CLINICAL INVESTIGATION

OUTCOMES AFTER ACCELERATED PARTIAL BREAST IRRADIATION IN PATIENTS WITH ASTRO CONSENSUS STATEMENT CAUTIONARY FEATURES

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Purpose: To evaluate outcomes among women with American Society for Radiation Oncology (ASTRO) consensus statement cautionary features treated with brachytherapy-based accelerated partial breast irradiation (APBI).

Methods and Materials: Between March 2001 and June 2006, 322 consecutive patients were treated with high-dose-rate (HDR) APBI at the University of Wisconsin. A total of 136 patients were identified who met the ASTRO cautionary criteria. Thirty-eight (27.9%) patients possessed multiple cautionary factors. All patients received 32 to 34 Gy in 8 to 10 twice-daily fractions using multicatheter (93.4%) or Mammosite balloon (6.6%) brachytherapy.

Results: With a median follow-up of 60 months, there were 5 ipsilateral breast tumor recurrences (IBTR), three local, and two loco-regional. The 5-year actuarial rate of IBTR was 4.8% ± 4.1%. The 5-year disease-free survival was 89.6%, with a cause-specific survival and overall survival of 97.6% and 95.3%, respectively. There were no IBTRs among 32 patients with ductal carcinoma in situ (DCIS) vs. 6.1% for patients with invasive carcinoma (p = 0.24). Among 104 patients with Stage I or II invasive carcinoma, the IBTR rate for patients considered cautionary because of age alone was 0% vs. 12.7% in those deemed cautionary due to histopathologic factors (p = 0.018).

Conclusions: Overall, we observed few local recurrences among patients with cautionary features. Women with DCIS and patients 50 to 59 years of age with Stage I/II disease who otherwise meet the criteria for suitability appear to be at a low risk of IBTR. Patients with tumor-related cautionary features will benefit from careful patient selection.

INTRODUCTION

Several single-arm, Phase II trials have reported a low incidence of ipsilateral breast tumor recurrence after accelerated partial breast irradiation (APBI) in well-selected low-risk patients (1–8). Among a cohort of 258 such women with early-stage breast cancer, a recent prospective randomized trial from NCI Hungary showed there was no difference in local recurrence at 5 years between partial and whole breast irradiation (WBI) (9). Larger, multi-institutional Phase III randomized trials (NSABP B-39/Radiation Therapy Oncology Group (RTOG) 0413 and GEC-ESTRO APBI Trial) are currently underway to evaluate the effectiveness, cosmesis, and toxicity in comparison to adjuvant WBI for early stage breast cancer.

In June 2008, the American Society for Radiation Oncology (ASTRO) approved the formation of a task force to develop a consensus statement regarding patient selection, appropriateness, and best practices for the use of APBI, the results of which have been recently published (10, 11). The ASTRO consensus statement identifies and defines both a “suitable” and “unsuitable” group for treatment with APBI outside of the context of a clinical trial that reflects the conservative patient selection criteria used in currently published trials with extended follow-up (Table 1). In addition, the task force identified a “cautionary” group of patients for whom uncertainty exists regarding the appropriate use of APBI because of the limited scope of published data. It is within this group of women that the consensus statement acknowledges an inability to offer evidence-based guidance, advising caution and proper informed consent when selecting women for treatment outside of a clinical trial.
Table 1. ASTRO consensus statement guidelines regarding patient selection for accelerated partial breast irradiation

<table>
<thead>
<tr>
<th>Suitable</th>
<th>Cautionary</th>
<th>Unsuitable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>≥60</td>
<td>50–59</td>
</tr>
<tr>
<td>Tumor</td>
<td>T1</td>
<td>2.1–3 cm</td>
</tr>
<tr>
<td>Node</td>
<td>pN0</td>
<td>—</td>
</tr>
<tr>
<td>ER status</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Margins</td>
<td>&gt;2 mm</td>
<td>≤2 mm</td>
</tr>
<tr>
<td>DCIS</td>
<td>—</td>
<td>≤3 cm</td>
</tr>
<tr>
<td>LVSI</td>
<td>—</td>
<td>Focal</td>
</tr>
<tr>
<td>Other</td>
<td>Lobular</td>
<td>Neoadjuvant</td>
</tr>
<tr>
<td></td>
<td>histology</td>
<td>—</td>
</tr>
<tr>
<td>EIC</td>
<td>Multifocal/multicentric</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: ASTRO = American Society for Radiation Oncology; DCIS = ductal carcinoma in situ; EIC = extensive intraductal component (defined as ≥25% in situ component of primary tumor); LVSI = lymphovascular space invasion.

Note: The absence of axillary assessment in the form of either sentinel lymph node biopsy or axillary dissection is also considered an unsuitable feature.

