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ORIGINAL ARTICLE

Comparison of subjective, objective and patient-reported cosmetic outcomes between accelerated partial breast irradiation and whole breast radiotherapy: a prospective propensity score-matched pair analysis

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Abstract

Background To compare the early cosmetic outcomes after whole breast radiotherapy (WBRT) and accelerated partial breast irradiation (APBI) by various cosmetic assessment methods.

Materials/methods APBI was delivered using multiplane interstitial brachytherapy as per standard guidelines. Majority of women in WBRT cohort received hypo-fractionated external beam radiotherapy using bitangential portals and mega-voltage photons along with sequential boost to the tumor bed. Single cross-sectional assessment (18–36 months post-treatment completion) of the breast cosmesis was done by RO, SO and the patient using the modified Harvard scale and by photographic assessment using the BCCT.core software. The two cohorts were propensity score-matched using menopausal status, size of surgical cavity, size of tumor in greatest dimension, median number of lymph nodes dissected, treatment with adjuvant chemotherapy and treatment with hormonal therapy.

Results A total of 64 APBI patients were matched with 99 WBRT patients of the entire cohort of 320. At a median follow-up of 25 months, cosmetic results were significantly better for APBI as compared to WBRT cohort by all methods of evaluation (excellent/good: RO:75% vs 38.4%, $p=0.0001$; SO: 54.7% vs 37.4%, $p=0.009$; patient: 87.5% vs 58.6%, $p=0.001$ and BCCT: 73.4% vs 51.6%, $p=0.001$). Individual parameters that were significantly better in APBI cohort included size and shape of breast as well as location and shape of NAC. Better results for individual BCCT parameters (pLBC, pBRE, pBAD) were also seen.

Conclusions Overall cosmetic outcomes as well as individual subdomains are significantly better with APBI as compared to WBRT by all methods of assessment of cosmesis when matched for various factors.

Keywords APBI · Cosmesis · Brachytherapy · Late toxicity

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Introduction

Hypo-fractionated whole breast radiotherapy (WBRT), using conformal techniques, is currently the gold standard for adjuvant RT in early breast cancer (EBC). It involves daily outpatient visits to the radiation facility during the week days and the entire course is completed in approximately 3–4 weeks [1]. APBI (Accelerated Partial Breast Irradiation) is one of the emerging standards of care for carefully selected patients with early breast cancer (EBC) who have undergone breast conservation [2]. The distinct advantage of APBI over WBRT is the further abbreviation of the radiation course which is typically completed in 1–2 weeks making it an attractive treatment option both for the patient as well as physician.

The success and outcome of APBI largely depends upon patient selection as well as the technique chosen to offer APBI. Randomized trials have evaluated the impact of the radiotherapy target volumes (APBI vs WBRT) on cosmetic outcome as one of the secondary endpoints [3–6]. The analysis is restricted to simple subjective scoring by patient and physician in most of the trials. Moreover, although retrospective analysis of various institutional cohorts have demonstrated equivalent quality of life and cosmesis for APBI and WBRT, the APBI and WBRT cohorts were not matched for known factors that can affect cosmesis per se [7–11].

Multiple factors have been shown to affect cosmesis adversely. These include the type of surgery, radiotherapy, chemotherapy, hormonal therapy, age, number of lymph nodes dissected and menopausal status [12]. However, matching each factor individually would require a large sample size for comparison which may be practically not possible. We, therefore, performed a propensity score-matched pair analysis to compare the early cosmetic outcomes of APBI and WBRT in a prospective study. The cosmetic outcome was graded subjectively by the physician and patient as well as objectively using the BCCT.core software.

Materials and methods

This prospective observational cross-sectional study was approved by the institutional review board of Tata Memorial Hospital.

Patients

Patients with breast cancer who were treated with adjuvant RT (teletherapy/brachytherapy) after breast conservation surgery (BCS) and were on six monthly follow-up were screened for this study. However, only patients between a period of 18–36 months post-completion of adjuvant RT were accrued in this study after obtaining informed consent. The exclusion criteria were patients with bilateral breast cancers or reconstructive procedure and patients who did not consent for clinical photographs.

