

Scientific Article

Definitive hypofractionated radiation therapy for early stage breast cancer: Dosimetric feasibility of stereotactic ablative radiotherapy and proton beam therapy for intact breast tumors

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Abstract

Purpose: Few definitive treatment options exist for elderly patients diagnosed with early stage breast cancer who are medically inoperable or refuse surgery. Historical data suggest very poor local control with hormone therapy alone. We examined the dosimetric feasibility of hypofractionated radiation therapy using stereotactic ablative radiotherapy (SABR) and proton beam therapy (PBT) as a means of definitive treatment for early stage breast cancer.

Methods and Materials: Fifteen patients with biopsy-proven early stage breast cancer with a clinically visible tumor on preoperative computed tomography scans were identified. Gross tumor volumes were contoured and correlated with known biopsy-proven malignancy on prior imaging. Treatment margins were created on the basis of set-up uncertainty and image guidance capabilities of the three radiation modalities analyzed (3-dimensional conformal radiation therapy [3D-CRT], SABR, and PBT) to deliver a total dose of 50 Gy in 5 fractions. Dose volume histograms were analyzed and compared between treatment techniques.

Results: The median planning target volume (PTV) for SABR, PBT, and 3-dimensional CRT was 11.91, 21.03, and 45.08 cm³, respectively, and were significantly different ($P < .0001$) between treatment modalities. Overall target coverage of gross tumor and clinical target volumes was excellent with all three modalities. Both SABR and PBT demonstrated significant dosimetric improvements, each in its own unique manner, relative to 3D-CRT. Dose constraints to normal structures including ipsilateral/contralateral breast, bilateral lungs, and heart were all consistently achieved

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using SABR and PBT. However, skin or chest wall dose constraints were exceeded in some cases for both SABR and PBT plans and was dictated by the anatomic location of the tumor.

Conclusions: Definitive hypofractionated radiation therapy using SABR and PBT appears to be dosimetrically feasible for the treatment of early stage breast cancer. The anatomical location of the tumor relative to the skin and chest wall appears to be the primary limiting dosimetric factor. © 2018 The Author(s). Published by Elsevier Inc. on behalf of the American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The incidence of breast cancer in the elderly population cannot be understated, with a rate of 47% in women aged ≥ 70 years.¹ However, the management of elderly patients continues to be an area of controversy with undertreatment of this group becoming more common in the modern era.¹ Recent data suggest that surgical treatment of patients aged ≥ 75 years with stage I-III breast cancer has declined from 90.8% in 1995 to 69.9% in 2011.² Even in patients who undergo surgery, adjuvant therapy recommendations continue to be nebulous.

Much of the controversy revolves around patients with multiple medical comorbidities that are expected to independently limit their life expectancy. This premise was the impetus for several prospective trials that sought to identify a low-risk cohort of elderly women with early stage breast cancer amenable to treatment de-escalation.^{3,4} Some of these patients may have such severe medical comorbidities that they are rendered ineligible for primary surgical resection.

Comorbidities increase dramatically with age, from 9% in patients aged < 50 years to 56% in patients aged ≥ 80 years.⁵ Despite these independently life-limiting comorbidities, breast cancer continues to be a significant cause of death in elderly women. A population-based study in the Netherlands reviewed records of patients with a median age of 85.9 years from 1995 to 2005 who were diagnosed with resectable breast cancer but did not undergo surgical resection. The review found that breast cancer was the primary cause of death in 34% of cases.⁶

Historically, few definitive treatments have been available for medically inoperable patients or those who refuse surgery. Historical data suggests very poor local control with hormone therapy alone and significant toxicity with conventionally fractionated, definitive, whole-breast radiation therapy.^{7,8} The inferiority of definitive tamoxifen versus surgery was firmly established in a Cochrane review, with a progression-free survival hazard ratio of 0.65, favoring surgery.⁹

