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Decline of Cosmetic Outcomes Following Accelerated Partial Breast Irradiation Using Intensity-Modulated Radiotherapy: Results of a Single Institution Prospective Clinical Trial

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Abstract

Purpose—To report the final cosmetic results from a single-arm prospective clinical trial evaluating accelerated partial breast irradiation (APBI) using intensity-modulated radiotherapy (IMRT) with active-breathing control (ABC).

Methods/Materials—Women greater than 40 years old with stages 0–1 breast cancer who received breast-conserving surgery were enrolled in an institutional review board-approved prospective study evaluating APBI using IMRT administered with deep-inspiration breath-hold. Patients received 38.5 Gy in 3.85 Gy fractions given twice daily over 5 consecutive days. The PTV was defined as the lumpectomy cavity with a 1.5 cm margin. Cosmesis was scored on a 4 category scale by the treating physician. Toxicity was scored according to the National Cancer Institute Common Terminology Criteria For Adverse Events (CTCAE v. 3.0). We report the cosmetic and toxicity results with a median follow-up of 5 years.

Results—A total of 34 patients were enrolled. Two patients were excluded because of fair baseline cosmesis. The trial was terminated early because fair/poor cosmesis developed in 7 of 32 women with a median follow-up of 2.5 years. At a median follow-up of 5 years, further decline in the cosmetic outcome was observed in 5 women. Cosmesis at time of last assessment was 43.3% excellent, 30% good, 20% fair, and 6.7% poor. Fibrosis according to the CTCAE at last assessment is as follows: 3.3% grade 2 toxicity and 0% grade 3 toxicity. There was no correlation of CTCAE grade 2 or greater fibrosis with cosmesis. The 5-year rate of local control was 97% for all 34 patients initially enrolled.

Conclusions—In this prospective trial with 5 year median follow-up, we observed an excellent rate of tumor control using IMRT-planned APBI. Cosmetic outcomes, however, continued to

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Disclosure Statement

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decline, with 26.7% of women having a fair to poor cosmetic result. These results underscore the need for continued cosmetic assessment for patients treated with APBI by technique.

Introduction

The standard of care for the majority of women who elect breast conserving surgery (BCS) for early stage invasive breast cancer and ductal carcinoma in situ (DCIS) is adjuvant radiation to the whole breast. The disease control and excellent cosmesis associated with whole breast irradiation (WBI) has set a high standard for comparison of newer techniques^{1–3}. The drawbacks of WBI include cost, duration of treatment, and inconvenience to patients⁴. Recently, accelerated partial breast irradiation (APBI) has been proposed as an alternative to WBI following BCS. Typically, APBI involves 10 radiation fractions administered to the lumpectomy cavity in five, twice-daily treatments using external beam radiation, interstitial brachytherapy, or intracavitary brachytherapy⁵. Although APBI offers decreased treatment time and decreased dose to breast tissue beyond the lumpectomy cavity, concerns exist about long-term disease control and cosmetic outcomes.

Multiple large, randomized trials comparing WBI to APBI have recently completed accrual with early outcomes reported^{6–8}. The preliminary results regarding cosmetic outcomes are conflicting. We previously reported an increased rate of unacceptable cosmetic outcomes using an APBI technique somewhat different than that used in the multi-institutional randomized trials when compared to historical controls treated with WBI⁹. We now report the final cosmetic outcomes and toxicities from this prospective clinical trial evaluating APBI using intensity-modulated radiotherapy (IMRT) with active-breathing control (ABC).

Methods and Materials

Patient eligibility

Our protocol was described previously⁹. To summarize, selected patients, greater than 40 with breast cancer stages 0-I (American Joint Committee on Cancer, seventh edition) were enrolled in a prospective, institutional review board-approved study beginning in 2004 at the University of Michigan. Patients were required to have unifocal disease with negative margins >3mm. Patients with lobular histology, diffuse calcifications, lymphovascular invasion, extensive DCIS or contraindications for radiation therapy were not eligible. Patients were not allowed to receive neoadjuvant or concurrent chemotherapy. Following completion of APBI, patients could receive chemotherapy or endocrine therapy if clinically indicated. Only patients with excellent or good baseline cosmesis (assessed following surgery and prior to APBI) were included in the final analysis.

