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Research Letter

Accelerated Partial Breast Irradiation: Association of Dosimetric Parameters With Patient-Reported Outcomes

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Abstract

Purpose: Accelerated partial breast irradiation (APBI) after breast-conserving surgery offers a well-tolerated adjuvant radiation therapy option for patients with breast cancer. We sought to describe patient-reported acute toxicity as a function of salient dosimetric parameters during and after an APBI regimen of 40 Gy in 10 once-daily fractions.

Methods and Materials: From June 2019 to July 2020, patients undergoing APBI were assigned a weekly, response-adapted, patient reported outcomes-common terminology criteria for adverse events-based acute toxicity assessment. Patients reported acute toxicity during treatment and for up to 8 weeks after treatment. Dosimetric treatment parameters were collected. Descriptive statistics and univariable analyses were used to summarize patient-reported outcomes and their correlation to corresponding dosimetric measures, respectively.

Results: Overall, 55 patients who received APBI completed a total of 351 assessments. Median planning target volume was 210 cc (range, 64-580 cc), and median planning target volume:ipsilateral breast volume ratio was 0.17 (range, 0.05-0.44). Overall, 22% of patients reported moderate breast enlargement and 27% reported maximum skin toxicity as severe or very severe. Furthermore, 35% of patients reported fatigue, and 44% of patients reported pain in the radiated area as moderate to very severe. Median time to first report of any moderate to very severe symptom was 10 days (interquartile range, 6-27 days). By 8 weeks after APBI, most patients reported resolution of symptoms, with 16% reporting residual moderate symptoms. Upon univariable analysis, none of the ascertained salient dosimetric parameters were associated with maximum symptoms or with the presence of moderate to very severe toxicity.

Conclusions: Weekly assessments during and after APBI showed that patients experienced moderate to very severe toxicities, most commonly skin toxicity, but that these typically resolved by 8 weeks after radiation therapy. More comprehensive evaluations among larger cohorts are warranted to define the precise dosimetric parameters that correspond to outcomes of interest.

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Data sharing statement: Research data are stored in a secure, institutional database and will be shared upon request to the corresponding author.

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Introduction

Breast-conserving surgery followed by adjuvant radiation therapy represents an effective and often-preferred treatment option for patients with early-stage breast cancer compared with mastectomy.[1-3] Although whole-breast irradiation (WBI) has been the longstanding adjuvant approach of choice, accelerated partial breast irradiation (APBI) is a convenient and well-tolerated alternative for appropriately selected patients.[4-7] Unlike WBI, which treats the entire involved breast over 1 to 6 weeks and may confer modest heart and lung exposure, APBI is typically administered over an abbreviated treatment period (1 to 2 weeks) and limits exposure to the tumor bed and a surrounding breast tissue margin. Additionally, APBI has been associated with improved cosmetic outcomes, such as lower rates of breast edema, breast shrinkage, and pigmentation changes, compared with WBI, and it represents a more convenient option for patients.[8]

There is a growing body of literature suggesting that several APBI regimens are feasible and effective.[4-6,9,10] However, toxicity assessments may vary by regimen and less is known about patient-reported outcomes associated with each regimen. To optimize the balance of convenience and anticipated toxicity, we adopted a regimen of 40 Gy delivered in 10 once-daily fractions over 2 weeks and have previously reported on oncologic outcomes.[4] Herein, we describe patient-reported acute toxicity according to weekly assessments during and after an APBI regimen of 40 Gy in 10 once-daily fractions. We also examine salient dosimetric parameters and their correlation with patient-reported outcomes of APBI.

Methods and Materials

A subset of patients at a multicenter comprehensive cancer center were assigned weekly acute toxicity assessments. We retrospectively reviewed the assessments of patients who underwent an APBI regimen of 40 Gy in 10 once-daily fractions for their early-stage breast cancer. The assessment instrument was previously described in detail.[11] Assessments were administered via an online patient portal and could be completed remotely on a personal device, such as a computer, tablet, or smart phone. Tablets were also available in clinical waiting rooms for patients to complete assessments. Symptoms assessed included pain in the radiated area, fatigue, breast enlargement, and skin toxicity (Supplementary Material). Patients were sent assessments weekly during the 2-week treatment period and for up to 8 weeks after treatment. Patients were included in this institutional review board-approved study if they were assigned at least 1 assessment.