Fennessy et al. reported late follow-up (median: 12.7 years) of 455 elderly patients aged > 70 years who were randomized to surgery plus tamoxifen versus tamoxifen-alone.⁷ The 5-year rates of local progression after treatment with mastectomy plus tamoxifen, breast conservation plus tamoxifen, and tamoxifen alone were 8%, 18%, and 64%,

respectively.⁷ These high rates of local recurrence in the tamoxifen-alone arm translated into significantly higher rates of breast cancer-related mortality and overall mortality.⁷ Elsewhere in the literature, the rates of local relapse with tamoxifen treatment alone have ranged from 40% to 81% with longer follow-up.¹

The elevated risk of local recurrence with tamoxifen alone and its lack of efficacy in hormone-receptor-negative tumors prompted an investigation into definitive radiation therapy as a possible treatment for inoperable patients. Thomas et al. report the results of a French retrospective review of 319 patients treated with definitive radiation therapy using 45 Gy delivered to the whole breast with a 20 to 45 Gy boost. When stratified by individual patient risk, patients with low-risk tumors achieved 80% to 90% 5-year local control.⁸ The authors also noted that tumor size and histological grade were intricately associated with local control after definitive radiation therapy. Unfortunately, patients treated to doses > 75 Gy in this era were observed to have very poor cosmetic results, including nipple displacement and breast retractions.¹⁰

The expanding use of accelerated partial breast irradiation (APBI) for patients with favorable early stage disease has allowed for a volumetric de-escalation by focusing dose to a localized portion of breast tissue at highest risk of recurrence (eg, adjacent to the lumpectomy cavity and/or index quadrant).¹¹ Extrapolation of this principle to the definitive setting may allow for several advantages, including more accurate target volume delineation, minimization of irradiated uninvolved breast tissue even when compared with adjuvant APBI, delivery of higher doses of radiation to achieve tumor ablation, and significantly improved local control compared to hormone therapy alone.¹²

Given these potential advantages, we explore the feasibility of stereotactic ablative radiotherapy (SABR) and proton beam therapy (PBT) for the definitive hypofractionated treatment of early stage breast cancer. These distinct radiation therapy systems may provide excellent local control and minimize treatment-related toxicity by utilizing a minimally invasive method with each modality providing unique normal tissue sparing. In the present study, we examine the dosimetric feasibility of definitive SABR and PBT with comparative analysis to 3-dimensional conformal radiation therapy (3D-CRT) for the definitive hypofractionated treatment of early stage breast cancer.

Methods and materials

Patients included in this analysis were required to have biopsy-proven invasive carcinoma and/or in situ disease on the basis of a preoperative needle biopsy. All patients were evaluated by a board-certified breast surgical oncologist and were determined to have early stage breast cancer (clinical T1 N0 M0) that was amenable to surgical resection. In addition, all patients were required to have preoperative computed tomography (CT) scans that showed a visible tumor correlating with the known site of malignancy identified on mammogram, ultrasound, and breast magnetic resonance imaging (MRI). Preoperative imaging was reviewed by the same radiation oncologists (B.T.C. and M.C.R.) to confirm accurate identification of the malignant lesion. All tumors were <2 cm in largest diameter on the basis of CT scan measurements. All patients were reviewed with respect to radiological CT maximum diameter, which was correlated with subsequent surgical pathological size. Spherical tumor volume was created on the basis of the largest dimension of the surgically resected tumor to correlate with target volumes.

Preoperative CT scans were obtained with patients in the supine position and were loaded into treatment planning software that was specific for the modality of radiation therapy used. Organs at risk (OARs) were contoured on the basis of the National Surgical Adjuvant Breast and Bowel Project/Radiation Therapy Oncology Group standard contouring guidelines. CT findings including visualized biopsy clips were correlated with mammographic and/or MRI findings to create a gross tumor volume (GTV). The distance from the GTV to the chest wall and skin was defined as the minimum distance identified between the surfaces of the GTV to the surface of the chest wall or skin contours and calculated using custom Matlab software (The MathWorks, Natick, MA). A 5-mm uniform expansion from the GTV was used to create a clinical target volume (CTV), which was cropped from anatomic borders including the chest wall and skin. Clinical target volumes were the same for all plans regardless of the radiation technique utilized. Given the unique set-up, tracking, and image-guidance specifications for each radiation therapy modality, the planning target volume (PTV) created for each plan took into consideration the specific requirements of each system. As such, each treatment plan was thought to be a practical demonstration of the target volumes utilized for a given radiation modality (eg, 3D-CRT, SABR, and PBT).