A total of 320 consecutive patients were accrued in this study from January 2017 to June 2018 (duration of adjuvant RT for these patients was from January 2015 to November 2016). Out of these 320 patients, 64 patients treated with multichannel interstitial brachytherapy were propensity score matched to a similar cohort of WBRT patients accrued in the same study.

Treatment

APBI was performed either intraoperatively ($n=36$) or postoperatively ($n=28$) following breast conservation surgery (BCS) using open cavity technique. Flexible nylon catheters (Kalyani Enterprises Inc.) were used for the implant which was done by an experienced radiation oncologist. The details of patient characteristics and implant procedure including dosimetric audit have been reported earlier [13]. The dose prescribed to the CTV was 34 Gy in 10 fractions ($n=56$) or 32 Gy in 8 fractions ($n=8$) delivered twice daily, 6 h apart. Brachytherapy was initiated on the same day of implant in post-operative patients and on third day in the intra-operative patients. A gap of 2–3 weeks was given between starting (intra-operative) or completion (post-operative) of chemotherapy (if required) and APBI. All hormone-receptor-positive patients received appropriate hormonal therapy (as per institutional protocol).

In patients who received EBRT, RT was started 2–4 weeks after chemotherapy completion (in patients receiving adjuvant chemotherapy) or 4–6 weeks following surgery (in patients who did not receive adjuvant chemotherapy). Computerized tomography(CT) based planning was done for all patients. Majority of the patients [$n=95$ (96%)] were treated with 3-Dimensional Conformal Radiotherapy (3D-CRT) technique and bitangential portals, although some [$n=4$ (4%)] were treated with intensity-modulated radiotherapy (IMRT). The dose prescription most commonly used was 40 Gy/15#/3 weeks ($n=89$) to the entire breast followed by a tumor bed boost of 12.5 Gy/5#/1 week with electrons ($n=84$)/3D-CRT ($n=3$)/interstitial brachytherapy ($n=1$). Supraclavicular nodes were routinely treated for patients with $\geq$T3 disease or who were node positive either clinically or pathologically. Axillary and/or internal mammary nodes were not treated routinely unless gross residual disease was left post-surgery or there was unequivocal evidence of positive internal mammary lymph node. Hormonal therapy was allowed to continue during WBRT.

Cosmetic assessment

The methodology and results of cosmetic assessment used in this protocol have been recently published for the APBI cohort [14]. Briefly, a one-time cross-sectional subjective cosmesis assessment was done by a single experienced radiation oncologist (RO) and a single experienced surgical oncologist (SO) separately using the Harvard 4-point scale for overall cosmesis proposed by Aronson et al. [15]. The individual parameters such as the size of breast, the shape of breast, location of nipple-areola complex (NAC) etc. were also documented separately. All the 4-point scale (excellent/good/fair/poor and no difference/small difference/moderate difference/large difference) variables were dichotomized to a 2-point scale for the purpose of improving agreement as has been described in the literature [16].

For the objective assessment, BCCT.core software (Breast Cancer Conservative Treatment. cosmetic results 3.1) was used after obtaining a user license from INESC Porto breast research group [17]. Clinical photographs were taken in standing position with arms overhead and by the side using a 16-megapixel camera with 4 × optical zoom. The methodology of assessment and analysis have been described in previous studies. Along with overall cosmesis, individual BCCT parameters were compared which included breast retraction assessment (BRA), lower breast contour (LBC), upward nipple retraction (UNR), breast compliance evaluation (BCE), breast contour difference (BCD), breast area difference (BAD), and breast overlap difference (BOD).

Matching/statistics

Propensity score matching using nearest neighbourhood algorithm (caliper width 0.2) was done for matching the covariates known to effect cosmesis significantly. A calliper width 0.2 was chosen as this is the standard recommendation for estimating difference in mean (continuous outcomes) and risk differences (binary outcomes) [18]. These included menopausal status, size of surgical cavity (less than 100 cc vs more than 100 cc), size of tumor in greatest dimension (pT size < 2 cm vs ≥ 2 cm), treatment with adjuvant chemotherapy, treatment with hormonal therapy and number of lymph nodes dissected.