Patients who underwent an APBI regimen of 40 Gy in 10 once-daily fractions over the course of 2 weeks were included. Radiation therapy was delivered using intensity modulated radiation therapy. The planning target volume (PTV) was defined as the clinical target volume (ie, the resection cavity or postoperative seroma) plus a 1.5- to 2.0-cm margin.[4] The PTV needed to be less than 35% of the total ipsilateral breast volume.[4] Patients were seen weekly while on treatment and were routinely prescribed topical Triamcinolone cream, which they were instructed to apply twice a day during treatment and for 2 weeks after treatment. Patient and clinicopathologic characteristics were collected from medical records. Dosimetric treatment parameters were collected from the treatment planning system and included PTV, breast volume, PTV: ipsilateral breast volume ratio, maximum hotspot dose, breast V20, heart mean dose, and ipsilateral lung V5.

Descriptive statistics were used to summarize patient-reported outcomes and dosimetric measures. Patients were included in this portion of the analysis if they completed at least 2 assessments. Univariable analysis with linear and logistic regression models was performed to determine whether dosimetric parameters could predict patient-reported outcomes. We used Spearman correlation to assess correlations between different patient-reported toxicity outcomes. Using the Bonferroni correction to adjust for comparisons, statistical significance was defined as $P < .01$.[12]

Results

Overall, 55 of 101 (54%) patients who received APBI from June of 2019 to July of 2020 completed at least 2 assessments during or after treatment. A total of 351 assessments were included in this analysis: 21% (n = 75) were completed during treatment and 79% (n = 276) were completed after treatment. Patients completed a median of 7 assessments (interquartile range, 3-9), and only 10

Table 1 Descriptive statistical summary of dosimetric parameters

Characteristic	N = 55 Median (range)
PTV, cc	210 (64-580)
Ipsilateral breast volume, cc	1091 (267-3051)
PTV:ipsilateral breast volume	0.17 (0.05-0.44)
Maximum global dose, %	112% (108%-115%)
Ipsilateral breast V20 Gy, %	45% (16%-65%)
Ipsilateral breast V20 Gy outside PTV, %	33% (12%-50%)
Heart mean, cGy	45 (3%-135%)
Ipsilateral lung V5 Gy, %	0.90% (0%-26%)

Abbreviation: PTV = planning target volume.

