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ORIGINAL ARTICLE – BREAST ONCOLOGY

A Single-Institution Review of Accelerated Partial Breast Irradiation in Patients Considered "Cautionary" by the American Society for Radiation Oncology

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ABSTRACT

Background. The American Society for Radiation Oncology (ASTRO) issued a consensus statement in 2009 regarding patient selection for accelerated partial breast irradiation (APBI) following breast-conserving surgery (BCS) for breast cancer (BC). We reviewed our single-institution experience with APBI in patients considered "cautionary" by ASTRO to determine patterns of recurrence.

Methods. An institutional review board-approved, retrospective chart review was conducted from January 2004 to November 2009. We identified 106 "cautionary" patients with 109 BC. All patients were treated with BCS followed by APBI via balloon catheter brachytherapy. "Cautionary" criteria include patients aged 50–59 years, tumor size 2.1–3.0 cm, close margins (<2 mm), focal lymphovascular invasion, estrogen receptor (ER)-negative tumors, invasive lobular carcinoma, or ductal carcinoma in situ (DCIS) $\leq$ 3 cm. Rates of recurrence at any site were evaluated.

Results. Median follow-up was 3 years. There were 3 IBTR (2.8%) at a median of 3.2 years. The 3-year actuarial IBTR rate was 1.8%. Patients with ER-negative invasive cancers had a higher IBTR rate compared with ER-positive patients (11.8% vs. 2.2%), although this did not reach statistical significance ($P = 0.18$). There were no IBTR in 46 patients with DCIS. On univariate analysis, there was no association between "cautionary" criteria and risk of local, regional, or distant recurrence.

Conclusions. Patients considered "cautionary" for APBI based on ASTRO guidelines had low rates of IBTR. ER-negative patients trended toward a higher IBTR rate with APBI compared with ER-positive patients. Longer follow-up is needed to establish the safety of APBI in "cautionary" patients.

Based on data from six randomized, prospective trials, breast-conserving surgery followed by whole breast irradiation (WBI) has been shown to be equivalent to mastectomy with regard to overall survival in women with early-stage breast cancer.[1–6] Moreover, the addition of WBI after lumpectomy compared with lumpectomy alone significantly reduces the likelihood of local failure at or near the site of initial surgical resection.[7–12] However, recurrences in different quadrants of the breast, so-called "elsewhere" recurrences, are unaffected by the addition of WBI. Data from clinical studies have demonstrated that patients treated with lumpectomy alone have low rates of "elsewhere" recurrences and that the rates of these recurrences are similar to rates seen in patients treated with WBI.[13] Because most in-breast recurrences occur near the previous lumpectomy site, the question has been raised as to whether WBI may result in overtreatment of many patients with early-stage breast cancer.[14]

Based on clinical data regarding patterns of in-breast recurrence following breast-conserving surgery, accelerated partial breast irradiation (APBI) has emerged as an alternative to WBI.[12,15,16] APBI effectively treats the

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lumpectomy bed plus a margin of surrounding breast tissue, thereby avoiding radiation to the remainder of the "normal" breast. Because of the reduction in radiation exposure to normal breast tissue, as well as the decreased treatment times, APBI has gained significant popularity with both physicians and patients. However, during a time when there is increasing evidence that WBI significantly improves overall survival after breast-conserving surgery, the greatest concern with APBI is that foci of cancer elsewhere in the breast are left untreated.[17]