Treatment technique

Patients were simulated on a breast board in the supine position following placement of radio-opaque catheters delineating the clinical borders used to create a standard tangent field. A breath-hold computed tomography (CT) simulation scan was performed using an ABC device (vMax; Sensitymedics, Yorba Linda, CA) to suspend the patient's breath at deep inspiration (65–80%). The lumpectomy cavity was contoured by the treating radiation oncologist. A 1 cm Clinical Tumor Volume (CTV) margin, and a 0.5 cm planning target

volume(PTV) margin were added to the cavity. The final PTV was edited to ensure that it did not extend to within 0.5 cm of the skin surface. A treatment planning system, developed in-house, was utilized to generate the IMRT plan using 3 to 5 6 MV photon beams. Treatment was initiated approximately 2 weeks after CT simulation and consisted of administering 38.5 Gy in 10 twice-daily fractions to the PTV, with at least a 6 hour interval between treatments over 5 consecutive days. The patient's target position was determined with daily imaging at the breath-hold state.

Patient follow-up

Patients were seen during follow-up visits by the treating radiation oncologist at 1 week, 1 month, and 6 months post-treatment. Each patient was seen again every 3–6 months for the first 2 years and then every 6 months until reaching 5 years from completing APBI.

Cosmesis and toxicity assessment

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, version 3) was used to assess cosmetic toxicity at each follow-up visit. Cosmesis was also assessed using four-category scale developed at Harvard as excellent, good, fair, or poor using the same criteria indicated on the multi-institutional randomized trial (Radiation Therapy Oncology Group [RTOG] 0413 and National Surgical Adjuvant Breast and Bowel Project[NSABP] B-39)¹⁰. Briefly, the size, shape, color, and texture of the treated breast were compared to the contralateral breast and/or original appearance of the treated breast. Excellent cosmesis was defined as minimal or no difference in appearance of the treated breast and the contralateral breast and/or pretreatment breast; good cosmesis was defined as a slight difference; fair cosmesis was defined as an obvious difference involving a quarter or less of the breast; and poor cosmesis was defined as a marked or obvious change involving more than a quarter of the breast.

Dosimetric assessment

To determine if dosimetric factors were related to cosmetic outcomes, several parameters were assessed. As previously described, a whole- breast volume (WBV) corresponding to the region typically encompassed by traditional tangent fields, was created retrospectively to allow for comparison to other APBI studies.⁹ The volume of whole breast receiving a given percentage of prescription dose was determined for 5%, 20%, 50%, 80%, and 100% of the prescription dose (V5-V100). The maximum dose to 1% of volume (Dmax to 1%), tumor bed volume, PTV and PTV-to-WBV ratio were also assessed. Patients who developed fair or poor cosmetic outcomes were compared to those who maintained good or excellent cosmesis.

Statistical considerations

Continuous dosimetric parameter comparisons were conducted using *t* tests and non-parametrically using the Wilcoxon rank-sum test. Categorical parameter comparisons were performed using Fisher's exact test. All statistical analyses were performed using SAS, version 9.2 software (SAS Institute, Cary, NC).

Results

Thirty-four patients were initially enrolled on the study from 2004–2007. Two patients were excluded from subsequent analyses given fair baseline cosmesis prior to initiation of radiotherapy. The trial was terminated early because fair/poor cosmesis developed in 7 women (21.9%) at a median follow-up of 2.5 years. Here we report the cosmetic and toxicity results at a median follow-up of 5 years. Cosmesis could not be assessed at 5 years for 2 patients who underwent either a therapeutic (1) or prophylactic (1) mastectomy. Thirty patients were therefore included in this final report.