Each plan for all three radiotherapy types was created to deliver a prescription dose of 50 Gy in 5 fractions to the PTV—biological effective dose (BED) of 175 Gy and equivalent dose in 2 Gy fractions (EQD2) of 116.7 Gy using an alpha-beta ratio of 4 for breast cancer cells.¹³ Proton beam orientation was adjusted in an effort to maximize PTV coverage and minimize the maximum dose to the OARs, including the chest wall and skin. Of note, PTV coverage

was reduced if the maximum dose to the skin and chest wall exceeded planning guidelines (Table 2).

The prescription dose was chosen for its ablative potential in other cancer sites including non-small cell lung cancer as well as the higher BED relative to a previously reported 5-fraction schedule used in the adjuvant breast cancer setting.^{14,15} In addition, prior clinical research on definitive radiation treatment for breast cancer identified that an EQD2 of 75 Gy is required to achieve clinical outcomes similar to those of surgery plus adjuvant radiation.¹⁶

Dose constraints used in this report (Table 2) were based on TG 101 and the recently reported phase 1 dose escalation trial for early stage breast cancer using 5-fraction (maximum dose of 40 Gy) stereotactic body radiation therapy for partial-breast radiation.^{14,17} This phase 1 dose escalation trial reported excellent clinical outcomes, minimal toxicity, and good cosmesis using these OAR dose constraints.¹⁴ An additional chest wall dose constraint was applied on the basis of Memorial Sloan Kettering data evaluating the risk of chest wall toxicity in patients treated with 5-fraction stereotactic body radiation therapy for early stage non-small cell lung cancer.¹⁸

For SABR treatment plans, PTV was set to CTV plus an additional 2 mm expansion. This was under the assumption of highly accurate daily image guided radiation therapy using fiducial-based inter- and intrafractional motion management with the CyberKnife Synchrony Respiratory Tracking System (Accuray, Sunnyvale, CA) using at least 4 fiducial markers. This technique, in the context of adjuvant therapy, was evaluated in an early feasibility study.¹⁹ The MultiPlan 5.2.1 nonisocentric inverse-planning algorithm was used to create conformal treatment plans utilizing the Monte Carlo method.

For PBT treatment plans, PTV was set to CTV plus an additional 5 mm expansion in beam direction to account for 3.5% range uncertainty and 3 mm expansion in the remaining directions. All PBT plans used a single-beam arrangement that was oriented to minimize dose to surrounding normal structures. All plans were calculated using inverse planning techniques with range and modulation on the basis of PTV. The air gap utilized was 4 cm for all plans. These expansions were thought to be reasonable under the assumption of daily cone beam CT scans for interfractional PBT image guidance. RayStation 6.112 treatment planning software (RaySearch Laboratories, Stockholm, Sweden) was used to deliver 50 Gy in 5 fractions to 95% of the PTV. The IBA Proton System with a dedicated snout was used for pencil-beam scanning treatment planning. A range shifter with 7.5 cm water equivalent thickness was used if necessary on the basis of the target volume anatomical location.

Three-dimensional CRT plans were generated for the same patients to develop conventional comparison plans for dose-volume histogram (DVH) evaluation. Of note, 3D-CRT treatment volumes were created using the National Surgical Adjuvant Breast and Bowel Project protocol B-39 (Radiation Therapy Oncology Group protocol 0413)

volumetric parameters with expansions that were edited from the skin and chest wall to create a PTV_eval structure that was used for dosimetric comparisons. A noncoplanar beam technique was created to treat each lesion with a minimum of four beams. For 3-dimensional CRT plans, previously defined CTVs were utilized with a 1 cm margin added to create PTV and an additional 0.5 cm margin to block edge to account for dose build-up. The same dose-fractionation schedule as SABR and PBT plans of 50 Gy in 5 fractions was used and prescribed to the 95% isodose line.

