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Clinical Investigation

Once Daily Versus Twice Daily External Beam Accelerated Partial Breast Irradiation: A Randomized Prospective Study

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Purpose: The aim of the current study was to compare toxicity, cosmesis, and local control between the once daily and the twice daily fractionation schemes for external beam accelerated partial breast irradiation.

Methods and Materials: From December 2012 to June 2018, we enrolled 113 patients with ductal carcinoma in situ or invasive breast cancer, node negative disease, and tumors less than 3 cm in size to receive accelerated partial breast irradiation (APBI) to a total dose of 38.5 Gy over 10 fractions given either once (oAPBI) or twice daily (tAPBI). Sixty patients were included in the tAPBI arm and 53 patients were included in the oAPBI arm.

Results: Median follow-up was 74 months (range, 24-105). The median pain score during treatment was 3 out of 10 in the oAPBI and 5 in the tAPBI ($P = .001$). No differences were observed in GIII early skin toxicity ($P = .4$) or GI early pulmonary toxicity ($P = 1.0$) between the 2 treatment arms. GIII late skin toxicity developed in 3.8% and 11.7% of patients in the oAPBI and tAPBI arms, respectively ($P = .001$). GIII subcutaneous fibrosis developed in 1.9% and 8.3% of patients in the oAPBI and tAPBI, respectively ($P = .001$). The rate of patients with adverse cosmesis (poor/fair) was 7.5% at 12 months and at 24 months in the oAPBI arm compared with 21.7% and 26.7% in the tAPBI arm ($P = .03$ and .008, respectively).

Conclusions: oAPBI is a safe, well-tolerated schedule with more favorable outcomes than the tAPBI schedule with regards to late toxicity and cosmesis.

Introduction

The highest level of clinical evidence available to date supports the use of adjuvant whole breast irradiation after breast conserving surgery.[1-3] The standard of care consists of 50 Gy in 2 Gy per fraction delivered over 5 weeks, given to the whole breast ± regional lymph nodes.

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Over the past 2 decades there has been growing interest in adopting different radiation therapy schedules and treatment volumes.[4,5] One of the new emerging modalities is the accelerated partial breast irradiation (APBI) for patients with early stage breast cancer. APBI is carried out using brachytherapy, intraoperative radiation therapy, or external beam radiation therapy. The treatment course usually consists of 32 to 40 Gy given in 2 daily fractions with at least a 6 hour interval.

Toxicities of APBI are supposed to be minimal as a consequence of the small volumes treated; however, several investigators have reported poor cosmesis and heightened toxicity results.[6-8] The total radiation dose, fraction size, and interfraction interval have all been suspected as potential causes for these results.[9]

The aim of the current study was to compare cosmetic outcome and normal tissue toxicity in patients treated with once daily versus twice daily 3-dimensional external beam APBI.

Methods and Materials

In the period from December 2012 to June 2018, 177 female patients $\geq$18 years old who underwent breast conserving surgery for invasive breast cancer or ductal carcinoma in situ, had tumors $\leq$3 cm, had negative nodes, and had negative surgical margins were enrolled into the current study. Institutional review board approval was obtained, and all patients signed informed consent.

Randomization

At randomization, patients were stratified according to age (<50 or >50 years), type of cancer (invasive or ductal carcinoma in situ), and hormonal receptor status. Patients were allocated 1:1 into either once daily APBI arm (oAPBI) or twice daily APBI arm (tAPBI).

Technique

All patients underwent computed tomography based simulation within the first 42 days after surgery before resolution of the postoperative seroma, which was used to guide delineation of the tumor bed. Surgical clip insertion was allowed but not mandated by the protocol. A clinical target volume expansion of 1 to 1.5 cm was used, and then another 1cm isotropic expansion as a planning target volume (PTV) was added. The PTV was trimmed anteriorly to 5 mm below the skin and limited posteriorly to the anterior surface of the ribs/chest wall to generate the evaluation planning target volume.

Most of the patients (n = 108) were treated with 2 mini tangential photon fields and en-face electron field. Eight patients were treated with 4 noncoplanar fields. The dose received by 95% of the PTV should not be less than 95% of the prescribed dose while the maximum dose to the PTV should not exceed 110% of the prescribed dose.