NSABP B-39/RTOG 0413 continues to enroll high-risk women (<50 years of age, estrogen receptor negative, one to three nodes positive without extracapsular extension), and it is anticipated that accrual will be complete by December 2010. It will be approximately 6 to 8 years, however, before mature results will be available to influence clinical decision making regarding the appropriate use of APBI for patients with early-stage breast cancer and ductal carcinoma in situ (DCIS). In the interval, determining which women are candidates for APBI will remain a relevant and pressing issue within the radiation oncology community. The purpose of the current report is to evaluate the rate of ipsilateral breast tumor recurrence (IBTR) and locoregional recurrence (LRR) according to ASTRO consensus statement risk group and to perform an exploratory analysis of clinical outcomes within the cautionary group, for which there is considerable uncertainty in patient selection.

METHODS AND MATERIALS

Between March 2001 and June 2006, a total of 322 women were treated with APBI and followed prospectively at the University of Wisconsin. Eligibility included women ≥18 years with unifocal Tis, T1, or T2 if a lesion was ≤3 cm, negative surgical margins and pN0 to pN1 without extracapsular extension. From October 2004 on, APBI patients were enrolled on a prospective, institutional review board (IRB)–approved Phase II APBI trial. All data collection for patients not enrolled on the Phase II trial was conducted with the approval of the institutional review board. For the entire cohort, 79 patients were considered “suitable,” 136 patients “cautionary,” and 107 patients “unsuitable” according to the ASTRO consensus statement. Patients classified as unsuitable who also possessed cautionary features were not included in the analysis of the cautionary group. All patients received breast-conserving surgery with axillary assessment consisting of either sentinel lymph node biopsy or axillary lymph node dissection. Re-excision was permitted to achieve negative resection margins. A post-lumpectomy mammogram was required to exclude residual microcalcifications in the affected breast. Chemotherapy and endocrine therapy were given at the discretion of the treating medical oncologist.

Technique

All patients received either interstitial multicatheter brachytherapy (n = 127) or intracavitary brachytherapy using the MammoSite balloon (Hologic, Bedford, MA) (n = 9). All interstitial catheters were placed with either a template-based, stereotactically guided prone or free-handed, ultrasound-guided supine technique using multiple rows with 1.5-cm catheter spacing. Our interstitial techniques have been described previously in detail (12, 13). Since 2002, three-dimensional computed tomography–based treatment planning with geometric optimization using the Nucleron Plato brachytherapy platform (Veendal, the Netherlands) has been used in all cases (13). The planning target volume was defined as the seroma cavity plus a 1.5- to 2-cm margin contained within 5 mm of the skin surface and the pectoralis fascia or chest wall. For intracavitary patients, the MammoSite device was placed postoperatively, and the target volume was defined as the volume of the balloon with a 1-cm concentric breast tissue margin. A minimum balloon-to-skin surface distance of 5 mm was required for MammoSite. The prescription dose was 32 to 34 Gy in 8 to 10 twice-daily fractions over 4 to 5 days using high-dose-rate 192Ir brachytherapy with a remote afterloader. A ≥6-h interval was required between treatments.

Assessments

All follow-up care was arranged in accordance with American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) recommended surveillance guidelines in the adjuvant setting (14). This included interval history and breast examination every 3 to 6 months for the first 3 years, then annually thereafter. Ipsilateral diagnostic mammogram of the affected breast was performed every 6 months for the initial 3 years posttreatment. IBTR was defined as recurrence of invasive carcinoma after lumpectomy and APBI within the parenchyma or skin of the treated breast either before or concurrent with regional or distant metastases. In patients treated for DCIS, this definition was expanded to include either DCIS or invasive carcinoma. A “true recurrence/marginal miss” was defined as IBTR within 2 cm of the post-treatment lumpectomy bed, whereas “elsewhere” breast recurrences encompassed IBTR in the remainder of breast tissue. Loco-regional recurrence (LRR) included failures within the regional axillary, internal mammary, infraclavicular, or supraclavicular lymphatics, either of an isolated nature or concurrent with IBTR. Disease-free survival (DFS) was defined as all local, regional, contralateral, or distant events related to breast cancer. Cause-specific survival (CSS) was defined as all deaths related to breast cancer, and included any death with concurrent distant metastases. Overall survival (OS) encompassed deaths from any cause.

All intervals were calculated from the date of breast cancer diagnosis. Estimates of IBTR, LRR, DFS, CSS, and OS were made using the Kaplan–Meier method (15). The log-rank test was used to assess differences between patient groups. Two-tailed p values >0.05 were considered statistically significant. Stepwise regression analysis was performed using a Cox proportional hazards model. All data were examined using SPSS version 16.0 (SPSS Inc, Chicago, IL).

