Ann Surg Oncol
DOI 10.1245/s10434-012-2489-x

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Tumor Bed Control with Balloon-Based Accelerated Partial Breast Irradiation: Incidence of True Recurrences Versus Elsewhere Failures in the American Society of Breast Surgery MammoSite® Registry Trial

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ABSTRACT

Background. Randomized trials demonstrate that lumpectomy plus whole-breast irradiation (WBI) yields survival equivalent to mastectomy. Studies that use WBI, however, typically report higher tumor bed recurrence rates than elsewhere failures (EF) (historically considered new primary lesions). The rate of true recurrence (TR) versus EF was queried for a large patient cohort treated with accelerated partial breast irradiation (APBI).

Methods. A total of 1,449 cases of early-stage breast cancer were treated on the American Society of Breast Surgeons MammoSite® Registry Trial with lumpectomy plus balloon-based APBI (34 Gy, 10 BID fractions). A total of 1,255 cases (87 %) had invasive breast cancer, and 194 patients (13 %) had ductal carcinoma in situ. Rates of TR versus EF were calculated and compared to historical WBI controls.

Results. Median follow-up was 60 (range 0–109) months. Fifty patients (3.5 %) developed an ipsilateral breast tumor recurrence (IBTR). The 5-year actuarial rate of IBTR was 3.6 % (invasive breast cancer 3.6 %, ductal carcinoma in situ 3.4 %). Fourteen IBTR (1.1 %) were TR, while 36 (2.6 %) were EF. Estrogen receptor–negative status was associated with IBTR for invasive malignancies as well as for EF only ($p < 0.001$). Trends for increased rates of EF were noted for increased tumor size ($p = 0.067$) and extensive intraductal component ($p = 0.087$). No pathologic factors were explicitly associated with TR.

Conclusions. IBTR after balloon-based APBI is low and similar to rates reported for WBI. In this data set, APBI had fewer tumor bed recurrences (presumably initial cancer recurrences) than EF (presumably new primary lesions). This suggests that balloon-based APBI has a tumor bed control rate that is at least equal to (and potentially higher than) WBI.

Breast-conserving therapy (partial mastectomy with whole-breast irradiation, WBI) has been demonstrated in numerous studies to be equivalent in survival to modified radical mastectomy.[1,2] However, there is a risk of ipsilateral breast tumor recurrence (IBTR) after breast conservation therapy. Studies generally report breast recurrence as either ipsilateral or contralateral without specifying a location relative to the tumor bed. However, some studies have examined the location of the IBTR after WBI and have demonstrated a larger percentage of these recurrences to be in or near the tumor bed itself compared to elsewhere in the breast.[3–9] These tumor bed recurrences are presumably an actual recurrence of the initial breast cancer, although there have been no definitive studies to prove this. Recurrences

First Received: 17 April 2012

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Published online: 27 July 2012

outside of the tumor bed are classified as elsewhere recurrences and are thought to be a new or second primary lesion in that breast (similar to new contralateral primary lesions). Prognosis for a true recurrence (TR) has been demonstrated to be worse than an elsewhere failure (EF), which is thought to be due to its status as recurrent versus new tumor.[10] In studies comparing WBI to observation after lumpectomy, WBI has not been demonstrated to decrease the incidence of elsewhere recurrences.[11,12]

Radiotherapy restricted to the lumpectomy site (e.g., accelerated partial breast irradiation, APBI) has been demonstrated to produce acceptable clinical outcomes in properly selected patients.[13–15] APBI has several theoretical advantages, including decreased overall treatment time, reduced radiation dose to normal tissue (ipsilateral breast, heart, lung, chest wall), increased utilization of adjuvant radiotherapy, and, potentially, decreased mastectomy rates for patients where travel time to WBI centers is a primary consideration.[16–18] However, a concern with some physicians regarding APBI is that potential occult foci of cancer elsewhere in the breast may remain untreated, which could lead to increased elsewhere recurrences.

In this study, we examined the American Society of Breast Surgeons (ASBrS) MammoSite® Registry Trial to determine the effect of APBI on patterns of failure after breast-conserving therapy as compared to historical series that used WBI.

