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Axillary Failure in Patients Treated with MammoSite Accelerated Partial Breast Irradiation

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ABSTRACT

Background. The risk of axillary failure (AF) after accelerated partial breast irradiation (APBI) using MammoSite brachytherapy is unknown and has been source of concern as the axillary region is not treated with this technique. We aimed to determine the rate of AF in patients treated with APBI and identify factors associated with its occurrence.

Methods. Data from the American Society of Breast Surgeons MammoSite Registry Trial were reviewed and patients with AF were identified. Clinical, pathologic and treatment-related variables were analyzed to determine which factors were associated with AF.

Results. A total of 1440 patients underwent MammoSite APBI. A total of 1449 cases were treated (9 patients received bilateral treatment), 1255 cases (87%) of invasive breast cancer and 194 cases (13%) of ductal carcinoma in situ (DCIS). The median length of follow-up was 59 months. There were 10 patients who had an AF. Of these, 9 patients had an initial diagnosis of invasive cancer and 1 had an initial diagnosis of DCIS. The 5-year actuarial rate of AF was 0.79%. The only independent risk factor for AF identified by multivariate analysis was the presence of high-grade disease ($P = .008$). The 5-year overall survival rate in patients with an AF was 77.8% (there was 1 death related to breast cancer).

Conclusions. The rate of AF after MammoSite APBI is low and appears to be similar to that achieved with whole-breast irradiation.

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The role of radiation therapy as an adjunct to breast-conserving surgery has been established in large, prospective randomized trials.[1,2] Radiation therapy after partial mastectomy reduces the risk of recurrence in the ipsilateral breast and is associated with a modest but significant survival benefit.[1,3–5] Traditional whole-breast irradiation (WBI) involves daily treatments for 6–7 weeks. The inconvenience of this treatment schedule, coupled with the paucity of radiation treatment centers in some geographic areas, lead many patients who might benefit from radiation therapy to forego WBI.[6–9] Accelerated partial breast irradiation (APBI) has been explored as a treatment modality with the potential to provide a therapeutic benefit similar to that afforded by WBI without the aforementioned limitations. A number of approaches to APBI have been used, including multicatheter interstitial brachytherapy, intracavitary multiple-lumen catheter brachytherapy, single-lumen balloon-catheter brachytherapy, and 3-dimensional conformal external beam radiation therapy (EBRT). These approaches are currently being evaluated in a phase III randomized trial conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP). This trial, NSABP-B39, will evaluate the effectiveness of APBI compared with WBI following partial mastectomy for early-stage breast cancer and will compare overall survival, recurrence-free survival, and distant disease-free survival in women receiving PBI and WBI.[10]

The MammoSite, a single-lumen balloon-tip brachytherapy catheter (Cytyc, Bedford, MA), has been studied for use in the treatment of early breast cancer. The device was first approved by the U.S. Food and Drug Administration in May 2002. Soon after, the manufacturer established the MammoSite Registry Trial as a data collection program with the purpose of analyzing outcomes in patients treated with the MammoSite. In 2003, the American Society of Breast Surgeons assumed management of the registry trial. Results from the first 1419 patients enrolled were presented at the San Antonio Breast Cancer Symposium, and multiple interval updates to these results have subsequently been published.[11–14]

Despite the apparent advantages of APBI, some reservations regarding its application persist. In contrast to WBI, APBI does not treat the ipsilateral axillary region. Whether or not this results in a higher rate of AF than that seen after WBI remains unknown. The purpose of the present study was to evaluate the rate of AF among patients treated with APBI using MammoSite brachytherapy and factors associated with its occurrence.

MATERIALS AND METHODS

Between May 4, 2002, and July 30, 2004, 1440 patients were enrolled in the MammoSite Registry Trial. Enrolled patients were required to give informed consent, and patients treated on or after April 14, 2003, were additionally required to sign a Health Insurance Portability and Accountability Act agreement. Trial enrollment was closed in July 2004, and all patients were required to return for follow-up annually for 7 years. A total of 233 investigators at 97 Institutions participated. Of the 1440 enrolled patients, 9 were treated bilaterally.