RESULTS

Of 322 women treated between November 2000 and June 2006, 136 patients (42.2%) met the ASTRO consensus
statement cautionary criteria. Of the remaining women, 79 patients (24.5%) and 107 patients (33.2%) were identified as “suitable” and “unsuitable,” respectively. The 5-year actuarial incidence of IBTR by ASTRO consensus statement classification was as follows: suitable, 1.6% (95% confidence interval [CI], 0.0–4.8%); cautionary, 4.8% (95% CI, 0.7–8.9%); and unsuitable, 6.6% (95% CI, 1.7–11.5%). There were no isolated nodal failures in the suitable or cautionary groups. There were two isolated axillary failures observed in the unsuitable group. The 5-year LRR was as follows: suitable, 1.6% (95% CI, 0.0–4.8%); cautionary, 4.8% (95% CI, 0.7–8.9%); and unsuitable, 8.7% (95% CI, 3.4–14.4%).

An exploratory analysis was performed for ASTRO consensus statement cautionary patients. The median follow-up for the cautionary cohort was 60 months (range, 1.2–92.4 months). Eight women were lost to follow-up. Patient and treatment-related characteristics for all 136 women included in the analysis are listed in Table 2. By definition, all women were ≥50 years of age and pN0. The median age was 57 years at the time of diagnosis, with 86 women (63.2%) between the ages of 50 and 59 years. The remainder of ASTRO consensus statement cautionary features included: 32 patients (23.5%) with pure DCIS ≤ 3 cm, 17 patients (12.5%) with extensive intraductal component (EIC), 13 patients (9.6%) with tumors 2.1 to 3 cm, 11 patients (8.1%) with estrogen receptor (ER)–negative tumors, 10 patients (7.4%) with lobular histology, and 10 patients (7.4%) with margins <2 mm. In all, 38 patients (27.9%) possessed multiple cautionary factors.

There were a total of five ipsilateral breast tumor recurrences (IBTR) within the cautionary cohort. Three recurrences were in-breast only, and two included concurrent regional nodal failure. Of five observed IBTRs, four were considered “true recurrence/marginal miss” and one an “elsewhere” breast failure. The latency to IBTR ranged from 24 to 50 months. Two of 5 patients were successfully salvaged with mastectomy and had no evidence of disease at last follow-up. The characteristics and outcomes of IBTRs are outlined in Table 3. Including contralateral events, the 5-year disease-free survival was 89.6%, with a cause-specific survival and overall survival of 97.6% and 95.3%, respectively. There were no ipsilateral failures among 32 patients with DCIS, with an actuarial LRR rate of 0% vs. 6.1% for patients with invasive carcinoma (p = 0.24; Figure 1). Among 104 patients with stage I or II invasive carcinoma, the actuarial LRR rate for patients considered cautionary by virtue of age 50 – 59 alone is 0% vs. 12.7% in those deemed cautionary due to clinical or pathologic factors (p = 0.018; Figure 2). Local recurrences were observed in 1 of 17 patients with EIC, 2 of 11 with ER-negative tumors, 1 of 10 with margins <2 mm, 2 of 10 with lobular histology, and 2 of 13 with tumor size 2.1 to 3 cm. Both an ER-negative receptor status and lobular histology increased the risk of IBTR on univariate analysis (p = 0.002 and p = 0.004, respectively). However, multivariate analysis did not identify any individual cautionary features predictive of local failure given the small absolute number of IBTRs.

**DISCUSSION**

There continues to be significant interest among physicians and patients alike in the use of APBI for early-stage breast cancer, with rapid proliferation of techniques, devices, and number of patients being treated off clinical trial. Multiple attempts have been made to delineate patient candidacy for brachytherapy-based APBI, including specific guidelines from the American Brachytherapy Society (ABS) (16). The recent publication of the ASTRO consensus statement
regarding the appropriateness of APBI offers further guidance in patient selection. The formation of the consensus statement reflects the conservative patient selection to date, with “suitability” for APBI off clinical trial derived from clinical and pathologic criteria of the women included in currently published series showing a low rate of IBTR with at least 4 years of follow-up. Our 5-year experience redemonstrates a low rate of IBTR in ASTRO consensus statement “suitable” patients, at 1.6% (95% CI, 0.0–4.8%). By comparison, we observed a 5-year rate of IBTR and LRR of 6.6% (95% CI, 1.7–11.5%) and 8.7% (95% CI, 3–14.4%), respectively, among women with ASTRO consensus statement “unsuitable” features. Although confidence intervals are broad and overlapping the suitable group, higher rates of IBTR and LRR are expected, consistent with known risk factors for local recurrence after breast-conserving therapy. Given the lack of additional published data for this group of women, however, few conclusions can be drawn, and clinical trial participation continues to be encouraged, with treatment off clinical trial not advised.