Dose to >50% of the uninvolved breast volume is limited to <50% of the prescribed dose. Less than 10% of the ipsilateral lung received 30% of the prescribed dose. For left-sided lesions, the volume of the heart receiving 5% of the prescribed dose (V5) should be less than the V5 if the whole breast was treated using tangential fields. For right sided lesions, $\leq$10% of the heart received 5% of the prescribed dose. Minor deviations were allowed from these constraints.

Patients in the oAPBI arm received 38.5 Gy in 10 fractions given once daily, while patients in the tAPBI arm received 38.5 Gy in 10 fractions given twice daily with a minimum of 6 hours interfraction interval.

Outcomes

The primary aim of the current study was to compare the rate of adverse (fair/poor) cosmesis and toxicity between the 2 treatment arms. Secondary endpoints included rates of locoregional recurrence, distant metastases, and overall survival.

Follow-up

After the end of radiation treatment, patients were assessed at 6 weeks, every 3 months for the first 2 years, biannually for the second 3 years, and annually thereafter. Acute toxicities were assessed twice (every 5 fractions) during treatment and up to 90 days after the end of radiation using the Radiation Therapy Oncology Group acute morbidity scoring schema.[10]

Late toxicities were assessed at each follow-up visit after treatment using the National Cancer Institute Common Terminology Criteria for Adverse Events V 4.0. The highest toxicity grade recorded was used for the purpose of the current analysis. Pain during radiation was assessed using a 0 to 10 numerical rating scale. Cosmesis was evaluated by the treating physician using the European Organization for the Research and Treatment of Cancer Breast Cancer Cosmetic Rating System.[11] Assessment was carried out at baseline (before radiation treatment), at 12 months, and 24 months after the end of radiation treatment.

Statistics

Taking power of 0.8 and alpha error of 0.05, a minimum sample size of 87 patients in each treatment arm was calculated based on an assumed 35.1% rate of adverse cosmesis (from the APBI arm of the Canadian RAPID trial[12]). A total of 177 eligible patients were included in the study. Patients with complete follow-up data and 2 post-radiation cosmesis assessments were included in the current analysis (113 patients). Sixty-four patients (35 patients in the oAPBI arm and 29 patients in the tAPBI arm) dropped

out during the follow-up period owing to unwillingness to show for the extra visits needed for the cosmesis assessment (39 patients did not have any cosmesis assessment after treatment and 25 patients had only 1 cosmesis assessment). Continuous variables were expressed as the median (range), and the categorical variables were expressed as a number (percentage). Mann-Whitney *U* test was used to compare 2 groups of nonnormally distributed data. Percent of categorical variables was compared using Pearson's χ^2 test or Fisher's exact test when appropriate. All tests were 2 sided. A P value $< .05$ was considered significant. All statistics were performed using SPSS 22.0 for windows (IBM Inc, Chicago, IL).

Results

Median follow-up was 74 months (range, 24-105 months). Patient, tumor, and treatment characteristics were well balanced between the 2 treatment arms and are summarized in Table 1.

Median age was 49 years in the oAPBI group and 47 years in the tAPBI group ($P = .1$).

Median tumor size was 2 cm and 2.2 cm in the oAPBI and the tAPBI arms, respectively ($P = .2$).

Forty-two patients (79.2%) in the oAPBI arm had hormone receptor-positive disease compared with 49 patients (81.6%) in the tAPBI arm; however, the difference was not statistically significant ($P = .7$). Adjuvant chemotherapy was given to 30.2% of the patients in the oAPBI arm and 30% of the patients in the tAPBI arm ($P = .9$).

Dosimetry

The median evaluation planning target volume D95 was 97% in the oAPBI group and 98% in the tAPBI group ($P = .7$). The median ipsilateral uninvolved breast V50% was 43% in the oAPBI and 42% in the tAPBI ($P = .07$). The rest of the dose-volume parameters are summarized in Table 2.