Participating patients received 3.4 Gy twice daily over 5 treatment days (34 Gy over 10 fractions) using the MammoSite balloon catheter. The dose was calculated at 1 cm from the balloon surface. Although there were no strict guidelines regarding the timing of chemotherapy, the majority of patients received their first dose of chemotherapy >3 weeks after the final MammoSite procedure. Most patients (75%) were treated with doxorubicin-based chemotherapy.[13] The primary endpoints of the study were disease-free survival, cause-specific survival, recurrence in the ipsilateral breast, and recurrence in the contralateral breast. Secondary endpoints were the number and type of serious adverse device-related events and other adverse events, including skin necrosis, infection, nonhealing of the surgical wound, poor cosmesis, persistent severe pain, skin burn, wound dehiscence, and seroma or hematoma formation.

All axillary failures were identified, including those that occurred in the setting of a concurrent ipsilateral breast tumor recurrence (IBTR), contralateral breast cancer, or distant recurrence. Clinical variables (patient age at diagnosis, bra size, and tumor location), pathologic variables (tumor size, grade, estrogen receptor status, margin status, nodal status, and presence of extensive intraductal component), and treatment-related variables (use of systemic chemotherapy, use of tamoxifen or anastrozole, and method of catheter placement) were analyzed to determine which factors were associated with AF. Positive margins were defined as tumor on the inked surface, and close margins were defined as tumor less than 2 mm from the inked surface.

Patient Eligibility Criteria

The recommended patient selection criteria were based on previous publications on the use of brachytherapy from the American Brachytherapy Society.[5,15] These included: patient age ≥45 years, T1–2 (<3 cm), N0, M0 tumor, and negative margins. Patients who were breast-feeding, who were pregnant, or who had collagen-vascular disease were excluded. Other exclusion criteria included the presence of an extensive intraductal component (Harvard definition, >25% DCIS) and lobular pathology.

Technical Eligibility Criteria

It was recommended that the applicator be placed within 10 weeks after partial mastectomy and that radiation treatment be started no earlier than 2 weeks after chemotherapy. A balloon-to-skin distance of 5 mm or greater, and preferably 7 mm or greater, was recommended. In addition, good balloon-cavity conformance and symmetry of the center catheter shaft were emphasized.

Statistical Methods

Statistical analyses were performed using the SAS statistical software package (SAS Institute, Cary, NC). A P value of ≤.05 was considered significant. Univariate associations between clinical, pathologic, and treatment-related variables and recurrence event rates were analyzed by fitting parametric models to the recurrence time data and examining the significance of the parameter estimates. Additionally, a multivariate analysis was done by including variables in a Cox proportional hazards model and generating odds ratios and 95% confidence intervals.

RESULTS

Clinical and pathologic characteristics of the 1440 patients (1449 breasts) treated in the study are summarized

in Table 1. While the majority (87%) of the patients had invasive ductal disease, 192 patients (13%) had DCIS. The median sizes of invasive and in situ tumors were 10 and 8 mm in greatest dimension, respectively. Fifty-six percent of the patients received adjuvant endocrine therapy alone (i.e., tamoxifen or anastrozole), 5.7% received chemotherapy alone, and 5.8% received both chemotherapy and endocrine therapy. The median duration of follow-up was 59 months.

Initial Axillary Status

While the majority (83.2%) of the patients did not have nodal metastases at diagnosis, 206 patients (14.2%) did not have nodal status assessed, and 38 patients (2.6%) had node-positive disease (N1). Among patients with invasive disease, 91.8% were node-negative and 3.0% had node-positive disease. The majority (72.7%) of patients with DCIS did not undergo surgical nodal staging (i.e., sentinel lymph node biopsy or axillary dissection). Fifty-three patients with DCIS (27.3%) underwent surgical nodal staging and, in all cases, the nodes were proven to be negative (Table 1).

Axillary Recurrence

There were 10 patients who developed an axillary recurrence. Of these patients, 9 had an initial diagnosis of invasive cancer; the remaining patient had an initial diagnosis of DCIS (Table 2). The 5-year actuarial rate of AF was 0.79%; in patients with an initial diagnosis of invasive cancer the rate of AF was 0.81%, and in patients with DCIS it was 0.56%.