To address these questions, several randomized, prospective trials, including NSABP B39/RTOG 0413, have been initiated to assess the effectiveness and safety of APBI compared with WBI in patients with early-stage breast cancer.[18] Unfortunately, data from this trial will not be available for several years. Because of the growing interest in the use of APBI and the paucity of clinical data, the American Society of Radiation Oncology (ASTRO) Health Services Research Committee convened a Task Force of breast cancer experts to help guide physicians on best practice for the use of APBI outside of a clinical trial. In July 2009, the Task Force published a consensus statement (CS) based on review of the literature that stratified patients being considered for APBI into three major groups: suitable, cautionary, and unsuitable.[19] Criteria for these categories were established primarily on patient, tumor, and treatment characteristics. It is important to note that the CS groupings were not based on data that identified groups of patients with higher or lower rates of in-breast recurrence with APBI but rather a paucity of data supporting its use. Particular interest in the appropriateness of APBI in cautionary patients exists because these patients (except for women with ER-negative invasive tumors) are not eligible for NSABP B-39/RTOG 0413, which closed to: (a) patients older than age 50 years with DCIS and (b) patients with estrogen receptor-positive, node-negative invasive cancer who were older than age 50 years as of December 30, 2006.

In this report, we reviewed our single-institution experience with APBI in patients considered cautionary by ASTRO to determine patterns of breast treatment failures, regional recurrence, and distant metastasis.

MATERIALS AND METHODS

After permission was obtained from our institutional review board, a retrospective chart review was performed for patients who underwent APBI at our institution. A total of 106 patients with 109 breast cancers treated between January 2004 and November 2009 were identified that fell into the cautionary group per the ASTRO guidelines. Of the 106 patients, 1 had bilateral breast cancer and 2 had metachronous contralateral breast cancers (CBC), giving rise to 109 cancers. Cautionary criteria included patients aged 50–59 years, tumor size 2.1–3.0 cm, close margins (<2 mm), focal lymphovascular invasion, estrogen receptor (ER)-negative tumors, invasive lobular carcinoma, or ductal carcinoma in situ (DCIS) $\leq$ 3 cm.

All patients were treated with breast-conserving surgery at a single institution by one of two surgeons and subsequently received APBI via balloon catheter brachytherapy. Of the 109 cancers, 106 (97.3%) were treated with MammoSite single-lumen catheters (Hologic Inc., Bedford, MA) and 3 (2.7%) were treated with Contura multilumen catheters (SenoRx, Irvine, CA). All invasive cancers had axillary evaluation with sentinel lymph node biopsy and were pathologically node negative.

Catheter Insertion Technique

Fifty-two of the 109 balloons (48%) were placed percutaneously in the office via a lateral approach or from the inframammary fold. Fifty-seven (52%) balloons were placed in the operating room. Thirty-five of the 57 (61%) catheters placed in the operating room were done via an open cavity technique at a separate operation or during re-excision for margins. None were placed at the time of the initial lumpectomy. The remaining 22 (39%) were placed percutaneously in the operating room with ultrasound assistance. All patients had pre-placement ultrasound confirming adequate skin-to-seroma distance $\geq$7 mm (Fig. 1).