Dose volume histogram data was extracted from each of the aforementioned treatment planning software and imported into a custom Matlab (The MathWorks, Natwick, MA) analysis program for dosimetric analysis. Dosimetric comparisons between treatment modalities were made using Student's *t* test, 2-sided, equal variance (Microsoft Excel 2007, Seattle, WA).

Results

Patient and tumor characteristics

A total of 15 patients with early stage breast cancer and preoperative imaging were identified and available for our analysis. Eight patients were diagnosed with left-sided breast tumors, with the remainder being right-sided tumors. The majority of tumors were localized to the upper outer breast

quadrant; specifics of the location distribution are shown in Table 1. The mean GTV as defined on CT imaging was $3.37 \pm 3.93 \text{ cm}^3$ (range, 0.09-13.55 cm^3). The mean CTV as defined on CT imaging was $12.53 \pm 10.20 \text{ cm}^3$ (range, 2.15-35.73 cm^3).

As described, PTV expansion was dictated by the radiation modality utilized. The mean PTV volume for SABR, PBT, and 3D-CRT was 19.11, 28.57, and 53.07 cm^3 , respectively. The median PTV volume for SABR, PBT, and 3-dimensional CRT was 14.23, 18.49, and 28.34 cm^3 , respectively. Not surprisingly, PTV was significantly different ($P < .0001$) among all 3 radiation techniques. The specific target characteristics is also shown in Table 1.

In an effort to demonstrate the correlation between radiologic target volume and pathologic tumor size, pathologic spherical tumor volumes were created and compared with radiation target volumes. Pathologic spherical tumor volume was not significantly different from GTV. Clinical target volume was nominally larger for nearly all pathologic spherical tumor volumes and was significantly larger than pathologic spherical tumor volume ($P = .001$).

Dosimetric characteristics

Overall, target coverage of GTV was excellent for all three modalities, with >99% coverage averaged across all plans for a given modality group. Similarly, CTV coverage was excellent with >97% for all modality types, with

Table 1 Tumor characteristics

Side	Location	Path size (cm^3)	GTV (cm^3)	CTV (cm^3)	PTV_SABR (cm^3)	PTV_PBT (cm^3)	PTV_CRT (cm^3)
R	6:00	28.7	8.32	26.36	36.66	54.43	91.43
R	5:00	4.84	3.99	15.50	25.45	35.46	66.14
L	3:00	0.38	0.88	6.50	10.70	19.43	44.22
L	2:00	14.13	13.55	35.73	51.22	66.43	102.82
R	7:00	14.13	8.67	27.03	40.20	56.69	105.24
L	1:00	-	0.09	2.15	4.33	8.91	22.76
R	10:00	4.19	1.29	7.40	11.91	21.03	45.08
L	8:00	0.38	0.58	4.92	9.23	14.25	31.57
L	3:00	-	0.65	4.19	7.69	11.50	24.54
R	12:00	8.18	3.85	15.12	22.82	33.13	56.69
R	8:00	5.57	1.19	6.05	9.68	15.49	31.71
L	7:00	0.07	0.24	3.17	5.28	9.99	22.26
L	3:00	2.57	2.72	11.99	17.25	29.11	53.92
L	2:00	0.11	0.54	5.05	8.84	14.61	31.27
R	10:00	5.57	4.03	16.76	25.32	38.03	66.37
	Mean	6.83	3.37	12.53	19.11	28.57	53.07
	Median	4.84	3.93	10.20	14.23	18.49	28.34
	Std	8.13	1.29	7.40	11.91	21.03	45.08
	Min	0.07	0.09	2.15	4.33	8.91	22.26
	Max	28.7	13.55	35.73	51.22	66.43	105.24

PTV_SABR, PTV_PBT, and PTV_CRT all demonstrate statistically significant differences in volume ($P < .0001$).

CRT, conformal radiation therapy; CTV, clinical target volume; GTV, gross tumor volume; L, left; Max, maximum; Min, minimum; PBT, proton beam therapy; PTV, planning target volume; R, right; Std, standard deviation.