The median age at time of treatment for the 30 evaluable patients was 55.4 years. The majority of women did not receive chemotherapy (83.3%) whereas most did receive endocrine therapy (63.3%). Fifteen of 30 (50%) of the women in the study required a second operation to achieve widely negative final surgical margins prior to the initiation of radiation therapy. Additional patient characteristics are summarized in Table 1.

With 2.5 years of additional follow-up, further decline in the cosmetic outcome was observed in 5 women: excellent to good decline in 3, good to fair decline in 1, and fair to poor decline in 1. The average time to late cosmetic decline for these 5 patients was 42 months. Cosmetic outcomes at baseline (pre-APBI), and 6 months to 5 years post-treatment are summarized in Figure 1A. At the time of last assessment, 13 patients (43.3%) had an excellent cosmetic outcome, 9 patients (30%) had a good outcome, 6 patients (20%) had a fair outcome, and 2 patients (6.7%) had a poor outcome. The cosmetic toxicity of ABPI was also assessed using the following CTCAE (version 3.0) factors: induration or fibrosis, volume loss or hypoplasia, nipple or areolar deformity, telangiectasia, deep connective tissue fibrosis, fat necrosis, breast pain, and hyperpigmentation. Of the 30 patients eligible for assessment at 5 years, 23.3% had no toxicity, 40% had at least one grade 1 toxicity, 30% had at least one grade 2 toxicity, and 6.7% had at least one grade 3 toxicity. There was a low rate of CTCAE fibrosis with 3.3% of patients developing grade 2, and 0% of patients developing grade 3 fibrosis at 5 years. There was no correlation of grade 2 or greater CTCAE fibrosis with cosmetic outcomes assessed per the 4-category scale. Table 2 lists the grade and toxicity of the aforementioned CTCAE toxicities present 5 years after APBI.

To assess whether treatment factors were different between patients who maintained an excellent/good cosmetic result and those who developed a fair/poor result, we compared the 22 patients with excellent/good cosmesis to the 8 patients with fair/poor cosmesis at 5 years. The use of chemotherapy was not significantly different between the 2 groups of patients with 13.6% of patients with excellent/good cosmesis and 25.0% of patients with fair/poor cosmesis receiving chemotherapy ($P=.589$). The use of endocrine therapy tended to be more common in patients with excellent or good cosmesis (72.7%) than in those with fair/poor cosmesis (37.5%) ($P=.104$). Half of the patients in each group required a second surgical excision to achieve final negative margins. The excision cavity and PTV tended to be larger in patients with fair/poor cosmesis (excision cavity: 35.2 cm³ vs. 62.4 cm³, respectively, ($P=.098$ and PTV: 171.5 cm³ vs. 245 cm³, $P=0.099$). Because the average WBV was similar for both groups of patients, the ratio of PTV to WBV was greater for the fair/poor cosmesis group (13.4% vs. 18.4%, $p=0.051$).

The volume of breast that received 20%, 50%, 80% and 100% of the prescription dose was significantly higher in the group of patients with fair/poor cosmesis at 5 years as compared to those with excellent/good cosmesis. The V20/WBV was 61% versus 51.3% in patients with excellent/good cosmesis ($P=.037$); the V50/WBV was 45% versus 34.3% ($P=.004$), respectively; the V80/WBV was 35.2% versus 25.1% ($p=0.004$), respectively; and the V100/WBV was 22.4% versus 15.4% ($P=.006$), respectively. The volume of breast that received lower doses of radiation (5% of the prescription dose) was not statistically different between those patients with excellent/good and those with fair/poor cosmesis but tended to be higher for patients with a fair/poor result (66.4% versus 74.5%, $P=.087$). Table 3 lists all dosimetric parameters calculated. Given the small number of patients in the study, a multivariate analysis was not attempted.

One of 34 patients initially enrolled on the study developed an ipsilateral (presumed) second breast cancer of different histology at the previous lumpectomy site 4 years after APBI for a 5-year rate of local control of 97%. She underwent a mastectomy and currently has no evidence of disease.