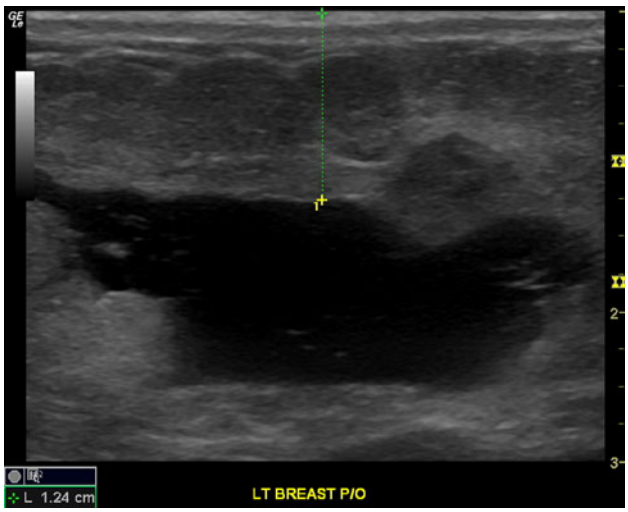

FIG. 1 Pre-placement ultrasound demonstrating adequate skin-to-seroma distance

Radiation Treatment

Within 24–48 h of balloon placement, patients were seen in the Radiation Oncology Department for high-dose rate (HDR) CT-based 3D treatment planning to produce an optimal plan in accordance with volume definition and dose requirements. Radioactive source location and number of positions and dwell times were determined to deliver 34 Gy at 10 mm from the balloon surface in ten fractions over five treatment days. On the CT scan, the target and normal tissue structures were outlined and the balloon surface, clinical target volume, and planning target volume contoured, as well as volume of trapped air/fluid accounted for in terms of displacement percentage of the target at 1 cm from the balloon surface. Appropriateness for treatment was determined by tissue-balloon conformance, balloon symmetry, minimal balloon surface–skin distance, and normal breast tissue dose volume parameters for dose homogeneity. A total of 34 Gy was given at approximately 1 cm distance from the balloon surface, at two fractions of 3.4 Gy each per day, separated by approximately 6 h given over 5 treatment days. To ensure continued integrity of the balloon throughout treatment, a modified CT was obtained before each morning treatment and ultrasound before each afternoon treatment.

Outcome Measures

Ipsilateral breast tumor recurrence (IBTR) was defined as recurrence in the bed of the resected tumor as well as "elsewhere" breast recurrences encompassing the other quadrants of the breast. Regional recurrences included failures in the axillary, internal mammary, inframammary, and supraclavicular lymph nodes. Contralateral breast cancer was defined as a subsequent cancer in the opposite breast not identified at the time of initial diagnosis. Distant metastases were defined as recurrence of disease outside of the breast or regional nodes.

Statistical Analysis

Crude IBTR rates were compared between ER-negative and ER-positive patients using continuity corrected chi-square (due to small number of events). Simple predictions of recurrence over time from each of the cautionary criteria were obtained with Cox Models (proportional hazards analysis), which provide a hazard ratio (related to a relative risk or odds ratio) and 95% confidence interval. When one of the groups had no events (such as DCIS), the Cox model could not be used, and a Kaplan-Meier comparison with log-rank test was instead used to obtain a P value. IBTR as a function of DCIS or non-DCIS also was explored with Kaplan–Meier curves.

RESULTS

Of the 109 cautionary cases, 62 (56.9%) were in a single cautionary group, 38 (34.9%) were in two groups, 8 (7.3%) were in three, and 1 (0.9%) was in four. Table 1 demonstrates the breakdown of the study cohort according to cautionary criteria. Patients with close margins or DCIS comprised 58% of the cautionary cases. Median age at diagnosis was 68 years. Median follow-up was 3 (range, 0.4–6.1) years. Of the 63 invasive cancers, 9 (14.3%) received adjuvant chemotherapy. Fifty-one of the 106 patients (48%) received adjuvant hormonal therapy; 31 (49.2%) with invasive cancer and 20 (43.5%) with DCIS.

Ipsilateral Breast Tumor Recurrences

There were three IBTR (2.8%) at a median of 3.2 years. The 3-year actuarial IBTR rate was 1.8% (Fig. 2). Patients with ER-negative invasive breast cancer had a higher crude IBTR rate compared with ER-positive patients (11.8% vs. 2.2%), although this did not reach statistical significance ($P = 0.18$). Of the three IBTRs, one was a true local recurrence in an ER-negative patient with a disease-free interval of 3.2 years. There were two "elsewhere" recurrences at 4.1 (ER-negative and close margins) and 2.8 (close margins) years. Two IBTRs were treated with salvage mastectomy. The third, an elsewhere recurrence, was treated with wide segmental resection and APBI. No IBTRs occurred in the 46 patients with DCIS. Figure 3 shows the IBTR-free survival of cautionary patients with DCIS versus invasive carcinoma.

Regional and Distant Recurrences

There were two regional recurrences (1.8%) with an average DFI of 2.4 years. Both were axillary recurrences.