In contrast, several observations within the cautionary group have potential implications on patient selection for APBI. We reviewed in depth the University of Wisconsin experience with brachytherapy-based APBI among the ASTRO consensus statement cautionary group of women >50 years of age (Table 1). With the exception of women with estrogen receptor–negative tumors, these patients would not be eligible for NSABP B-39/RTOG 0413, which closed to node-negative patients more than 50 years of age in January 2007. As we await mature, Phase III data, there remains considerable interest in the appropriateness of APBI among this patient demographic. With no clinical trial currently available to the majority of these patients, radiation oncologists are routinely forced to make clinical recommendations regarding the appropriateness of APBI with very little data specific to these patients available to guide decision making. In the current analysis, we observed a low rate of IBTR and loco-regional recurrence among this cohort of patients, with a 5-year loco-regional control rate of 95.2% (95% CI, 91.1–99.3).

For many years, age has been recognized as an independent predictor for local recurrence after breast-conserving therapy. The median age of patients in mature, published APBI trials is >60 years, establishing this age as the measure of suitability off trial. We observed no local recurrences among 52 women 50 to 59 years of age who otherwise meet the criteria for suitability. This was a statistically significant difference \( p = 0.018 \) in comparison to those deemed cautionary because of adverse histopathologic features. In a recent pooled analysis of five NSABP trials with 3,799 node-negative women undergoing breast-conserving surgery and WBI, the 12-year incidences of IBTR for women aged ≤49 years, 50 to 59 years, and ≥60 years were 9.6%, 5.8%, and 5.6%, respectively (17). A nationwide Danish population-based study from 1989 to 1998 of 3,758 women receiving traditional breast-conserving therapy demonstrated
almost identical rates of IBTR when analyzed by the same age breakdown (18). In the Danish study, age ≥50 was associated with a significant reduction in the risk of IBTR with a hazard ratio of 0.60 (95% CI, 0.45–0.80), which was not significantly different from those ≥60 years of age (18). Based on these data and the observations of the current study, it has become our institutional practice not to allow an age of <60 years alone to preclude a patient from being an APBI candidate off study.

The rate of IBTR among women with other cautionary features was 12.7% at 5 years, reinforcing the ASTRO consensus guidelines that treating such patients with APBI off trial should be approached cautiously and judiciously until a more comprehensive, randomized comparison with WBI is established. We recognize that the primary limitation of this study is the small absolute number of local failures with a relatively small sample size. Clearly this limits the power to further analyze individual cautionary factors that may be associated with a higher incidence of IBTR. As a group, however, tumor-related cautionary features appear to confer an increased risk of IBTR in women treated with APBI, and both estrogen receptor negativity and infiltrating lobular carcinoma were associated with higher rates of local recurrence on univariate analysis. It is not entirely clear that the higher observed rate of local recurrence is a result of treating partial breast volumes or rather poor tumor biology. Only with randomized data will we be able to answer this question. However, a case-matched analysis of cautionary patients comparing APBI to WBI as the subject of future investigation would provide further insight into patient selection as we await completion of NSABP B-39/RTOG 0413.

There are very limited published data regarding the use of APBI in women with DCIS. The American Society of Breast Surgeons (ASBS) MammoSite trial includes a total of 1,449 women, of whom 194 (13%) have pure DCIS (6). The recently published 4-year update of the initial 400 women included 48 patients with pure DCIS. In the ASBS study, no IBTRs were observed among women with DCIS (6). The current analysis included 32 patients with pure DCIS and, likewise, we observed no IBTRs at 5 years. It is important to point out, however, that the current analysis includes a fairly select group of women with DCIS: age ≥50 years, unifocal, <3 cm, and negative margins. The merits of adjuvant radiotherapy after lumpectomy are based solely on breast conservation and the ultimate prevention of mastectomy, as there has never been a proven overall survival benefit to the addition of WBI to breast-conserving surgery (19–22). Given the overall lack of impact on mortality and low reported recurrence rates, we are comfortable offering APBI to appropriately selected women with DCIS at the University of Wisconsin. Despite limited data, our experience in conjunction with that of the ASBS MammoSite trial suggests that the use of APBI is not negatively affecting breast conservation.

CONCLUSION

In summary, we observed relatively few IBTRs in women with ASTRO consensus statement cautionary features. Women 50 to 59 years of age who otherwise satisfy suitability criteria and those with DCIS appear to be at low risk for local recurrence. Women with lobular histology, tumors 2.1 to 3 cm, ER-negative tumors, margins ≤2 mm, and EIC should be approached with caution and will benefit from careful patient selection. However, we recognize that further corroborative data are still needed to supplement this exploratory analysis as we await mature Phase III trial results.

REFERENCES