Statistical analysis was done in SPSS version 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Chi-square test was used to detect a difference in overall cosmetic outcomes between the two groups and to detect differences in individual subjective parameters such as the shape of breast, size of breast, etc. Kruskal–Wallis test was used to detect any difference in the individual BCCT.core parameters (eg: pBRA, pUNE, pBCD, etc.) between the two groups.

Results

The entire study population of 320 patients was used for propensity matching. Of these, 99 patients from WBRT cohort could be matched with the 64 patients in the APBI cohort for the covariates mentioned in the previous section. The median follow-up for the APBI and WBRT cohorts was 26 months and 24 months, respectively (median for the entire cohort was 25 months). The mean age in APBI cohort was 59 years (range 44–80 years), while in WBRT, it was 56 years (range 30–82 years). The demographic features of both the cohorts are described in Table 1.

Median cavity volume was 118.1 cc in WBRT cohort and 99 cc in APBI cohort. Overall cosmesis was significantly better (excellent/good) by all four methods of assessment in APBI cohort as compared to WBRT: excellent/good: RO: 75% vs 38.4%, $p = 0.0001$; SO: 54.7% vs 37.4%, $p = 0.009$; patient: 87.5% vs 58.6%, $p = 0.001$ and BCCT: 73.4% vs 51.6%, $p = 0.001$) (Table 2).

Individual subjective parameters significantly better in APBI cohort for excellent/good cosmesis were size of breast (53.8% vs 89.1%, $p = 0.0001$), shape of breast (65.7% vs 87.5%, $p = 0.001$), location of nipple areola complex (NAC) (53.5% vs 75.0%, $p = 0.006$), shape of NAC (79.8% vs 92.2%, $p = 0.03$) and appearance of scar (29.3% vs 53.1%, $p = 0.002$) in the assessment by RO. In assessment by SO, size of breast (49.5% vs 64.1%, $p = 0.05$), shape of breast (47.5% vs 62.5%, $p = 0.03$), colour of breast (66.7% vs 81.3%, $p = 0.04$), location of NAC (44.4% vs 71.9%, $p = 0.001$), shape of NAC (58.6% vs 82.8%, $p = 0.001$) and appearance of scar (23.2% vs 42.2%, $p = 0.01$) were significantly better in APBI cohort. Amongst the individual BCCT.

Table 1 Demographics

	WBRT ($n = 99$)	APBI ($n = 64$)	p value
Age (mean)	55 years	60 years	0.24
Menopausal status			0.84
Peri/premenopausal	3 (3%)	1 (1.5%)	
Postmenopausal	96 (97%)	63 (98.4%)	
Diabetes mellitus	18 (18%)	13 (20.3%)	0.73
T stage			0.33
T1	34 (35%)	28 (43.75%)	
T2	62 (62%)	36 (56.25%)	
T3	3 (3%)	0	
Median number of LN-dissected	13 (3–36)	10 (1–36)	0.23
Chemotherapy	80 (80%)	44 (68.7%)	0.28
Hormonal therapy	61 (61%)	41 (64.1%)	0.55
Median cavity volume in cc	118.1 cc	99 cc	0.33

Table 2 Overall cosmesis

Cosmetic outcomes	APBI ($n=64$)		WBRT ($n=99$)		Significance
	Excellent/good	Fair/poor	Excellent/good	Fair/poor	
Cosmesis by RO	48 (75.0%)	16 (25.0%)	38 (38.4%)	61 (61.6%)	0.0001
Cosmesis by SO	35 (54.7%)	29 (45.3%)	37 (37.4%)	62 (62.6%)	0.009
Cosmesis by BCCT.core	47 (73.4%)	17 (26.5%)	51 (51.6%)	48 (48.4%)	0.004
Patient assessment	56 (87.5%)	8 (12.5%)	58 (58.6%)	41 (41.4%)	0.004