TABLE 1 Breakdown of study cohort according to cautionary criteria

Criteria	*N*	%
Total[a]	166	100
Age 50–59 years	29	17.5
Tumor size 2.1–3.0 cm	8	4.8
Close margins	50	30.1
Focal LVI	7	4.2
ER-negative	17	10.3
ILC	9	5.4
DCIS	46	27.7

LVI lymphovascular invasion, *ER* estrogen receptor, *ILC* invasive lobular carcinoma, *DCIS* ductal carcinoma in situ

[a] Some patients met more than one criterion

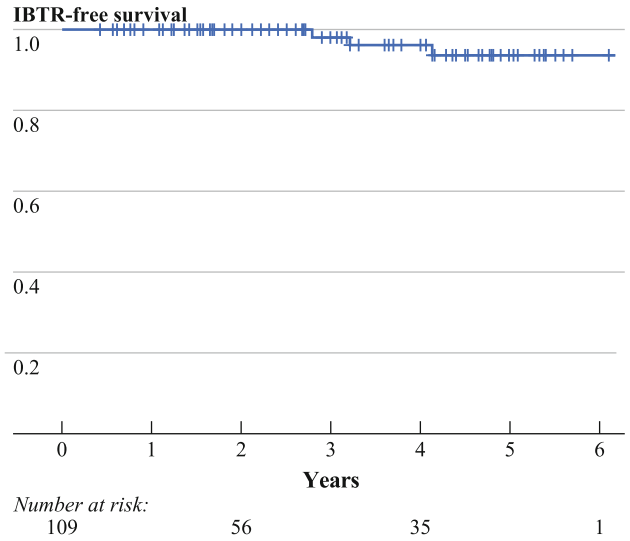

FIG. 2 Ipsilateral breast tumor recurrence-free survival for 109 cautionary cases

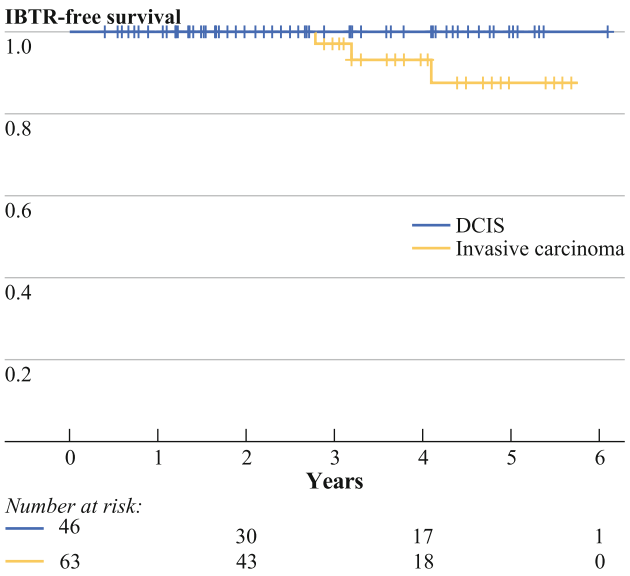

FIG. 3 Ipsilateral breast tumor recurrence-free survival of cautionary patients with DCIS and invasive carcinoma

One patient with focal lymphovascular invasion and close margins was diagnosed with a concomitant lung metastasis. The second patient, whose cautionary criteria included ER-negative and age 50–59 years, had an isolated regional recurrence.

Contralateral Breast Cancers

Three patients developed a contralateral breast cancer (2.75%) at a median of 1 year. All three patients were ER-negative, and one patient also had a tumor size 2.1–3.0 cm. Two of these patients' contralateral breast cancers were in the cautionary group and were treated with balloon-based APBI.

Patterns of Tumor Recurrence

Of the 109 cancers, there were 6 (5.5%) events (local, regional, or systemic) in 5 patients with a median disease-free interval of 2.8 (range, 2.3–4.1) years. On univariate analysis, there was no correlation between individual cautionary criteria and risk of local, regional, or systemic recurrence (Table 2). Table 3 shows the patterns of tumor recurrence and outcomes in our cohort of cautionary patients. In the five patients who developed a recurrence, there have been no breast cancer-specific deaths.