Table 2 Dose-volume histogram comparison

Structure	DVH parameter	PBT	SABR	3D-CRT	PBT vs SABR	SABR vs 3D-CRT	3D-CRT vs PBT
GTV	V50Gy >99%	99.99 ± 0.03%	99.93 ± 0.15%	99.59 ± 1.53%	.186	.379	.344
CTV	V50Gy >98%	99.02 ± 1.27%	98.60 ± 2.24%	97.97 ± 3.99%	.747	.373	.437
PTV	V50Gy >95%	92.08 ± 2.53%	94.47 ± 5.75%	88.97 ± 15.40%	.094	.105	.480
Ipsilateral breast	V40 Gy <20%	6.89 ± 3.16%	4.79 ± 2.60%	12.76 ± 5.10%	< .0001 ^a	< .0001 ^a	< .0001 ^a
	V20 Gy <40%	12.57 ± 3.97%	10.27 ± 4.60%	27.25 ± 8.49%	.001 ^a	< .0001 ^a	< .0001 ^a
Contralateral breast	D _{max} <1.2 Gy	0.00 ± 0.00 Gy	0.89 ± 1.38 Gy	1.63 ± 1.85 Gy	.038 ^a	0.077	0.006 ^a
Ipsilateral lung	V12 Gy <10%	0.30 ± 0.68%	0.67 ± 0.76% Gy	1.91 ± 2.60%	.100	.077	.040 ^a
Contralateral lung	V2 Gy <10%	0.00 ± 0.00%	0.35 ± 1.12%	1.20 ± 3.36%	.287	.464	.202
Heart (left-sided tumor)	V2 Gy <40%	0.05 ± 0.13%	8.91 ± 10.75%	7.48 ± 19.54%	.101	.102	.354
Heart (right-sided tumor)	V2 Gy <5%	0.00 ± 0.00%	6.88 ± 12.84%	7.07 ± 12.19%	.201	.919	.176
Thyroid	D _{max} <1.2 Gy	0.00 ± 0.00 Gy	0.12 ± 0.22 Gy	0.17 ± 0.13 Gy	.084	.150	.001 ^a
Ipsilateral skin	D _{max} <39.5 Gy	42.91 ± 4.73 Gy	39.80 ± 12.20 Gy	46.51 ± 9.18 Gy	.129	.010 ^a	.081
	V36.5 Gy <10 cm ³	4.08 ± 3.01 cm ³	1.13 ± 1.44 cm ³	2.56 ± 2.32 cm ³	< .0001 ^a	.019 ^a	.013 ^a
Ipsilateral chest wall	D _{max} <43 Gy	46.21 ± 11.06 Gy	46.02 ± 10.48 Gy	51.11 ± 6.18 Gy	.824	.033 ^a	.024 ^a
	V40 Gy <31.5 cm ³	2.25 ± 2.05 cm ³	1.33 ± 1.37 cm ³	11.70 ± 8.58 cm ³	0.014 ^a	< .0001 ^a	< .0001 ^a
Global maximum dose	D _{max} <60 Gy	52.97 ± 0.24 Gy	58.95 ± 2.48 Gy	55.13 ± 2.43 Gy	< .0001 ^a	< .0001 ^a	.007 ^a
Breast integral dose	1e5 · cGy · cm ³	5.76 ± 3.51 Gy	6.28 ± 5.02 Gy	12.96 ± 6.45 Gy	.413	< .0001 ^a	< .0001 ^a
Lung integral dose	1e5 · cGy · cm ³	0.26 ± 0.55 Gy	2.71 ± 1.73 Gy	3.04 ± 1.84 Gy	< .0001 ^a	.785	< .0001 ^a
Heart integral dose	1e4 · cGy · cm ³	0.01 ± 0.04 Gy	2.13 ± 2.41 Gy	3.76 ± 4.60 Gy	.004 ^a	.280	.009 ^a

^a Statistically significant.

Indicates statistically significant difference.