Of the 9 patients with an axillary recurrence and an initial diagnosis of invasive cancer, 8 had node-negative disease at diagnosis (nodal status determined by sentinel lymph node biopsy only in 4 patients, axillary lymph node dissection only in 3 patients, and both sentinel lymph node biopsy and axillary lymph node dissection in 1 patient); the patient who did not undergo surgical nodal staging at diagnosis was a 57-year-old woman with a 10-mm estrogen-receptor-positive tumor.

TABLE 1 Clinical and pathologic characteristics of 1440 patients treated with MammoSite accelerated partial breast irradiation for early breast cancer

Characteristic	All cases (1440 patients; 1449 breasts)	Invasive breast cancer (1248 patients; 1255 breasts)	Ductal carcinoma in situ (192 patients; 194 breasts)
Median age at diagnosis (range), years	65.5 (31.8–93.5)	65.9 (31.8–93.5)	62.1 (40.7–88.0)
Age, years, No. of patients (%)			
≥60 years	929 (64.5)	814 (65.2)	115 (59.9)
50–59 years	380 (26.4)	324 (26)	56 (29.2)
40–49 years	126 (8.8)	105 (8.4)	21 (10.9)
<40 years	5 (0.3)	5 (0.4)	0 (0.0)
Median tumor size (range), mm	10.0 (1.0–45.0)	10.0 (1.0–42.0)	8.0 (1.0– 45.0)
Tumor size, mm, No. of patients (%)			
<5	130 (9.0)	89 (7.1)	41 (21.1)
≥5 to <10	482 (33.3)	431 (34.3)	51 (26.3)
≥10 to ≤20	705 (48.7)	652 (52.0)	53 (27.3)
>20	91 (6.3)	79 (6.3)	12 (6.2)
Unknown	41 (2.8)	4 (0.3)	37 (19.1)
Nodal status, No. of patients (%)			
N0	1205 (83.2)	1152 (91.8)	53 (27.3)
Not assessed	206 (14.2)	65 (5.2)	141 (72.7)
N(+)	38 (2.6)	38 (3.0)	0 (0.0)
Margin status, No. of patients (%)			
Positive	13 (0.9)	11 (0.9)	2 (1.0)
Negative	1326 (91.5)	1155 (92.0)	171 (88.1)
Close	110 (7.6)	89 (7.1)	21 (10.8)
Systemic therapy, No. of patients (%)			
Chemotherapy alone	82 (5.7)	82 (6.6)	0 (0.0)
Hormonal therapy alone	800 (55.6)	698 (55.9)	102 (53.1)
Both chemotherapy and hormonal therapy	84 (5.8)	84 (6.7)	0 (0.0)

TABLE 2 Characteristics of 10 patients with axillary recurrence

Case No.	Age at Dx (y)	Tumor size (cm)	Tumor type at Dx	Tumor location	Nodal status	Method of nodal staging	ER status	Chemo use	Tamoxifen and/or anastrozole use	Type of recurrence	Months to recurrence	Distant mets?
1	57	1	Invasive	L, U, O	NA	Unk	+	Yes	Yes	Isolated	20.1	No
2	86	1.8	Invasive	L, M, O	Neg	A	+	No	Yes	Isolated	5.9	No
3	55	2.2	Invasive	R, U, O	Neg	S	−	Yes	No	w/IBTR	19.2	No
4	65	0.8	Invasive	L, U, M	Neg	S	+	Yes	Yes	Isolated	24.7	No
5	79	0.6	Invasive	R, M, O	Neg	A	−	Yes	No	w/IBTR	22.1	No
6	46	1	DCIS	R, U, I	NA	Unk	−	Yes	No	w/IBTR	10.1	Yes
7	59	2	Invasive	R, U, O	Neg	S	+	No	Yes	Isolated	43.1	No
8	65	0.9	Invasive	L, L, O	Neg	S	+	No	Yes	Isolated	28.3	No
9	60	1	Invasive	L, M, O	Neg	A	Unk	No	No	Isolated	27.4	No
10	71	1.2	Invasive	R, L, O	Neg	S, A	−	No	No	Isolated	72.5	No

Dx diagnosis, *ER* estrogen receptor, *Chemo* chemotherapy, *S, A* sentinel lymph node biopsy and axillary lymph node dissection, *S* sentinel lymph node biopsy only, *A* axillary lymph node dissection only, *unk* unknown, *L* lower, *O* outer, *M* medial, *I* inner, *w/IBTR* with ipsilateral breast tumor recurrence, *NA* not assessed