RO radiation oncologist, *SO* surgical oncologist

Table 3 Individual subdomains by radiation oncologist (RO) (excellent/good)

Subdomains	APBI (%) ($n=64$)	WBRT (%) ($n=99$)	Significance
Subjective size	89.1	53.8	0.0001
Subjective shape	87.5	65.7	0.001
Colour of breast	100	94.0	0.06
Location of NAC	75.0	53.5	0.006
Shape of NAC	92.2	79.8	0.03
Appearance of scar	53.1	29.3	0.002

NAC nipple areola complex

Table 4 Individual subdomains by surgical oncologist (SO) (excellent/good)

Subdomains	APBI (%) ($n=64$)	WBRT (%) ($n=99$)	Significance
Subjective size	64.1	49.5	0.05
Subjective shape	62.5	47.5	0.03
Colour of breast	81.3	66.7	0.04
Location of NAC	71.9	44.4	0.001
Shape of NAC	82.8	58.6	0.001
Appearance of scar	42.2	23.2	0.01

NAC nipple areola complex

core parameters lower breast contour (pLBC) ($p=0.04$), breast compliance evaluation (pBCE) ($p=0.006$) and breast area difference (pBAD) ($p=0.02$) were significantly better in APBI cohort (Tables 3, 4, 5). There was no significant difference in patient satisfaction with respect to the cosmesis outcome between the two cohorts (extremely satisfied/moderately satisfied: 97% vs 96.9%, $p=0.97$).

Discussion

In this prospective propensity score-matched pair analysis performed in a cohort having median follow-up period of approximately 2 years, we found that cosmesis was significantly superior in APBI by all methods of assessment after

Table 5 BCCT parameters in APBI vs WBRT

BCCT parameters	APBI ($n=64$)	WBRT ($n=99$)	Significance
pBRA	0.129	0.144	0.38
pLBC	0.050	0.790	0.04
pUNR	0.101	0.119	0.13
pBCE	0.187	0.392	0.006
pBCD	0.050	0.072	0.09
pBAD	0.094	0.119	0.02
pBOD	0.250	0.264	0.69

BRA breast retraction assessment, *LBC* lower breast contour, *UNR* upward nipple retraction, *BCE* breast compliance evaluation, *BCD* breast contour difference, *BAD* breast area difference, *BOD* breast overlap difference

matching for known factors that affect cosmesis. The size and shape of the breast were better preserved (in assessment by both: SO and RO) in the APBI cohort which are probably the most important factors for overall better cosmetic outcome. In the objective assessment also, parameters such as pLBC, pBCE and pBAD which are surrogates for size and shape of breast were better in APBI cohort.

Long-term survivorship of early hormone positive breast cancer is approximately 80–85% and hence all efforts should be made to decrease long-term morbidity/toxicity associated with treatment [19]. Cosmesis after BCS remains one of the most important endpoints affecting the body image of the woman. Hence, local treatment (both surgery and radiotherapy) has to be tailored to preserve the cosmesis of the treated breast. Adjuvant RT to the whole breast results in significant damage to the normal mammary tissue and the overlying skin which results in hyperpigmentation, scarring, telangiectasia, fibrosis and fat necrosis [20].

In APBI, partial breast irradiation, although results in a significantly lesser amount of normal breast tissue being irradiated, radio-biologically, a higher dose per fraction of RT delivered over a shorter period of time can theoretically have a higher incidence of late normal tissue toxicity including inferior cosmetic outcomes [21]. There have been multiple studies utilizing various techniques that have compared APBI and WBRT with respect to cosmesis. In the RAPID trial, which compared 3D-CRT-based APBI vs WBRT, adverse cosmesis at 3 years was increased among