DISCUSSION

Although limited long-term data are available regarding the safety of APBI, there continues to be significant interest in its use for early-stage breast cancer outside of a clinical trial. In particular, balloon catheter-based techniques for delivery of APBI have gained favor due to the shorter treatment times, ease of placement, decreased toxicity, and good/excellent cosmetic outcomes. In 2002, the FDA cleared the Mammosite Radiation Therapy System (Hologic Inc, Bedford, MA) for use in patients with early-stage breast cancer. According to data from Hologic, more than 50,000 women have been treated with Mammosite brachytherapy since its initial approval.[20] To help guide appropriate patient selection for brachytherapy-based APBI, the American Society of Breast Surgeons (ASBS) and the American Brachytherapy Society (ABS) developed specific guidelines for patient treatment off protocol.[21,22] The ASTRO CS was recently published to help further guide patient selection. The CS clearly defines "suitable"

TABLE 2 Correlation of cautionary criteria with risk of recurrence at any site in patient cohort ($n = 109$)

Variable	Hazard ratio [95% CI]	*P*
Age 50–59 years	0.57 [0.06–5.11]	0.61
Tumor size 2.1–3.0 cm[a]	–	0.48
Close margins	2.69 [0.45–16.16]	0.28
Focal LVI	3.94 [0.44–35.35]	0.22
ER-negative	2.87 [0.48–17.18]	0.25
ILC[a]	–	0.43
DCIS[a]	–	0.041

Recurrence considered any local, regional, or systemic recurrence

CI confidence interval, *LVI* lymphovascular invasion, *ER* estrogen receptor, *ILC* invasive lobular carcinoma, *DCIS* ductal carcinoma in situ

[a] Cox proportional hazards model could not be performed due to lack of events

TABLE 3 Patterns of tumor recurrence in 106 cautionary patients

Case no.	Age (years)	Cautionary criteria	Local failure	Nodal failure	Distant failure	Chemotherapy	Disease status[a]
50	69	ER-negative	Yes	No	No	No	NED
55	50	ER-negative, age 50–59 years	No	Yes	No	No	NED
60	78	ER-negative, close margin	Yes	No	No	No	NED
81	70	Focal LVI, close margin	No	Yes	Yes	No	AWD
84	80	Close margin	Yes	No	No	No	NED

ER estrogen receptor, *LVI* lymphovascular invasion, *NED* no evidence of disease, *AWD* alive with disease

[a] Disease status as of last follow-up

and "unsuitable" groups, which reflects conservative patient selection for use of APBI outside of a clinical trial. Uncertainty exists regarding the appropriate use of APBI in cautionary patients due to a paucity of clinical data. In this report, we present our single-institution experience with APBI given via balloon-based brachytherapy in patients identified as cautionary by the ASTRO guidelines.

The ASTRO CS groupings were constructed largely without the use of long-term clinical data on the efficacy of APBI and therefore may not be optimal in identifying suitable patients for this modality.[23] In fact, patients that are classified as cautionary or unsuitable may be appropriate candidates for accelerated radiation. We observed a 3-year actuarial IBTR rate of 1.8% in our cohort of 109 cautionary cases. This is similar to the 5-year actuarial IBTR rate of 2.59% reported by Shaitelman et al. in their cohort of 419 suitable patients from the Mammosite Registry. Furthermore, they found no difference in IBTR rates based on ASTRO CS groupings ($P = 0.19$).[24] Our data are limited by our short median follow-up (3 years); longer follow-up may demonstrate higher rates of recurrence. However, a recent study by Vicini et al. demonstrated low rates of IBTR for all CS groupings treated with APBI with a median follow-up of 9.3 years.[23] Based on accumulating data, the ASTRO CS groupings are poor predictors of eventual patient outcomes, and decisions regarding patient appropriateness for APBI should not be based on the CS groupings alone. The ASTRO Task Force acknowledges the need for continued data collection, particularly among the cautionary and unsuitable groups, and they anticipate that the guidelines will need to be periodically updated and revised.