Normal tissue toxicity

The median numerical pain score assessed during treatment was 3 out of 10 in the oAPBI group and 5 out of 10 in the tAPBI group ($P = .001$). Grade III early skin toxicity developed in 3 patients (5.7%) in the oAPBI arm and 7 patients (11.7%) in the tAPBI arm ($P = .4$). One patient in each treatment arm developed grade I early pulmonary toxicity ($P = 1.0$). Grade III late skin toxicity occurred in 2 (3.8%) patients in the oAPBI group and 7 (11.7%) patients in the tAPBI group ($P = .001$). Grade II telangiectasia developed in 1 patient (1.9%) in the oAPBI arm and 5 patients (8.3%) in the tAPBI arm ($P = .001$). Grade III subcutaneous fibrosis developed in 1 patient (1.9%) in the oAPBI arm and 5 patients (8.3%) in the tAPBI arm ($P = .001$).

Table 1 Patient, tumor, and treatment characteristics

	oAPBI (n = 53)	tAPBI (n = 60)	*P* value
Age			.18
<50 years	27 (50.9%)	38 (63.3%)	
≥50 years	26 (49.1%)	22 (36.7%)	
Laterality			.14
Left	39 (73.5%)	46 (76.6%)	
Right	14 (26.5%)	14 (23.4%)	
Cancer type			.71
Invasive	55	48	
Ductal carcinoma in situ	5	5	
Tumor size			.51
≤1.5 cm	13 (24.5%)	18 (30%)	
>1.5 cm	40 (75.5%)	42 (70%)	
Grade			.41
I	4 (7.5%)	2 (3.3%)	
II	45 (84.9%)	51 (85%)	
III	4 (7.5%)	7 (11.7%)	
Hormone receptor positive	42 (79.2%)	49 (81.6%)	.74
LVI present	3 (5.7%)	10 (16.7%)	.06
Adjuvant chemotherapy	16 (30.2)	18 (30%)	.98
Adjuvant hormone therapy	42 (79.2%)	50 (83.3%)	.57

Abbreviations: LVI = lymphatic vascular invasion; oAPBI = once daily accelerated partial breast irradiation; tAPBI = twice daily accelerated partial breast irradiation.

Table 2 Dose-volume parameters according to treatment arm

	oAPBI (n = 53)	tAPBI (n = 60)	*P* value
PTV Eval D95			.17
Mean	97.35	98.73	
Median	99	99	
IQR	95-100	96-100	
Ipsilateral breast V50%			.07
Mean	42.16	40.58	
Median	43	42	
IQR	29-50	28-52	
Ipsilateral lung V20 Gy			.42
Mean (%)	4.13	3.8	
Median (%)	4	3	
IQR (%)	1-9	1-16	
Heart mean dose			.15
Mean (cGy)	311	378	
Median (cGy)	273	334	
IQR (cGy)	29-496	24-386	

Abbreviations: D95 = dose received by 95% of the volume; IQR = interquartile range; oAPBI = once daily accelerated partial breast irradiation; PTV-Eval = evaluation planning target volume; tAPBI = twice daily accelerated partial breast irradiation; V20 Gy = volume receiving 20 Gy; V50% = volume receiving 50% of the dose.

Cosmetic outcomes

At baseline, 7.5% of the patients in the oAPBI arm and 15% of the patients in the tAPBI arm had poor/fair cosmesis ($P = .2$). At 12 months, the tAPBI arm had a significantly higher proportion of patients with poor/fair cosmesis compared with the oAPBI arm (21.7% and 7.5% respectively, $P = .03$). At 24 months, the percentage of patients with poor/fair cosmesis in the tAPBI arm increased to 26.7% compared with 7.5% in the oAPBI arm ($P = .008$). More patients in the tAPBI arm had deterioration in their cosmesis over time compared with patients in the oAPBI (36.7% vs 13.2%, $P = .002$). Changes in the European Organization for Research and Treatment of Cancer cosmesis rating score for patients in each arm are summarized in Table 3.

Local control and survival outcomes

One patient in the oAPBI arm and 2 patients in the tAPBI arm experienced locoregional relapse. The 5-year locoregional relapse free survival was 98.1% and 96.7% for oAPBI and tAPBI, respectively ($P = .5$). The 5-year estimated overall survival was 98.1% in the oAPBI group and 98.3% in the tAPBI group ($P = .2$).

Discussion

This was a prospective randomized single institutional study comparing 2 external beam APBI schedules, the once daily and the twice daily. Patients were treated to a total dose of 38.5 Gy given in either twice daily fractions of 3.85 Gy with a 6 hour interfraction interval or a once daily fraction of 3.85 Gy.