MATERIALS AND METHODS

Study Participants

After U.S. Food and Drug Administration (FDA) approval of the MammoSite® Radiation Therapy System (Hologic, Bedford, MA) for clinical use, 97 institutions participated in a registry trial designed to collect data on the optimal use of the device to deliver APBI between May 4, 2002, and July 30, 2004. Details of patient enrollment criteria and data collection and management have been extensively described in prior reports.[14,19,20] Briefly, recommended criteria for patient enrollment in the registry trial were based on guidelines published by the American Society of Brachytherapy on the use of APBI at that time.[21] Inclusion criteria included age ≥45 years, tumor size ≤2 cm, invasive ductal carcinoma or ductal carcinoma in situ (DCIS), negative surgical margins (per National Surgical Adjuvant Breast and Bowel Project criteria), and applicator placement within 10 weeks of final surgery. Exclusion criteria was pregnancy, collagen–vascular disease, an extensive intraductal component, or infiltrating lobular histology. Additional technical guidelines regarding appropriate balloon-to-skin distance (≥7 mm), cavity size, balloon–cavity conformance, and central cavity shaft symmetry were also provided. Statistical analysis of this trial for the ASBrS is currently provided by BioStat International (BSI, Tampa, FL). Because data entry and processing for the registry trial are ongoing, a data cutoff date of January 29, 2012, was used for the purposes of the current analysis. A total of 1,449 cases for 1,440 patients have been treated with the MammoSite® single-lumen breast brachytherapy device on this trial. All patients enrolled onto the study were required to provide written informed consent. Institutional review board approval was not required for participation in the registry trial but was recommended by the sponsor and obtained for over 80 % of participating sites.

Outcome Measures

IBTR was defined as a recurrence of cancer in the treated breast. Each recurrence was classified by the investigator as either a tumor bed/TR or an EF on the basis of the criteria established by Recht et al.[8] Close margins were defined as <2 mm. Patient demographics and tumor characteristics for both primary and recurrent tumors were analyzed for all treatment failures. Predictors of IBTR were assessed separately for patients with invasive breast cancer (IBC) and those with DCIS. Time to local recurrence was defined from the date of completion of radiotherapy to the date of second ipsilateral breast cancer.

Statistical Analysis

The estimated likelihood of events for IBTR and time to local recurrence were calculated by the life table method, and the statistical significance of differences between recurrence types were calculated by the log-rank test. Logistic regression was used to investigate associations between potential predictors and recurrence outcomes. A p value of <0.05 was considered statistically significant, and all statistical tests were two-tailed. Statistical analyses were performed by SAS software version 8.0 (SAS Institute, Cary, NC).

RESULTS

Median follow-up was 60 (range 0–109) months, and median tumor size was 1.0 (range 0.1–4.5) cm (Table 1). Most tumors were estrogen receptor (ER) positive (87.0 %) and had either a histologic grade of 1 or 2 (37.6 and 38.4 %, respectively). Fifty patients developed IBTR, for a 5-year actuarial IBTR rate of 3.6 % (Table 2). Of these, 42 patients with recurrent disease had an initial invasive breast cancer (IBC) (3.6 % 5-year actuarial), and 8 patients were initially diagnosed with DCIS (3.4 % 5-year actuarial). Recurrent tumors were, in general, larger than the primary lesion (median size 1.4 cm vs. 1.0 cm). Most tumor recurrences were IBC (IBC 78 % vs. DCIS 22 %), and this did not differ for TR (IBC 87.5 % vs. DCIS 12.5 %) versus

TABLE 1 Characteristics of tumors with local or elsewhere failure

Characteristic	All	Primary lesions that recurred locally	Primary lesions that recurred elsewhere in the breast	*p* value
No. of tumors	1408	14	36	
Tumor size (cm)				
Median	1.0	1.0	1.0	0.41
Range	0.1–4.5	0.6–1.7	0.1–2.6	
Histology				
Invasive	1255 (86.6 %)	11 (78.6 %)	31 (86.1 %)	0.67
DCIS	194 (13.4 %)	3 (21.4 %)	5 (13.9 %)	
Unknown	0	0	0	
Grade				
Gx	73 (5.0 %)	0 (0.0 %)	4 (11.1 %)	0.38
G1	545 (37.6 %)	4 (28.6 %)	7 (19.4 %)	
G2	557 (38.4 %)	5 (35.7 %)	18 (50.0 %)	
G3	269 (18.6 %)	5 (35.7 %)	7 (19.4 %)	
Unknown	0	0	0	
ER status				
Positive	930 (87.0 %)	9 (75.0 %)	19 (63.3 %)	0.91
Negative	139 (13.0 %)	3 (25.0 %)	11 (36.7 %)	
Unknown	380	2	6	