Discussion

Although APBI offers increased convenience over WBI for women electing BCS, as with any new treatment technique, questions regarding long-term disease control and treatment-related toxicity remain. We previously reported that this prospective, single-institution study of APBI was terminated prematurely due to the development of fair/poor cosmesis in 21.9% of patients with a median follow-up of 2.5 years. We now report the continued decline in cosmesis in patients treated on our protocol of IMRT-planned APBI with ABC with a median follow-up of 5 years. The initial result was unexpected and the continued cosmetic decline with extended follow-up underscores the importance of long-term cosmetic evaluation for patients treated with external beam APBI.

A similar, progressive cosmetic decline following APBI has been demonstrated in other multi-institutional studies (Fig. 1 B and C).^{6,11} The Randomized Trial of Accelerated Partial Breast Irradiation (RAPID) study randomized 2,135 women to WBI or APBI and recently reported their interim cosmetic and toxicity results at a median follow-up of 3 years. Cosmetic assessments were performed by nurses, physicians, and patients. A 35% rate of adverse cosmesis with APBI as compared to 17% with WBI (nurse assessment) as assessed using the European Organisation for Research and Treatment of Cancer Cosmetic Rating System 4-point scale was reported (adverse cosmesis was considered to be fair or poor). Furthermore, among the 171 of the patients randomized to APBI had 5 years of follow-up, the number of patients with fair/poor cosmesis continued to increase with longer follow-up (19% at baseline, 29% at 3 years, and 33% at 5 years)⁶. Declining cosmesis was not seen in the WBI cohort, including 164 patients with 5 years of follow-up (17% fair/poor cosmesis at baseline, 17% fair/poor cosmesis at 3 years, 13% fair/poor cosmesis at 5 years)⁶. The WBI and APBI cosmetic outcomes from the RAPID study are summarized in Figure 1C and 1D.

The RTOG recently published another multi-institutional study of APBI for early stage breast cancer (RTOG 0319)¹¹. This phase 2, feasibility study included 52 evaluable patients

with a median follow-up of 5.3 years. Although 84% patients were satisfied with their treatment based on results of post-treatment surveys, the cosmetic outcomes as assessed by radiation oncologists declined over the 3 year period of reported follow-up. Specifically, the rate of fair/poor cosmesis (using a four-category scale) at 6 months, 1 year, and 3 years post-APBI were 26%, 23% and 42%, respectively¹¹. Although the percentage of patients with late fair/poor cosmesis was higher in RTOG 0319 at last follow-up than in our study (fair/poor at 5 years, 27%) and the RAPID study (fair/poor at 5 years, 33%), the pattern of decline in cosmesis with longer follow-up in patients treated with external beam APBI was quite similar (Figure 1B).

It must be noted that results from other single-institution studies have not uniformly demonstrated the increased rate of poor cosmetic outcomes relative seen in our study and the reported multi-institutional series^{12–15}. Lei et al¹⁵ reported 5-year results using IMRT-based APBI with 87.8% of 36 patients having excellent to good cosmesis as rated by physicians. There appeared to be a trend toward continued decline in cosmesis over time in this series as well. Chen et al¹² reported long-term outcomes with APBI and demonstrated excellent or good cosmesis in 89% of 56 patients at 4 years and no declining trend in cosmetic outcome over time was observed.

The RTOG 0413/NSABP B-309 trial is the largest study of APBI compared to WBI. The trial recently completed accrual and early results have demonstrated a low rate of CTCAE fibrosis toxicity. Of 1094 patients in their third year of follow-up, the rate of grade 2 CTCAE fibrosis was <12% and the rate of grade 3 CTCAE fibrosis was <3%^{7,8}. While these results are encouraging, we have found that fibrosis as assessed by the CTCAE is not associated with clinical, 4-category based, cosmetic assessments. We observed only 3.3% grade 2 fibrosis and no documented grade 3 fibrosis toxicity. There was no correlation of grade 2 or greater CTCAE fibrosis and fair/poor cosmesis according to the four-category scale. The lack of correlation of breast cosmesis and grade 3 CTCAE toxicity was also noted in the RAPID study⁶. This apparent disconnect between CTCAE toxicities and cosmetic outcomes highlights the importance of including clinical cosmetic outcomes (assessed by a 4-category scale) with subsequent reports of trials assessing APBI.