One of the major downsides experienced with APBI is the poor cosmetic outcome reported by several investigators. The Christie hospital experience[13] with external beam APBI was one of the very early studies demonstrating poor cosmesis with APBI. These early results were mostly attributed to the noncontemporary radiation therapy techniques used at that time. However, results from more recent studies did not differ that much, with many investigators reporting heightened toxicities and poor cosmetic outcomes.[6-8]

Table 3 Changes in the EORTC cosmesis rating score at 24 months stratified according to the treatment arm

	oAPBI n (%)	tAPBI n (%)
Deterioration by 2 points	0 (0%)	1 (1.7%)
Deterioration by 1 point	7 (13.2%)	21 (35%)
No change	39 (73.6%)	38 (63%)
Improvement by 1 point	7 (13.2%)	0 (0%)

Abbreviation: EORTC = European Organization for Research and Treatment of Cancer; oAPBI = once daily accelerated partial breast irradiation; tAPBI = twice daily accelerated partial breast irradiation.

Benzen and Yarnold[9] suggested the short interfraction interval as one of the probable causes of the high rate of adverse cosmesis encountered with external beam APBI, especially that accurate estimation of the time needed for normal tissue repair is lacking for human. In the current study, the same fraction size and treatment volumes were used in both treatment arms. The interfraction treatment interval increased from 6 hours in the tAPBI arm to 24 hours in the oAPBI arm.

As acute toxicities are more influenced by the total dose, which was kept the same for the 2 treatment arms, no differences were observed in grade III early skin toxicity or grade I early pulmonary toxicity ($P = .4$ and 1.0, respectively). The 5.7% rate of grade III acute toxicity reported in the oAPBI arm of the current study comes very close to the 7% rate reported in the whole breast irradiation (WBI) arm of the National Surgical Adjuvant Breast and Bowel Project B-39 and better than the 10% rate reported in their tAPBI arm.[14]

We observed a decrease in the incidence of grade III late skin toxicity (3.8% vs 11.7%), grade III subcutaneous fibrosis (1.9% vs 8.3%), and grade II telangiectasia with the once daily fractionation versus the twice daily fractionation. These results contribute to the growing body of evidence suggesting lower rates of late toxic effects associated with APBI when the interfraction interval is increased to 24 hours.[15,16]

The interim analysis results from the external beam APBI Canadian ACCEL trial,[17] which used 27 Gy given in 5 daily fractions over 1 week, demonstrated very low late toxicity outcomes with no grade 2+ fibrosis or telangiectasia despite the high dose per fraction they used.

The Canadian Rapid trial[18] reported a 16.5% rate of adverse cosmesis among patients treated with whole breast irradiation at 3 years, a rate that is very close to our 15% rate of adverse cosmesis in the oAPBI arm. These results suggest that oAPBI is noninferior to WBI with regards to the cosmetic outcomes. Although better cosmetic results were expected with APBI compared with WBI owing to the small volume effect, it seems that the relatively higher dose per fraction used in the APBI negatively affected cosmesis even when more time was allowed for recovery between fractions.

The favorable toxicity and cosmetic outcomes with the oAPBI schedule come at the expense of a more protracted course of treatment (2 weeks instead of 1 week). To explore patients' preferences toward the overall treatment time, Hoopes and colleagues[19] surveyed 1807 women with breast cancer. Most of the women (70%) included in the survey preferred a once daily fractionation in 10 days over the twice daily fractionation in 5 days.

All patients in the current study belonged to either the "suitable" or the "cautionary" groups of the American Society for Radiation Oncology consensus statement[20] and its update[21] except for 2 patients (1 in each treatment group) who

did not meet the age limit criteria. This might be responsible for the high local control rates observed until the time of this analysis. Locoregional relapse free survival was 98.1% and 96.7% for oAPBI and tAPBI, respectively ($P = .5$).

One of the limitations of the current study was that cosmesis assessment was done by the same treating physician, which made the study liable to some bias.

In conclusion, the results of the current study suggest that once daily external beam APBI is safe for and tolerable by most patients, with a more favorable toxicity profile and cosmetic results than the twice daily regimen. Further randomized studies with a larger number of patients and cosmesis assessments beyond 24 months are needed to ascertain the superiority of this treatment schedule.

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