Scharff-Bloom-Richardson grade		
3	0% (0)	4% (7)
4	0% (0)	8% (16)
5	43% (3)	15% (30)
6	0% (0)	38% (75)
7	29% (2)	16% (32)
8	14% (1)	8% (16)
9	14% (1)	11% (21)

ER = estrogen receptor; HER-2/neu = human epidermal growth factor receptor 2; is = *in situ*; mi = micrometastasis; mic = microinvasion; N = node; PR = progesterone receptor; T = tumor.

Table 3
Univariate log-rank test p values for patient characteristics

Patient characteristic	Ipsilateral breast tumor control	Locoregional control	Relapse-free survival
Positive node(s)	0.045	0.001	0.055
Ductal carcinoma *in situ* or invasive Lobular carcinoma	0.38	0.31	0.89
Estrogen receptor (−)	0.48	0.09	0.04
Close margins (<2 mm)	0.52	0.63	0.91
Age <50 y	0.64	0.88	0.41
Tumor size = 21−30 mm	0.71	0.76	0.54

First, we examined ipsilateral breast tumor control and locoregional control in terms of axillary lymph node status. None of the 10 DCIS patients with 2002 American Joint Committee on Cancer (20) pNX axillary nodes relapsed. Two of the 176 pN0 patients relapsed in the ipsilateral breast. The breast failures occurred elsewhere in the breast 50−56 months after APBI. None of the pN0 patients relapsed in the axilla. None of the 3 pN1mi patients relapsed. One of the 15 pN1a patients with a metastasis in a solitary axillary node and no extracapsular extension failed elsewhere in the ipsilateral breast 12 months after APBI. One of the pN1a patients with a metastasis in a solitary axillary node and no extracapsular extension relapsed in the axilla 19 months after APBI. Three-year ipsilateral breast tumor control rates were 100% vs. 93% (95% confidence interval [CI], 79−100%), respectively, for pNX and pN0 vs. pN1 patients (Fig. 1). Three-year locoregional control rates were 100% vs. 85% (95% CI, 66−100%), respectively, for pNX and pN0 vs. pN1 patients (Fig. 2).

Next, we examined relapse at any site in terms of ER status. Four of the 174 ER (+) patients relapsed in the breast ($n = 2$) or distant sites (bones or brain) 40−56 months after APBI. Three of the 30 ER (−) patients relapsed in the breast, axilla, or lungs 19−50 months after APBI. Three-year relapse-free survival rates were 100% vs. 88% (95% CI, 72−100%), respectively, for ER (+) vs. ER (−) patients (Fig. 3).

Acute toxicity by brachytherapy technique is presented in Table 4. There was no significant difference in acute toxicity by treatment technique ($p = 0.09$). Two percent of patients have poor, 3% have fair, 23% have good, and 72% have excellent cosmetic results using the Harvard scale (21).

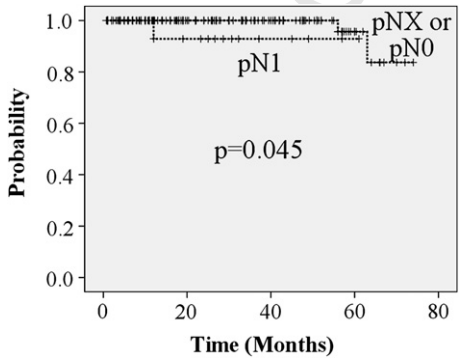

Fig. 1. The probability of ipsilateral breast tumor control after accelerated partial breast irradiation in terms of pathologic axillary lymph node status.

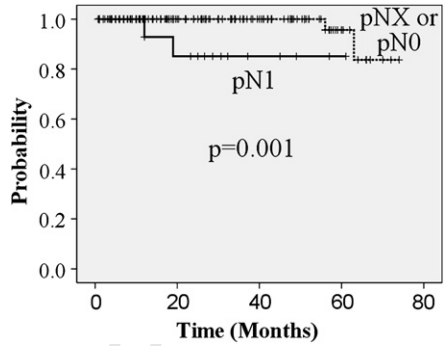

Fig. 2. The probability of locoregional control after accelerated partial breast irradiation in terms of pathologic axillary lymph node status.

Discussion

Invasive breast cancer patients in the Christie Hospital (22, 23) and Yorkshire Breast Cancer Group (24) randomized trials did not undergo complete pathologic lymph node assessment. These studies were also flawed in margin evaluation and included no radiotherapy quality control. The patients experienced higher ipsilateral breast (22, 23) and locoregional (24) recurrence rates when treated with APBI rather than whole breast irradiation. A sentinel lymph node biopsy is currently recommended for invasive breast cancer patients undergoing breast-conserving therapy (25). If a sentinel node is positive, then an axillary dissection should be performed and at least six nodes should be removed to reduce the risk of a regional recurrence (25).