There are multiple possible explanations for the increased rate of fair/poor cosmesis experienced by patients in our study. The volume of tissue that was irradiated was significantly higher for patients with fair/poor cosmesis, though all patients were treated with similar dose constraints similar to those patients enrolled in RTOG 0413/NSABP B-39¹⁰. A dose-volume association with fair/poor cosmesis following APBI has been noted by other institutions as well^{16,17}. In a study of 80 patients at a median follow-up of 32 months, a 19% rate of fair/poor cosmesis was noted¹⁷. The volume of breast receiving 50%, 80%, and 100% of the prescribed dose was associated with fair/poor cosmesis¹⁷. We found a statistically significant higher volume of breast receiving 20%, 50%, 80%, and 100% of the prescribed dose in patients who had fair/poor cosmesis.

To our knowledge, our protocol is the only study that mandated the use of respiratory control during treatment. Our intention was to maximize the dose to the PTV by minimizing respiratory variation. We have previously demonstrated breast target anterior-posterior

displacement of up to a 1.6cm and superior-inferior displacement of up to 1.3 cm from end-expiration to 80% of vital capacity; using ABC this is significantly reduced¹⁸. The lack of feathering of the dose at the periphery of the target resulted in a higher dose to the PTV; it is possible this affected cosmetic outcome.

Another possible explanation for the higher rate of poor cosmetic outcomes associated with external beam APBI is that the prescription dose of 38.5 Gy in 10 twice-daily fractions was too high as nicely discussed by the authors of RAPID⁶. In other single institution studies, dose/fractionations of 30 Gy in 5 fractions over 10 days and 32 Gy in 8 twice-daily fractions yielded excellent/good cosmetic outcomes ranging from 89%–97% with acceptable local control^{19–21}. This is in contrast to another report of higher doses used as part of a clinical trial²². Increased toxicity was seen with 42 Gy in 10 twice-daily fractions assessed as part of a dose escalation trial of APBI causing termination of patient recruitment to that dose²². Although the fractionation scheme used in our trial has yielded excellent local control, there is still much to be learned about the appropriate dose and fractionation for APBI using external beam radiation when considering cosmetic outcomes in addition to local control.

In contrast, reports of cosmetic outcomes following brachytherapy techniques for APBI demonstrate excellent results^{23–25}. Intracavitary balloon and multi-catheter interstitial brachytherapy techniques for administering APBI allow for steep dose fall-off and lesser volumes of irradiated normal breast tissue as compared to external beam techniques^{24,26,27}. The RTOG 0413/NSABP B-39 trial included patients treated with a variety of techniques and may provide more insight into the risks and benefits of each modality.

Although we conducted a prospective protocol at a median follow-up of 5 years for all evaluable patients, there are several limitations to our study. It is a single-arm feasibility study and therefore is without a randomized control comparison. Cosmetic assessments were made by the treating radiation oncologist, which may have contributed to biased observations, although if anything, bias of a treating physician would be expected to be toward under-estimation rather than overestimation of treatment related toxicity. Our results using IMRT-planned APBI with ABC may not be applicable to other APBI techniques. Finally, our study was a phase I study which was terminated prematurely. Therefore, there were fewer evaluable patients compared to other prospective studies, limiting our ability to assess for predictors of adverse cosmesis. Despite these limitations, the continued cosmetic decline in the patients in our study treated with external beam APBI was similar to that demonstrated in both the RAPID study and the RTOG 0319 study.