3D-CRT, 3-dimensional conformal radiation therapy; CTV, clinical target volume; DVH, dose-volume histogram; Dmax, maximum organ-at-risk dose; GTV, gross tumor volume; PBT, proton beam therapy; PTV, planning target volume; SABR, stereotactic ablative radiation radiotherapy.

no significant differences in coverage between treatment techniques. However, nominal decreases in PTV coverage were noted from SABR (94.5%) to PBT (92.1%) to 3D-CRT (89.0%), but none were statistically significant. **Table 2** illustrates the details of the DVH results for each radiation modality and DVH parameter. The DVH results represent mean dosimetric values for all plans generated for a given treatment modality.

Volume of ipsilateral breast tissue receiving ≥40 Gy was optimal with SABR (4.79% ± 2.60%) and significantly lower (*P* < .0001) than the other two radiation modalities (PBT: 6.89% ± 3.16%; CRT: 12.76% ± 5.10%). Similar results were observed for volume of ipsilateral breast tissue receiving ≥20 Gy. Maximum dose to ipsilateral skin, ipsilateral chest wall, and breast integral dose were all superior with SABR versus 3-dimensional CRT. Nonetheless, the mean global maximum dose was significantly higher (approximately 59 Gy; 118% hotspot) with SABR relative to both PBT (approximately 53 Gy; 106%

hotspot) and 3-dimensional CRT (approximately 55 Gy; 110% hotspot) plans.

Proton plans were significantly superior to 3D-CRT plans nearly across the board, with the exception of contralateral lung, heart, and ipsilateral skin doses. Finally, PBT plans were able to achieve lower contralateral breast, integral lung, and integral heart doses compared with equivalent SABR plans. Predefined OAR dose constraints were consistently achieved for all organs with the exception of the chest wall and skin.

General dosimetric characteristics for each radiation therapy modality are illustrated in **Figures 1 through 3**. Each figure demonstrates a color wash dose distribution in the axial (top), sagittal (middle), and coronal (bottom) planes for PBT (left), SABR (middle), and 3-dimensional CRT (right) treatment plans. **Figure 1** demonstrates a tumor localized in the middle of the breast tissue. **Figures 2 and 3** show tumors localized superficial adjacent to the skin and deep adjacent to the chest wall, respectively.