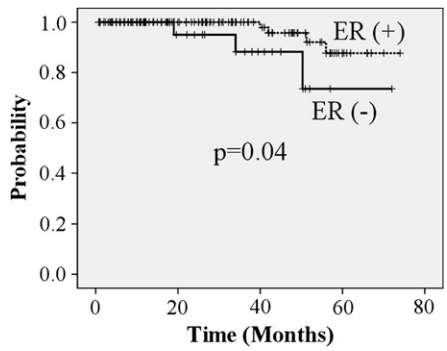

Fig. 3. The probability of relapse-free survival after accelerated partial breast irradiation in terms of estrogen receptor status.

Table 4
Acute toxicity by brachytherapy technique

Acute toxicity	Multicatheter brachytherapy ($n = 34$)	MammoSite brachytherapy ($n = 111$)	Contura brachytherapy ($n = 59$)
Infection	6% (2)	4% (4)	0% (0)
Breast pain	3% (1)	7% (8)	3% (2)
Breast fibrosis	0% (0)	1% (1)	0% (0)
Seroma	0% (0)	11% (12)	12% (11)
Infection and seroma	0% (0)	0% (0)	2% (1)
Rib pain	0% (0)	1% (1)	0% (0)
Fat necrosis	0% (0)	0% (0)	2% (1)
Total	9% (3)	24% (26)	19% (15)

In contrast, pathologic staging does not need to be performed in all the DCIS patients (26).

There is limited data in the literature on the results with APBI in breast cancer patients who were adequately staged and found to have positive axillary node(s) (7). In the Tufts trial, 2 of 3 pN1 patients treated with APBI failed elsewhere in the ipsilateral breast (27). However, the authors of the Tufts trial point out that the small number of events ''does not allow for a statistical correlation of clinical, pathologic, or treatment variables with outcomes.'' In our study, 1 of 18 pN1 patients treated with APBI failed elsewhere in the ipsilateral breast. Pathologic N1 patients were at higher risk for ipsilateral breast tumor relapse (Fig. 1, $p = 0.045$) and locoregional relapse (Fig. 2, $p = 0.001$) than pNX and pN0 patients who were treated with APBI. On the basis of the small number of events, our results must also be interpreted with caution. It is unclear whether the pN1 patients would have faired any better if they had received whole breast irradiation rather than APBI. For example, in a matched-pair analysis of 199 early stage breast cancer patients by Antonucci *et al.* (28), there was no difference in locoregional control between APBI and whole breast irradiation. Consequently, we do not believe that a modified radical mastectomy should be the standard of care in pN1 patients. In our study, ER (−) patients were at higher risk for relapse at any site (Fig. 3, $p = 0.04$) than the ER (+) patients who received APBI. It is unclear whether the ER (−) patients would have faired any better if they had received whole breast irradiation rather than APBI.

The patients treated on the NSABP B-39/RTOG 0413 intergroup trial are at ''high risk'' if they meet any of the following three criteria: (*1*) age between 18 and 49 years, (*2*) ER and progesterone receptor (−) cancer, or (*3*) one to three positive axillary nodes. At 5 years, Patel *et al.* (29) observed no significant difference in local control or overall survival between this high-risk patient subgroup and a ''low-risk'' patient subgroup that lacked all three risk factors. Patel *et al.* observed one isolated regional nodal recurrence in the high-risk group and none in the low-risk group. They did not analyze locoregional control in terms of axillary node or ER status. Physicians should encourage breast cancer patients to participate in studies, such as the NSABP B-39/RTOG 0413 intergroup trial. Mature results from the intergroup trial and others will help to define the role of APBI in patients with unfavorable features such as one to three positive axillary nodes or ER negative tumors.

Our incidence rates of acute toxicity in Table 4 are in accordance with those reported in the literature (30−32). Acute toxicity did not differ significantly based on brachytherapy technique ($p = 0.09$). Our cosmetic results are also similar to those reported by others (15, 31, 32).

Conclusion

We concur with the recent American Society for Radiation Oncology Task Force consensus statement that, outside the setting of a clinical trial, APBI is ''unsuitable'' for pN1 patients and should be used with caution in patients with ER (−) tumors (7). Pending results from large, randomized trials, we encourage physicians to treat high-risk breast cancer patients with APBI in the setting of a clinical trial, such as NSABP B-39/RTOG 0413.

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