Several studies have demonstrated that ER-negative status in patients with invasive carcinoma treated with APBI is associated with a higher risk of relapse in the breast.[24–26] In a recent retrospective review of the Mammosite Registry Trial, Beitsch et al. noted that the only significant predictor of IBTR in 1,255 patients with invasive cancer was negative ER status (odds ratio, 3.93; $P = 0.0002$).[25] An analysis of our data demonstrated a nonsignificant difference in crude IBTR rates in ER-negative patients compared with ER-positive patients (11.8% vs. 2.2%, $P = 0.18$). We feel that our results are consistent with the higher risk of in breast tumor recurrence in ER-negative patients noted by Beitsch et al., albeit not significant in this small dataset. It is difficult to determine whether these patients would have had a similar rate of recurrence with whole breast irradiation. Poor tumor biology, rather than inferiority of APBI, may be responsible for the increased risk of local recurrence seen in this and other studies. Until data from randomized, prospective trials is available regarding the use of APBI in ER-negative patients, strong consideration should be given to treating these patients inside of a clinical trial.

Few studies have documented the efficacy of APBI in patients with pure DCIS. As such, patients with DCIS $\leq$ 3 cm have been placed in the ASTRO CS cautionary group. In our 46 patients with pure DCIS, we observed no IBTRs at a median of 3 years. Again, our median follow-up is short, but our data are consistent with a study by McHaffie et al. who found no IBTRs in their DCIS subset of 32 patients with a median follow-up of 5 years.[27] Jeruss et al. recently updated the Mammosite Registry Trial experience and demonstrated a similarly low 5-year actuarial local recurrence rate of 3.39% in 194 DCIS patients.[28] DCIS is considered to be a nonobligate precursor to invasive carcinoma and therefore the goal of treatment, particularly radiation therapy, is to prevent cancer progression.[29] However, controversy exists regarding the natural progression of DCIS. Current therapy for DCIS may represent overtreatment for many women who may never progress to invasive cancer. Given this presumption, it seems appropriate that accelerated partial breast irradiation would be a viable alternative for treating this nonlethal condition. Irradiation of the lumpectomy cavity in low-risk patients with DCIS should be sufficient to control local disease and minimize recurrences. Our data support the evidence that carefully selected patients with DCIS are appropriate candidates for APBI, as these patients have excellent local control. Patients with high-risk (age <50 years, positive margins) or extensive DCIS (>3 cm) should be treated with mastectomy or whole

breast irradiation until mature data from randomized clinical trials are available.

Our study has several limitations. First, it is a nonrandomized, retrospective analysis of a small cohort of patients. In addition, the number of patients for each cautionary criterion is unbalanced because selection for APBI in these patients was at the discretion of the treating physicians. As such, there are more patients fulfilling certain cautionary criteria (i.e., close margins and DCIS) and fewer patients with other cautionary criteria (i.e., tumor size, focal lymphovascular invasion, and invasive lobular carcinoma). This, along with a small absolute number of recurrences, may make our study underpowered to detect an association between cautionary criteria and risk of recurrence. Another limitation is that adjuvant chemotherapy and hormonal therapy were given at the discretion of the treating physicians, which may bias the recurrence rates for individual patients. Finally, our median follow-up is short and, in fact, is shorter than our median time to IBTR. Longer follow-up is needed to ensure that the patients in our cautionary cohort continue to have acceptable rates of local and regional recurrence.

In summary, an analysis of 109 cautionary cancers treated with APBI demonstrated low rates of IBTR and regional recurrence. In particular, we had no IBTR in 46 patients with DCIS. The current ASTRO CS groupings are poor predictors of patient outcome and suitability for APBI. The decision for APBI should not be based on CS groupings alone. Patients with ER-negative invasive tumors had a higher crude rate of IBTR compared with ER-positive patients, although this did not reach statistical significance in this small dataset. It is possible that these patients would have had a similar rate of IBTR if treated with whole breast irradiation. Poor tumor biology may be responsible for the marginally worse patient outcomes in this group, rather than inferior disease control with APBI. Until mature data from randomized, prospective trials is available, strong consideration should be given to treating patients with ER-negative invasive tumors with APBI inside of a clinical trial.

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