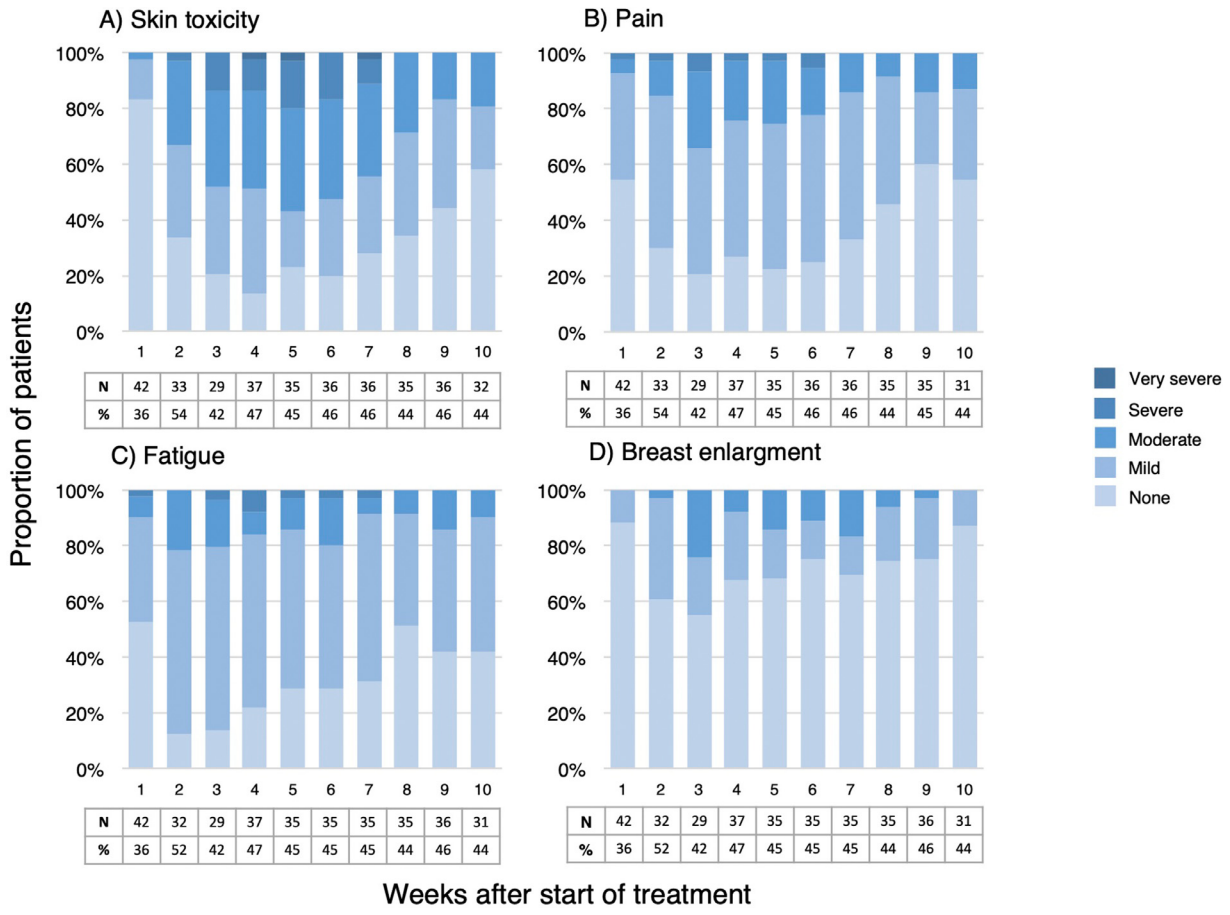

Figure 1 Trajectories of patient-reported acute toxicities over 2-week treatment period and 8-weeks posttreatment period. The legend under each graph provides the number (N) of survey items available at each timepoint and the percent (%) of assigned accelerated partial breast irradiation assessments this number represents.

patients completed the minimum of 2 assessments. Median patient age was 59 (range, 37-78).

Dosimetric parameters for the cohort are outlined in Table 1. Median PTV size (inclusive of the physician-delineated tumor bed and a 1.5-2-cm margin) was 210 cc (range, 64-580 cc), while median PTV:ipsilateral breast volume ratio was 0.17 (range, 0.05-0.44). The maximum hotspot dose ranged from 108% to 115% with a median of 112%. The proportion of the ipsilateral breast outside of the PTV that received ≥20 Gy (ie, ipsilateral non-PTV breast V20) ranged from 12% to 50% with a median of 33%. The volume of ipsilateral lung that received ≥5 Gy (ie, ipsilateral lung V5) ranged from 0% to 26% with a median of 0.90%. Median mean heart dose was 0.45 Gy (range, 0.03-1.35 Gy).

According to weekly patient assessments, median onset of any moderate to very severe symptoms from the start of treatment was 10 days (interquartile range, 6-27 days). Over two-thirds (69%) of patients reported maximum skin toxicity as moderate to very severe (42% moderate, 22% severe, 5% very severe). Onset of maximum skin toxicity occurred at a median of 3 weeks after the initiation of APBI (Fig. 1) or 1 week after the completion of APBI. Less commonly, 35% of patients reported maximum fatigue as moderate to severe (24% moderate, 11% severe). Onset of maximum fatigue occurred at a median of 1 week after the initiation of APBI (Fig. 1). Similarly, 22% of patients reported maximum breast enlargement as moderate, also with a median onset time of 3 weeks after the initiation of APBI. No patients reported severe or very severe breast enlargement during or after treatment. Overall, 44% of patients reported maximum pain in the radiated area as moderate to very severe (Fig. 1). At the end of the assessment period or 8 weeks after APBI, only 9 patients (16%) reported moderate symptoms and none endorsed severe or very severe symptoms.