On univariate analysis (Table 3), higher-grade disease ($P = .02$) and treatment with chemotherapy ($P = .05$) were associated with axillary recurrence. Patients treated with chemotherapy were more likely than patients not treated with chemotherapy to have lymph node metastases ($P = .02$) or a positive sentinel lymph node ($P = .05$), were less likely to have estrogen-receptor-positive disease ($P \leq .0001$), were more likely to have higher-grade (III) disease ($P \leq .0001$), were younger ($P \leq .0001$), and had larger tumors ($P \leq .0001$). On multivariate analysis, only high-grade disease ($P = .008$) was associated with AF (Table 4). The 5-year overall survival rate in patients with an AF was 77.8% (there was 1 death related to breast cancer).

DISCUSSION

APBI has rapidly been incorporated into the treatment paradigm for many patients with breast cancer. Indeed, in a recent of study of brachytherapy use, 5% of patients in a nationwide database of 6882 Medicare beneficiaries with private supplemental insurance received brachytherapy as the sole radiation therapy modality after breast-conserving surgery. Moreover, this trend of increasing brachytherapy use is continuing.[16] Although early data suggest acceptable locoregional disease control with this approach, long-term data are lacking.[12] In contrast, the use of EBRT after breast-conserving surgery is now buoyed by cumulative data from randomized trials with 60,000 to 100,000 of patient-years of follow-up.[9] Whether the definitive advantages of EBRT with regard to locoregional recurrence and disease-free and overall survival will be sustained by APBI remains to be seen.

A particular concern regarding the use of APBI is the potential for an increased risk of AF. In contrast to APBI, EBRT treats the ipsilateral axillary nodal basin; any divergence in the rates of AF observed with the 2 techniques may, therefore, be partly attributable to this difference. Average doses of radiation delivered to axillary levels I, II, and III using standard tangential radiation fields are 66%, 44%, and 31% of the prescribed dose, respectively. When high tangential fields are used, these percentages increase to 86%, 71%, and 73%.[17] The degree to which this axillary irradiation contributes to regional disease control is uncertain.

Published rates of axillary recurrence in patients treated with EBRT after negative sentinel lymph node biopsy were recently reviewed; at a median follow-up of 22 months, 0.4% of patients developed an axillary recurrence. This study also identified an association between treatment with EBRT and a decreased rate of axillary recurrence.[18] It is difficult to determine the true incidence of regional nodal recurrence after breast-conserving surgery and EBRT from previously published randomized trials, which frequently identify only first breast cancer events following treatment. Episodes of AF occurring after in-breast recurrence are not reflected in estimates of the rates of regional nodal recurrences. As a result, published rates of AF may underestimate the true incidence of this event. Accepting this significant limitation, a study of locoregional recurrences in patients with node-negative breast cancer at diagnosis in 5 National Surgical Adjuvant Breast and Bowel Project (NSABP) trials identified 5-year rates of regional nodal or ipsilateral chest wall recurrence ranging from 0.8% to 2.1%.[19] Recently published data from the American College of Surgeons Oncology Group Z011 randomized trial may also reflect a significant impact of WBI on axillary disease control. In this trial, the 5-year risk of AF was less than 1% in patients with sentinel lymph

TABLE 3 Clinical and pathologic factors associated with axillary recurrence among patients with invasive breast cancer treated with MammoSite accelerated partial breast irradiation