DCIS ductal carcinoma in situ, *ER* estrogen receptor

TABLE 2 Comparison of true and elsewhere 5-year recurrence rates

Characteristic	All cases ($N = 1,449$)		Invasive cases ($N = 1,255$)		DCIS cases ($N = 194$)	
	n (%)	5-year actuarial rate	*n* (%)	5-year actuarial rate	*n* (%)	5-year actuarial rate
All breast failures	50 (3.5)	3.60 %	42 (3.3)	3.63 %	8 (4.1)	3.36 %
TR	14 (1.0)	1.07 %	11 (0.9)	1.05 %	3 (1.5)	1.24 %
EF	36 (2.5)	2.55 %	31 (2.5)	2.61 %	5 (2.6)	2.14 %
*p**		0.002		0.002		0.480

DCIS ductal carcinoma in situ, *TR* true recurrence, *EF* elsewhere failure

* Log-rank test comparing TR versus EF

EF (IBC 75.0 % vs. DCIS 25.0 %). It was more common for an invasive cancer treated with balloon-based brachytherapy to recur elsewhere in the breast (5-year actuarial rate EF 2.6 % vs. TR 1.1 %, $p = 0.002$), while recurrences after treatment for DCIS were more balanced between elsewhere in the breast and the site of lumpectomy (EF 2.1 vs. TR 1.4 %, $p = 0.48$).

Factors associated with IBTR for both invasive and noninvasive tumors are listed in Table 3. In the invasive group, ER negativity ($p < 0.001$) was the only factor associated with IBTR. Other variables, such as age <50 ($p = 1.00$), close/positive margins ($p = 0.38$), tumor size ($p = 0.72$), positive nodes ($p = 1.00$), use of chemotherapy ($p = 1.00$), and American Society for Radiation Oncology (ASTRO) Consensus Panel groupings ($p = 0.24$–1.00) were not statistically associated with IBTR for invasive malignancies. In the DCIS group, however, both age <50 ($p = 0.04$) and close/positive margins ($p = 0.06$) were associated with increased IBTR, while other factors (tumors size, $p = 0.51$, and ER status, $p = 0.53$) were not.

An IBTR was considered a tumor bed failure (TR) in 14 patients (28 %) and an EF in 36 patients (72 %). The median time to tumor bed recurrence (40 months; range 7–63 months) was slightly shorter than that for elsewhere recurrence (43 months; range 7–94 months). There were 26 (1.8 %) contralateral recurrences, which is similar to the rate for elsewhere recurrences. Multiple variables were analyzed for their association with a TR IBTR versus an EF IBTR. ER-negative status was the only factor associated with IBTR for all patients with invasive carcinoma as well as for EF only ($p < 0.001$). For patients with invasive malignancies, trends for increased rates of EF were noted for increased tumor size ($p = 0.067$) and an extensive intraductal component ($p = 0.087$). No specific tumor characteristics were associated with increased recurrence at the lumpectomy bed (TR), although the number of events was quite small (Table 3). Factors for increased risk of recurrence after treatment for DCIS included young age (<50 years, $p = 0.03$) and an involved margin (close/positive vs. negative, $p = 0.04$). The low number of recurrences after treatment for DCIS precluded analyzing factors unique to TR or EF within this patient population.

DISCUSSION

The goal of breast cancer treatment is to achieve the longest possible survival with the best possible functional and cosmetic outcome. To these ends, we have made great strides in reducing the degree of local and regional treatment necessary to achieve these goals. Mastectomy has given way to lumpectomy and radiation for many patients, sentinel node biopsy has replaced complete axillary dissection for almost all patients with IBC, and oncoplastic techniques are becoming more widespread, improving cosmesis while not compromising oncologic care. Likewise, radiotherapy has become more focused with the advent of 3-D treatment planning, intensity-modulated radiotherapy, and, over the past 15 years, APBI. Each technique (both surgical and radiologic) requires proper patient selection and execution to optimize outcomes without increasing recurrence or decreasing survival.