Univariable analysis, in which toxicity assessments were analyzed as continuous variables in a linear model, found that dosimetric treatment variables were not associated with reported values of any of the symptoms assessed (Table 2). Similarly, a univariable logistic regression did not show any correlation between the dosimetric variables noted previously and reports of any severe to very severe toxicity compared

Table 2 Univariable linear models with toxicity as a continuous variable

	Max enlargement				Max tenderness				Max GAD sum			
Characteristic	**N**	**Beta**	**95% CI**	***P* value**	**N**	**Beta**	**95% CI**	***P* value**	**N**	**Beta**	**95% CI**	***P* value**
PTV	55	0.00	0.00, 0.00	.3	55	0.00	0.00, 0.00	.8	55	0.00	−0.01, 0.00	.3
Breast volume	55	0.00	0.00, 0.00	.7	55	0.00	0.00, 0.00	.4	55	0.00	0.00, 0.00	.070
PTV: breast volume	55	0.24	−2.8, 3.3	.9	55	0.91	−2.8, 4.6	.6	55	3.4	−1.5, 8.2	.2
Max global dose	55	−8.6	−17, 0.09	.052	55	−8.5	−19, 2.3	.12	55	0.56	−14, 15	>.9
WB V20	53	0.02	−0.01, 0.04	.13	53	0.03	0.00, 0.06	.035	53	0.02	−0.01, 0.06	.2
WB V20 not PTV	54	0.03	0.00, 0.05	.059	54	0.04	0.00, 0.07	.041	54	0.02	−0.02, 0.07	.3
	Max skin overall				**Max fatigue composite**				**Max pain composite**			
Characteristic	**N**	**Beta**	**95% CI**	***P* value**	**N**	**Beta**	**95% CI**	***P* value**	**N**	**Beta**	**95% CI**	***P* value**
PTV	55	0.00	0.00, 0.00	.5	55	0.00	0.00, 0.00	.6	55	0.00	0.00, 0.00	.6
Breast volume	55	0.00	0.00, 0.00	>.9	55	0.00	0.00, 0.00	.4	55	0.00	0.00, 0.00	.7
PTV: breast volume	55	−2.7	−6.7, 1.2	.2	55	−2.0	−4.9, 1.0	.2	55	−0.27	−3.3, 2.7	.9
Max global dose	55	−4.3	−16, 7.6	.5	55	−7.8	−17, 0.90	.078	55	−2.8	−12, 6.2	.5
WB V20	53	0.01	−0.02, 0.04	.6	53	0.01	−0.02, 0.03	.6	53	0.02	0.00, 0.04	.070
WB not PTV V20	54	0.00	−0.03, 0.04	.8	54	0.02	−0.01, 0.05	.2	54	0.03	0.00, 0.06	.052
Heart mean, cGy					55	0.00	−0.01, 0.01	>.9				
Ipsilateral lung V5					55	0.01	−0.03, 0.04	.7				
Ipsilateral lung V20					55	−0.08	−0.21, 0.05	.2				

Abbreviations: CI = confidence interval; GAD = Generalized Anxiety Disorder-2; PTV = planning target volume; WB = whole breast.

Table 3 Univariable logistic regression of dosimetric parameters and any, severe, and very severe toxicity

Characteristic	N	OR	95% CI	*P* value
PTV	55	1.00	0.99, 1.00	.6
Ipsilateral breast volume	55	1.00	1.00, 1.00	.8
PTV:ipsilateral breast volume	55	0.17	0.00, 379	.7
Maximum global dose	55	0.00	0.00, 6,507	.2
Heart mean	55	1.00	0.98, 1.01	.7
Ipsilateral lung V5 Gy	55	0.96	0.88, 1.04	.3
Ipsilateral lung V20 Gy	55	0.74	0.49, 1.07	.13
Ipsilateral breast V20 Gy	53	1.02	0.96, 1.09	.5
Ipsilateral breast V20 Gy not PTV	54	1.02	0.94, 1.10	.7

Abbreviations: CI = confidence interval; OR = odds ratio; PTV = planning target volume.

with no to moderate toxicity (Table 3). Spearman correlation revealed associations between pairs of toxicities: maximum reported breast enlargement and tenderness (ρ = 0.69), skin toxicity and pain (ρ = 0.66), and tenderness and pain (ρ = 0.68) (Fig. 2).