those treated with APBI compared with WBI as assessed by trained nurses (29% vs 17%; $p=0.001$), by patients (26% vs 18%; $p=0.0022$), and by physicians reviewing digital photographs (35% vs 17%; $p=0.001$) [10]. The authors attributed the inferior result to the RT techniques which may not have been sufficiently conformal, the dose/fractionation used (38.5 Gy/10 fractions) and to the less time interval (6 h) between two fractions which were delivered daily. However, cosmetic and toxicity outcomes of APBI with modern external beam radiotherapy techniques such as intensity-modulated radiotherapy (IMRT) are excellent. In the IMPORT LOW trial, the recorded adverse effects after reduced-dose or partial breast radiotherapy (with IMRT) were similar in APBI and WBRT arms with two parameters favoring the APBI arm: change in breast appearance and breast harder or firmer as compared with WBRT [7]. Similarly, in the FLORENCE Trial, APBI with IMRT had superior quality of life at 2 years as compared to WBRT [22]. Two parameters related to cosmesis: body image (BRBI, $p=0.0001$) and breast symptoms (BRBS, $p=0.0001$) were superior in APBI arm.

Perhaps, the most well-described modality for APBI in the literature is multichannel interstitial brachytherapy (MIB-APBI) [23]. Multiple randomized and non-randomized trials have demonstrated excellent cosmesis with MIB-APBI [5, 9, 24]. However, there is a steep learning curve associated with brachytherapy. One of the reasons for optimal cosmetic outcomes in the current study may be the fact that all procedures were done in a tertiary cancer care hospital in India with the radiation oncologists having large experience of performing MIB-APBI. We also attribute this to our treatment protocols, i.e., the optimal gap between the previous treatment (chemotherapy/surgery) and the start of radiotherapy (median 26 days for post-operative APBI and 27 days for intra-operative APBI) as well as CT-based planning for all patients involving meticulous contouring and planning. As compared to EBRT-based APBI, we prefer patients to be treated with MIB-APBI, because of the expertise available at our institute and excellent multidisciplinary coordination. IMRT-based APBI, although an attractive option, might be more prone to daily setup errors and geographical misses. It is offered at our institute only in those cases that are not suitable for brachytherapy.

Despite matching for most known factors affecting cosmesis, bias in the analysis could not be avoided completely. Besides radiotherapy, other treatment-related factors have been known to affect cosmesis adversely out of which chemotherapy and hormonal therapy are the most important ones [12]. Although this study was matched for overall use of chemotherapy, a significantly higher proportion of patients received taxanes in the WBRT cohort (25.9%) than APBI cohort (8%) which was because of 21.7% nodal positivity in the WBRT cohort. We could not find any data in the literature suggesting adverse impact of taxanes over anthracyclines with respect to cosmetic outcome. Hence, whether this could be one of the factors for inferior cosmetic outcomes in the WBRT cohort cannot be inferred convincingly. Tamoxifen is known to increase fibrosis in the breast and hence, it may affect cosmesis inferiorly [25]. Aromatase inhibitors such as letrozole have not been associated with such an effect. In our study, a higher proportion of patients in the WBRT cohort received tamoxifen ($n=43$, 33.3%) as compared to APBI cohort ($n=14$, 21.8%), as APBI is generally offered to post-menopausal women; however, it was not statistically significant. We chose the volume of the surgical cavity and the maximum dimension of pathological tumor size as surrogate for the volume of resection. Finally, the extent of axillary surgery can impact the surgical outcomes and baseline cosmesis. However, in the current analysis, we have matched for the median number of lymph nodes dissected and hence, the extent of axillary surgery is well matched between the two cohorts. Lumpectomy procedure was standard in the two groups, while axillary sampling was performed in 49 (50%) and 45 (71%) of the patients in the WBRT and APBI cohorts, respectively.

Some authors have suggested that the timing of brachytherapy (intra-operative vs post-operative) can significantly impact the cosmetic outcomes. However, in this study, there was no significant difference in the cosmetic outcomes between the intra-operative and the post-operative cohort (excellent/good, objective: 70.5% vs 72.1%, $p=0.57$).

Size of the breast, shape of the breast and location of the NAC are the most subjective important factors affecting cosmesis of the breast [26–28]. This was confirmed even in the objective cosmetic assessment where pBCE, pBAD and pLBC were significant for inferior cosmesis in the WBRT cohort. These parameters are largely dependent on the contour of the breast [17]. Hence, it is recommended that APBI (which radio-biologically may have a higher incidence of late side effects) should be avoided in patients with cavity size > 150 cc, despite being suitable for APBI. One should also avoid APBI for centrally located tumors (retro-areolar) to preserve the location and shape of NAC which might be altered due to post-RT fibrosis in APBI.