TABLE 3 Predictors of recurrence after balloon-based APBI

Factor	All invasive cases		TR		EF	
	OR (95 % CI)	*p*	OR (95 % CI)	*p*	OR (95 % CI)	*p*
IBC (n = 1,255)						
Tumor size (continuous variable)	0.585 (0.288–1.186)	0.137	1.011 (0.351–2.912)	0.983	0.416 (0.163–1.058)	0.067
ER status (negative vs. positive)	4.060 (1.830–9.007)	**<0.001**	2.616 (0.685–9.992)	0.160	5.035 (1.881–13.48)	**0.001**
EIC (positive vs. negative)	2.473 (0.839–7.284)	0.101	1.563 (0.197–12.37)	0.673	2.997 (0.853–10.53)	0.087
Age at diagnosis <50 years vs. ≥50	1.090 (0.327–3.638)	0.888	1.052 (0.133–8.295)	0.962	1.109 (0.255–4.824)	0.891
Margin status (positive/close vs. negative)	1.677 (0.576–4.880)	0.343	1.157 (0.147–9.128)	0.890	1.954 (0.566–6.750)	0.290
Tumor grade (grade 3 vs. grade 1,2)	1.137 (0.459–2.817)	0.781	1.710 (0.450–6.499)	0.431	0.848 (0.245–2.936)	0.795
Nodal status (positive vs. negative)	1.085 (0.144–8.190)	0.937	–	–	1.703 (0.221–13.10)	0.609
ASTRO consensus category (suitable vs. cautionary/unsuitable)	0.643 (0.288–1.436)	0.281	0.783 (0.228–2.691)	0.698	0.567 (0.198–1.622)	0.290
ASTRO consensus category (suitable/cautionary vs. unsuitable)	0.875 (0.328–2.337)	0.790	1.921 (0.244–15.11)	0.535	0.615 (0.198–1.910)	0.400
Chemotherapy (yes vs. no)	0.883 (0.342–2.280)	0.797	–	–	–	–
DCIS (n = 194)						
Margin status (positive/close vs. negative)	4.981 (1.106–22.42)	**0.037**				
Age (<50 vs. ≥50 years)	5.600 (1.235–25.39)	**0.026**				
Tumor size (continuous variable)	0.635 (0.163–2.466)	0.512				
ER status (negative vs. positive)	1.636 (0.155–17.23)	0.682				

APBI accelerated partial breast irradiation, *OR* odds ratio, *CI* confidence interval, *IBC* invasive breast cancer, *ER* estrogen receptor, *EIC* extensive intraductal component, *ASTRO* American Society for Radiation Oncology, *DCIS* ductal carcinoma in situ

The increased application of APBI, beginning in May 2002 after U.S. FDA clearance of the MammoSite® Radiation Therapy System, has caused continued controversy within the breast cancer community. Between 2002 and 2007, it was demonstrated that use of APBI increased 10-fold, which coincides with the adoption of the balloon-based brachytherapy technique.[22] Many breast cancer experts initially expressed concern that APBI would lead to increased IBTR rates and uncontrolled axillary disease. These apprehensions have now been lessened with 5-year local recurrence rates of <4 % in the ASBrS MammoSite® registry and in virtually all contemporary phase I/II and retrospective studies exploring this treatment approach. In addition, the 5-year axillary recurrence rates are also low, at <1 %.[23] The rationale for postlumpectomy radiation is to treat malignant cells that may remain within the breast after a negative-margin lumpectomy. Treating the entire breast after breast-conserving surgery (as opposed to only the lumpectomy cavity to begin with) was done in order to compensate for leaving the breast intact—the initial comparator being mastectomy. The concept was to substitute one treatment of the entire breast (mastectomy) for another (WBI). There were no studies to determine the best technique for radiation (e.g., bilateral, unilateral, partial, additional nodal fields) before adoption as part of breast-conserving therapy. If it could conclusively be established that there was no residual disease remaining within the breast, there would be no reason to irradiate the breast with its attendant (albeit low) complications. Thus, radiation is provided to the entire breast to treat residual cancer after breast-conserving surgery.

Others have postulated that the purpose of radiation is to prevent future breast cancers. WBI, however, does not sterilize the remainder of the breast, as EF continue to occur despite irradiation. If irradiation were prophylactic, it could be hypothesized that bilateral breast irradiation could be provided to breast cancer survivors (who are at a higher risk for contralateral disease) or possibly to women who have not yet received a diagnosis of cancer but who remain at high risk for eventually forming a breast malignancy. The issues with this logic are immediately apparent and, in part, extend to WBI, as it should be discussed whether prophylactic irradiation of the entire breast beyond the region at risk for a TR is indeed beneficial for all patients. Fortunately, the ongoing phase III trials evaluating WBI and APBI will help answer this question. Until these trials are published in final form, however, we must rely on the numerous studies that indicate that IBTR after APBI is on par with WBI.[12,24]