Discussion

Limited data exist describing patient-reported acute toxicity during and after an APBI regimen of 40 Gy in 10 once-daily fractions. The data presented here uniquely

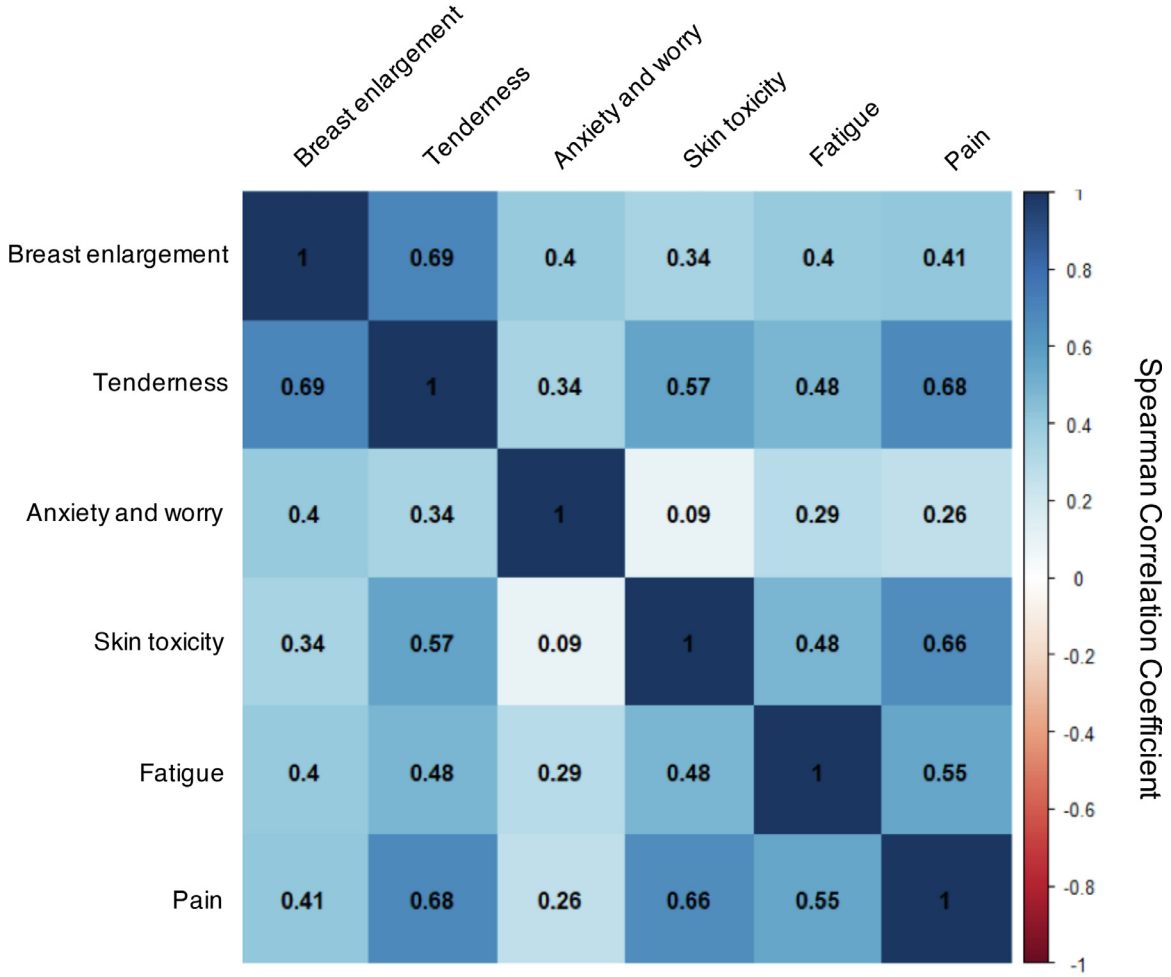

Figure 2 Correlation of patient-reported acute toxicities based on toxicity assessed.