Factor	No. of breasts with recurrence/No. of breasts in subgroup (%)[a]	5-year actuarial axillary recurrence rate (%)	*P* value
Margin status			.99
Positive	0/11 (0.0)	0.00	
Negative	9/1244 (0.7)	0.82	
Nodal status			
Positive	0/38 (0.0)	0.00	.99
Negative	8/1152 (0.7)	0.77	
Sentinel node status			.99
Positive	0/25 (0.0)	0.00	
Negative	7/981 (0.7)	0.74	
Tumor location			.99
Inner quadrant	0/263 (0.0)	0.00	
Outer quadrants	9/992 (0.9)	1.02	
Upper-outer quadrant	3/596 (0.5)	0.64	.38
Other quadrants	6/655 (0.9)	0.97	
Histologic grade			.02
Grade I/II	3/993 (0.3)	0.43	
Grade III	6/219 (2.7)	2.74	
Extensive intraductal component			.99
Positive	0/73 (0.0)	0.00	
Negative	9/1135 (0.8)	0.90	
Age at diagnosis			
<45 years	0/22 (0.0)	0.00	.99
≥45 years	9/1233 (0.7)	0.82	
Tumor size			.23
<2 cm	7/1124 (0.6)	0.67	
≥2 cm	2/127 (1.6)	2.25	
Bra cup size			.78
A or B	2/271 (0.7)	0.57	
C or D	4/695 (0.6)	0.73	
Method of MammoSite placement			.94
Closed cavity	4/566 (0.7)	0.89	
Open cavity	5/689 (0.7)	0.75	
Tamoxifen or anastrozole use			.44
Yes	5/786 (0.6)	0.74	
No	4/469 (0.9)	0.98	
Chemotherapy use			.05
Yes	4/166 (2.4)	2.79	
No	5/1089 (0.5)	0.50	

[a] Includes the total number of breasts for which information was available regarding the variable

node metastases irrespective of whether they underwent sentinel lymph node dissection or axillary lymph node dissection.[20] In the context of this experience, the rate of AF achieved with MammoSite APBI in the current study argues for the safety of this approach after appropriate surgical management of the axillary nodal basin. It should also be noted that the current study included a small cohort of patients with axillary nodal disease, none of whom experienced an axillary recurrence during the follow-up interval.

An assessment of the safety of APBI with regard to locoregional disease control must also be placed in the context of the impact of axillary recurrence when it does occur. Not surprisingly, regional nodal recurrence is frequently a harbinger of aggressive disease and a predictor of poor outcomes.[19,21–23] Among patients enrolled in the

TABLE 4 Multivariate analysis of factors associated with axillary recurrence among patients with invasive breast cancer treated MammoSite accelerated partial breast irradiation

	Axillary recurrence	
	Hazard ratio (95% confidence interval)	*P* value
Margin status (positive vs negative)	–	–
Nodal status (positive vs negative)	–	–
Sentinel node status (positive vs negative)	–	–
Histologic grade (grade III vs grade I/II)	11.3 (1.88–67.9)	.0081
Extensive intraductal component (positive vs negative)	–	–
Age at diagnosis (continuous)	1.07 (0.99–1.15)	.1069
Tumor size (continuous)	0.89 (0.22–3.59)	.8753
Tamoxifen use (no vs yes)	0.58 (0.11–3.15)	.5298
Chemotherapy use (yes vs no)	5.12 (0.66–39.8)	.1184

Margin status, nodal status, sentinel node status, and extensive intraductal component: too few events present for reliable HR estimates

NSABP trials 13, 14, 19, 20, and 23, for example, the 5-year overall survival rate was 34.9% after regional nodal or ipsilateral chest wall recurrence.[19] In a retrospective analysis of patients included in the British Columbia Cancer Agency Breast Cancer Outcomes Unit database, the 5-year survival rate estimate after axillary nodal recurrence was 49.3%.[21] Treatment must therefore be optimized to limit locoregional recurrence through careful patient selection for any given approach. In the current study, higher-grade disease was associated with AF as was treatment with chemotherapy, although the latter association was less strong. Despite these associations, the absolute risk of AF was small; it occurred in only 2.7% of the patients with high-grade (grade III) disease (Table 3). Stratification of data on the basis of chemotherapy exposure highlights a profile of patients who may be at higher risk for AF and may not be optimal candidates for APBI. Specifically, these are younger patients with larger, higher-grade tumors or lymph node involvement. Toward this end, a recent consensus statement by the American Society for Therapeutic Radiology and Oncology suggests that the use of APBI in patients with node-positive disease is inappropriate outside of a clinical trial until more long-term data emerges in this population of patients.[24]

In summary, MammoSite APBI is associated with rates of regional disease control similar to those previously reported with WBI. As the data on axillary recurrence after MammoSite APBI mature further, we may be able to better identify those patients who are best suited to this approach. We also anticipate that the NSABP B-39 trial, in which patients with stages 0–II breast cancer are randomly assigned to partial mastectomy with WBI or APBI, will elucidate which factors are associated with AF.[10]

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