Conclusion

In this prospective clinical trial with a median follow-up of 5 years, we observed excellent rates of tumor control following APBI using IMRT with ABC. Cosmetic outcomes, however, continued to decline, with 27% of women having a fair to poor cosmetic result at 5 years. Furthermore, cosmetic outcomes were not associated with CTCAE grade 2 and 3 fibrosis. Future studies should not rely on the CTCAE for the sole assessment of toxicity. Our results demonstrate the need for continued cosmetic assessment over time for patients treated with APBI, particularly using IMRT with ABC. Until further experiences with longer

follow-up are reported from the multi-institutional randomized trials, we recommend consideration of APBI for women with early stage breast cancer on a research protocol. If protocol-based treatment is not possible, we feel it is essential to thoroughly counsel women about the possibility of adverse cosmetic outcomes should they desire external beam APBI.

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Summary

The final cosmetic results of a prospective trial assessing accelerated partial breast irradiation intensity modulated radiation therapy with deep-inspiration breath hold are presented. The study included 30 patients with a median follow-up of 5 years. Although only 3.3% and 0% of patients had grade 2 or 3 Common Terminology Criteria For Adverse Events fibrosis toxicity, respectively, a continued cosmetic decline was observed with 26.7% of women having a fair to poor cosmetic result at time of last assessment.

Figure 1.

Cosmetic outcomes were determined for each patient using a four-category scale. University of Michigan 5 year results as assessed by radiation oncologists (A). 3 year results from RTOG 0139 also as assessed by radiation oncologists (B). 5 year results from RAPID as assessed by nurses for both treatment cohorts (APBI, WBI) (C,D).

Table 1

Characteristics of 30 patients with final outcomes assessment

		Number	%
Laterality	Left	9	30.0%
	Right	21	70.0%
Histology	DCIS	16	53.3%
	IDC	14	46.7%
Chemo	Yes	5	16.7%
	No	25	83.3%
Endocrine	Yes	19	63.3%
	No	11	36.7%
Re-excision	Yes	15	50.0%
	No	15	50.0%

Abbreviations: DCIS = ductal carcinoma *in situ*, IDC = invasive ductal carcinoma

Table 2

Five year radiation toxicities

CTCAE criteria	Grade 1	Grade 2	Grade 3
Volume Loss or Hypoplasia	33.3	30.0	6.7
Nipple or Areolar Deformity	13.3	26.7	6.7
Induration or Fibrosis	43.3	3.3	0.0
Telangiectasia	16.7	0.0	3.3
Hyperpigmentation	6.7	0.0	0.0
Fibrosis/Deep Connective Tissue	3.3	0.0	0.0
Fat Necrosis	0.0	0.0	0.0
Breast Pain	0.0	0.0	0.0
Other *	10.0	0.0	0.0
Highest Any Toxicity	40.0	30.0	6.7

* Other toxicities were grade 1 hypopigmentation (n=1), grade 1 erythema (n=1) and grade 1 scarring (n=1).

Table 3

Association of treatment and dosimetric factors with cosmesis

	E/G avg.	F/P avg.	p-value
Number	22	8	
Chemo use	13.6%	25.0%	0.5894
Endocrine use	72.7%	37.5%	0.1040
Re-excision	50.0%	50.0%	~1
Excision cavity (cm ³)	35.2	62.4	0.0976
PTV (cm ³)	171.5	245.0	0.0993
PTV/WBV ratio	13.4%	18.4%	0.0507
V5/WBV	66.4%	74.5%	0.0865
V20/WBV	51.3%	61.0%	0.0367
V50/WBV	34.3%	45.0%	0.0035
V80/WBV	25.1%	35.2%	0.0036
V100/WBV	15.4%	22.4%	0.0057
Dmax to 1% volume	39.9 Gy	40.2 Gy	0.5953

Abbreviations: E/G = excellent or good cosmesis, F/P = fair or poor cosmesis, PTV = planning target volume, WBV = whole breast volume, Dmax = maximum dose