We are therefore left with a clear directive to use radiotherapy to treat residual cancer surrounding the lumpectomy bed. APBI is designed to deliver radiation to

TABLE 4 Published reports of TR versus EF for breast-conserving therapy using WBI

Study	*n*	Follow-up (years)	IBTR	TR	EF	CBF	Comments
Smith et al.[3]	1,152	14.2	14 % (10 years)	4.3 % (5 years)[a]	3.0 % (5 years)[a]	NR	TR/NPT determined using location, histology, and subtype
Huang et al.[26]	1,339	12.4	10.4 % (12 years)	6.6 % ($n = 78$)	3.8 % ($n = 48$)	NR	EF defined as new quadrant or change in histology
Komoike et al.[27]	1,901	NR	9.0 % ($n = 172$)[a]	7.1 % ($n = 135$)	1.9 % ($n = 26$)		
Antonucci et al.[11]	199	8.8	4 % (10 years)	2 %	2 %	8 %	
Krauss et al.[5]	1,448	8.5	7 % (10 years)	5 %	2 %	9 %	
Abd-Alla et al.[28]	267	8.0	9.6 % (8 years)	7.0 %	2.6 %	NR	EF defined as new quadrant or change in histology
Seynaeve et al.[4]	174	6.1	7 % (5 years)	6.9 %	1.1 %	4.0 %	Rates for sporadic breast cancer

TR true recurrence, *EF* elsewhere failure, *IBTR* ipsilateral breast tumor recurrence, *CBF* contralateral breast failure, *NR* not reported, *NPT* new primary tumor, *WBI* whole breast irradiation

[a] Crude rate

this margin (while sparing normal breast and adjacent structures). This concept of focused tumor bed radiation is corroborated by numerous studies of WBI plus a boost to the tumor bed having lower recurrence rates than WBI alone.[25] Our analysis confirms the ability of targeted radiation to effectively treat the perilumpectomy tissues, and compared to historical controls with WBI, it appears to have at least an equal rate of local control in the region immediately contiguous with the brachytherapy applicator. As a point of discussion, studies reporting recurrences after WBI typically demonstrate a higher percentage of IBTR at the tumor bed (approximately two thirds of recurrences) compared to elsewhere in the breast (Table 4). This appears to be the opposite pattern of IBTR for APBI that uses the balloon-based technique in the present analysis. This can only be explained by either an exceptionally good tumor bed control with APBI, an extreme excess of elsewhere recurrences caused by the APBI, or by chance alone. Our study, however, indicates excellent rates of control both locally and elsewhere in the breast, which is comparable to the incidence of contralateral new breast primary lesions.

Limitations of the current analysis include its retrospective nature and issues inherent with inclusion of registry trial–style data. Although the number of patients included in the present series is large, there was no central review of pathology, margins, receptor testing, or recurrences as part of the registry trial. There is also a bias within this analysis toward balloon-based brachytherapy because it was the only form of APBI used, and thus the results herein may not apply to all forms of APBI. In addition, the historical controls used as comparison studies (Table 4) did not have the same selection criteria and, in some cases, were treated in a different era than registry trial patients, which makes direct comparison between studies difficult. Despite these limitations, however, this study represents an important perspective in the ongoing effort to define the clinical role and efficacy of APBI.

In conclusion, APBI that uses balloon-based brachytherapy provides excellent tumor bed control without increases in elsewhere recurrences. APBI that uses balloon-based brachytherapy offers excellent control of the tumor bed in a large series of patients treated with breast-conserving therapy. In addition, tumor bed control using this technique appears to be at least equal to (and potentially higher than) tumor bed control rates historically reported for WBI while maintaining similar elsewhere and contralateral recurrence rates. Ongoing phase III trials, such as the National Surgical Adjuvant Breast and Bowel Project (NSABP) B39 / Radiation Therapy Oncology Group (RTOG) 0413 trial, will add to our knowledge of local recurrence within and outside the tumor bed for early-stage breast cancer treated with both partial and whole-breast irradiation.

ACKNOWLEDGMENT We thank the numerous institutions, physicians, and health care personnel who participated in this trial and the patients themselves for allowing us to do this research. The American Society of Breast Surgeons MammoSite® Breast Brachytherapy Registry Trial was supported in part by an unrestricted educational Grant from Cytyc Corporation, a Hologic company, to the American Society of Breast Surgeons and BioStat International.

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