capture the early weeks after completion of radiation therapy, in which acute toxicity of breast radiation has been shown to peak.[11,13] We found that a significant portion of patients undergoing APBI experienced severe or very severe toxicities, although these outcomes were not associated with traditional dosimetric parameters. This is potentially because these dosimetric factors were strictly maintained within safe tolerances because of stringent treatment planning. Depending on type of toxicity, peak effect was noted as early as 1 week after the initiation of radiation therapy (for fatigue) or as late as 3 weeks after the initiation of radiation therapy (for skin toxicity and breast enlargement). However, most of these acute toxicities resolved by the end of the assessment period, at which point a minority of patients endorsed moderate symptoms.

Prior studies have demonstrated that APBI is a well-tolerated adjuvant radiation therapy option. The IMPORT LOW trial, in which patients received an APBI regimen of 40 Gy in 15 once-daily fractions, later reported on patient-reported outcomes at the 6-month, 1-, 2-, and 5-year timepoints after APBI.[14] Although approximately one-fifth of patients experienced an overall change in the appearance of the treated breast that persisted over the 5-year period, the rate of most adverse effects declined over time and was lower among patients who received APBI compared with WBI.[14] Unlike our study, a small proportion of patients experienced moderate skin toxicity according to patient-reported outcomes from IMPORT LOW. However, the earliest postradiation therapy timepoint at which IMPORT LOW collected patient-reported outcomes was 6 months and is not directly comparable to the acute outcomes presented here. Conversely, the RAPID trial, which compared WBI to an APBI regimen of 38.5 Gy in 10 twice-daily fractions, found that patient-reported adverse breast cosmesis was more common among patients who received APBI than those who received WBI at both 3- and 5-years postradiation therapy.[15] It is possible that these results were due to twice-daily fractionation as opposed to the once-daily fractionation studied here and on IMPORT LOW. Additional APBI studies have demonstrated acceptable rates of adverse effects[9] and favorable cosmetic outcomes with APBI[8,16]; however, the balance of these are based on clinician-reported rather than patient-reported outcomes.

As more data addressing the use of APBI become available, it is likely that more patients with breast cancer will opt for this convenient approach to adjuvant radiation therapy. Consensus guidelines for APBI were most recently expanded in 2017, now recommending that woman aged 50 years and older (as opposed to the previous "suitable" category of 60 years and older) and also those with ductal carcinoma in situ should be considered for APBI.[7] Indeed, we previously demonstrated excellent outcomes even among those in the "cautionary" and "unsuitable" categories when otherwise appropriately selected.[4,17]

Although several of the aforementioned trials have shown promising results with regards to APBI, there is no technique or dosing/fractionation regimen that is universally accepted, complicating patient eligibility and selection. There is also a need to more thoroughly evaluate how dosimetric parameters influence APBI outcomes and toxicity. We did not find a correlation between dosimetric parameters and patient-reported acute toxicity, similar to a previous study in which patients received an APBI regimen of 34 or 38.5 Gy in 10 once-daily fractions.[18] However, both studies were limited by a small sample size. An additional limitation to our study was that only about half of all patients who received APBI during the study period completed a minimum of 2 assessments. Improvements in onboarding patients to the patient portal and educating them on the clinical utility of the assessments may increase the likelihood that patients complete the assessments.[11]

Conclusion

Overall, the results of our study suggest that rates of moderate to very severe acute toxicity of 40 Gy in 10 once-daily fraction APBI vary by toxicity type but generally decline over time. Skin toxicity is the most commonly experienced acute toxicity, and peak effect is 1 week after the completion of APBI. More comprehensive evaluations among larger cohorts are needed to define the precise dosimetric parameters that correspond to clinical outcomes and patient-reported toxicity to aid in patient selection for APBI and acute toxicity management.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101263.

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