Standard dose volume constraints recommended by American Brachytherapy Society (ABS) were used at our institute and our earlier publication also reports the dosimetric audit of interstitial implants [13, 29] Three patients in the APBI cohort had a poor cosmesis by all methods of assessment. On retrospective analysis of implant dosimetry, out of these three only one patient (volume of tumor bed: 82.4 cc, volume of CTV: 120 cc) had a large volume of 150 and 200 percent of the prescription dose (volume receiving 150%: 42 cc, volume receiving 200%: 31.2 cc, conformity index: 0.71, Dose Homogeneity Index (DHI): 0.78). This suggests that in addition to implant quality, other factors

such as intrinsic radiosensitvity of the individual and baseline cosmesis may also have a role in determining post-treatment cosmesis. The ABS has also recently refined these dose constraints and reduced the acceptable volumes of 150% and 200% to less than 45 cc and 14 cc, respectively, with an acceptable DHI of more than 0.75 [29].

We did not find any significant difference between patient satisfaction levels for APBI vs WBRT (approximately 97% in both cohorts), although there was significant difference in patient-rated cosmesis assessment (excellent/good: 87.5% vs 58.6%, $p=0.001$). In literature, most studies demonstrate that cosmetic changes (especially the volume of breast tissue excised) do have an impact on the patient's satisfaction with breast conservation therapy [30, 31]. The reasons for high level of satisfaction reported by patients in the current cohort reflects the difference in the perception of the impact of cosmetic outcome on body image in our population as compared to western population.

A randomized controlled trial setting offers the best opportunity for balancing the baseline characteristics as well as treatment-related factors such as chemotherapy and hormonal therapy that have a significant impact on the cosmetic outcome. However, till date, limited data are available on cosmetic outcome from the randomized studies using the objective methods [6]. To the best of our knowledge, this is the first matched pair analysis of its kind which has matched most of the known factors affecting cosmesis for objective assessment. Also, the superior outcome of APBI in terms of individual objective parameters such as pBCE, pBAD, etc. has never been demonstrated before, which confirms the hypothesis that MIB-APBI offered in carefully selected patients is better in preserving the size and shape of breast due to a reduction in the volume of normal breast getting irradiated.

A limitation of our study was that we performed one-time cross-sectional assessment of cosmesis. Cosmetic outcomes are known to change over a period of time [32]. However, we chose a time period of 18–36 months from the date of completion of treatment as this is the time period when patients are most compliant to follow-up and the cosmetic changes start manifesting. Although this follow-up duration may seem short, most patients in both cohorts were assessed after 24 months (2 years) of implant [$n=49$ (76.5%)] and external radiotherapy [$n=65$ (66%)]. The other drawback of the study is the lack of information of the baseline cosmetic scoring which is an important factor determining the final outcome.

The overall rates of excellent/good cosmesis was low in the entire cohort as compared to some of the other studies. For e.g.: the rates of excellent/good cosmesis were in excess of 90% in both the APBI as well WBRT arms when rated both by the patients as well as the physician in the long-term outcomes of study reported by Polgar et al. [5]. In our opinion, the lower rates of excellent/good cosmesis in the current study could be attributed to inferior baseline cosmesis due to larger surgical resection in relatively larger tumors. The median tumor size in the WBRT and APBI cohorts in the current study was 2.5 cm and 2.2 cm, respectively, whereas it was 1.2 cm for both cohorts in the GEC-ESTRO study.

In summary, this study establishes the cosmetic superiority of MIB-APBI over traditional WBRT by all methods of assessment. No eligible patient should be denied the benefit of APBI using interstitial brachytherapy, which includes shortened overall treatment time and better late toxicity profile, ultimately leading to better long-term quality of life.

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Compliance with ethical standards

Conflict of interest None of the authors have any potential conflict of interest to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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