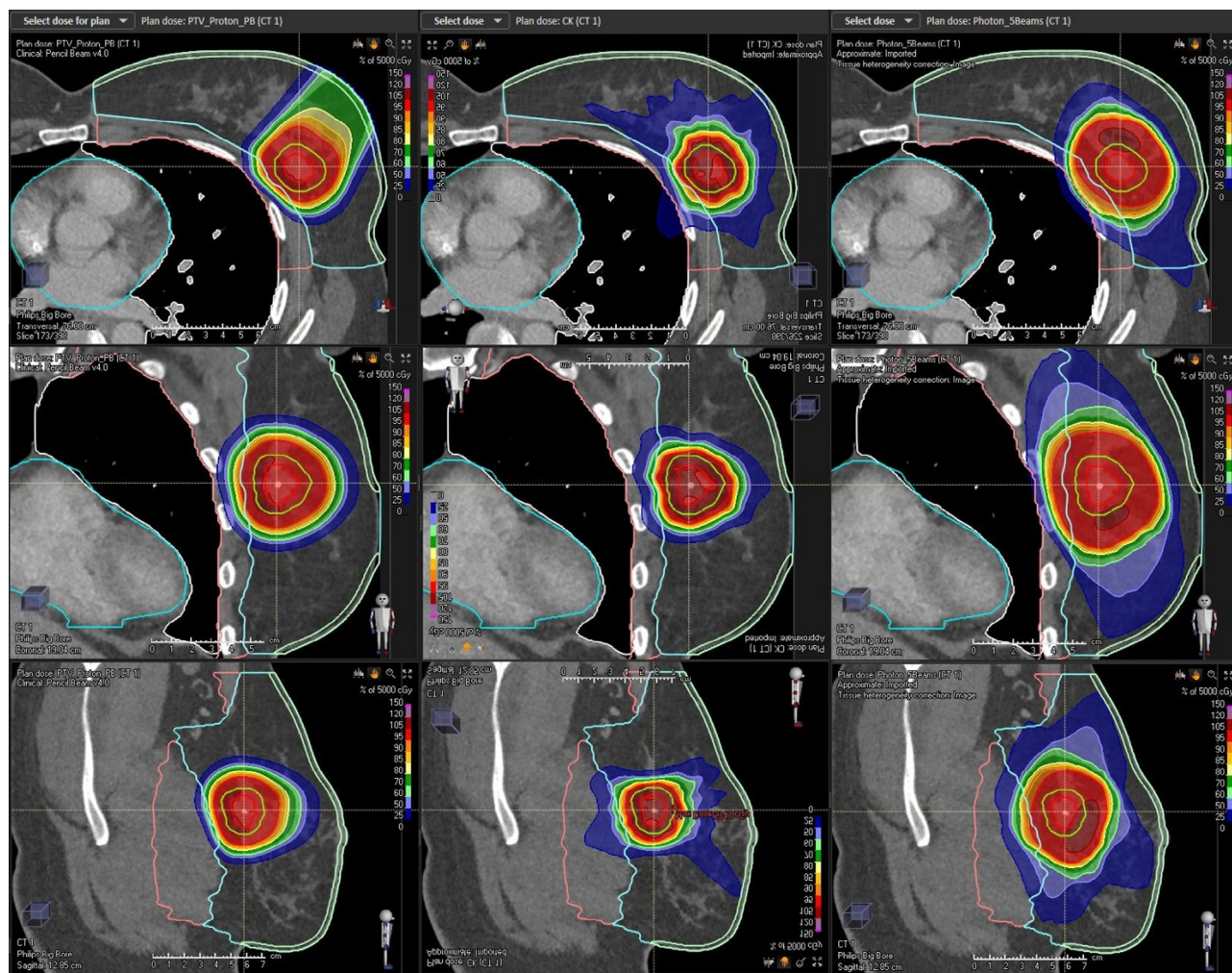


Figure 1 Tumor located in the left breast with gross tumor volume 6.70 mm away from the left chest wall and 3.77 mm away from the skin. All 3 modalities provide a conformal treatment plan with adequate dose coverage. The proton beam therapy (PBT) plan delivers less integral dose to the ipsilateral breast and ipsilateral chest wall and no dose to the ipsilateral lung and heart. Three-dimensional conformal radiation therapy delivers an additional high radiation dose to the chest wall relative to PBT and stereotactic ablative radiotherapy plans. PBT plan (left), stereotactic ablative radiotherapy (middle), and 3-dimensional conformal radiation therapy plan (right); axial (top), sagittal (middle), and coronal (bottom) planes.

Chest wall and skin dosimetry

The location of the tumor (from superficial to deep) dictated the achievability of the maximum-dose constraints for the skin and chest wall structures and interestingly was correlated with the radiation modality used. **Figure 4** illustrates GTV distance to the chest wall and skin versus the maximum OAR dose (D_{\max}). If GTV was within 7 mm of the chest wall, D_{\max} was similar among all 3 modalities and was typically 2 to 3 Gy higher than the prescription dose. However, when the GTV distance from the chest wall was >12 mm, both the PBT and SABR plans achieved D_{\max} doses of 12 to 15 Gy less than the corresponding 3D-CRT plans.

From 10 to 15 mm, SABR was nominally superior to PBT plans due to the larger expansions that were required

of the PBT in-beam direction relative to the SABR plans. Nevertheless, at greater distances, PBT plans approached 0 Gy to the chest wall. Overall, SABR and PBT plans demonstrated maximum chest wall doses that were significantly lower than the 3-dimensional CRT plans (46.0 ± 10.5 Gy and 46.2 ± 11.1 Gy vs 51.1 ± 6.2 Gy; $P = .033$ and $P = .024$, respectively). However, there was no significant difference between the PBT and SABR maximum chest wall doses ($P = .824$). Although the maximum chest wall dose constraints were challenging to meet, the volumetric constraint ($V_{40\text{ Gy}} < 31.5\text{ cm}^3$) was consistently achievable with all three modalities of treatment but optimal with SABR and PBT.

Similar to the chest wall D_{\max} , when the tumor was within 5 mm of the skin, all three modalities demonstrated

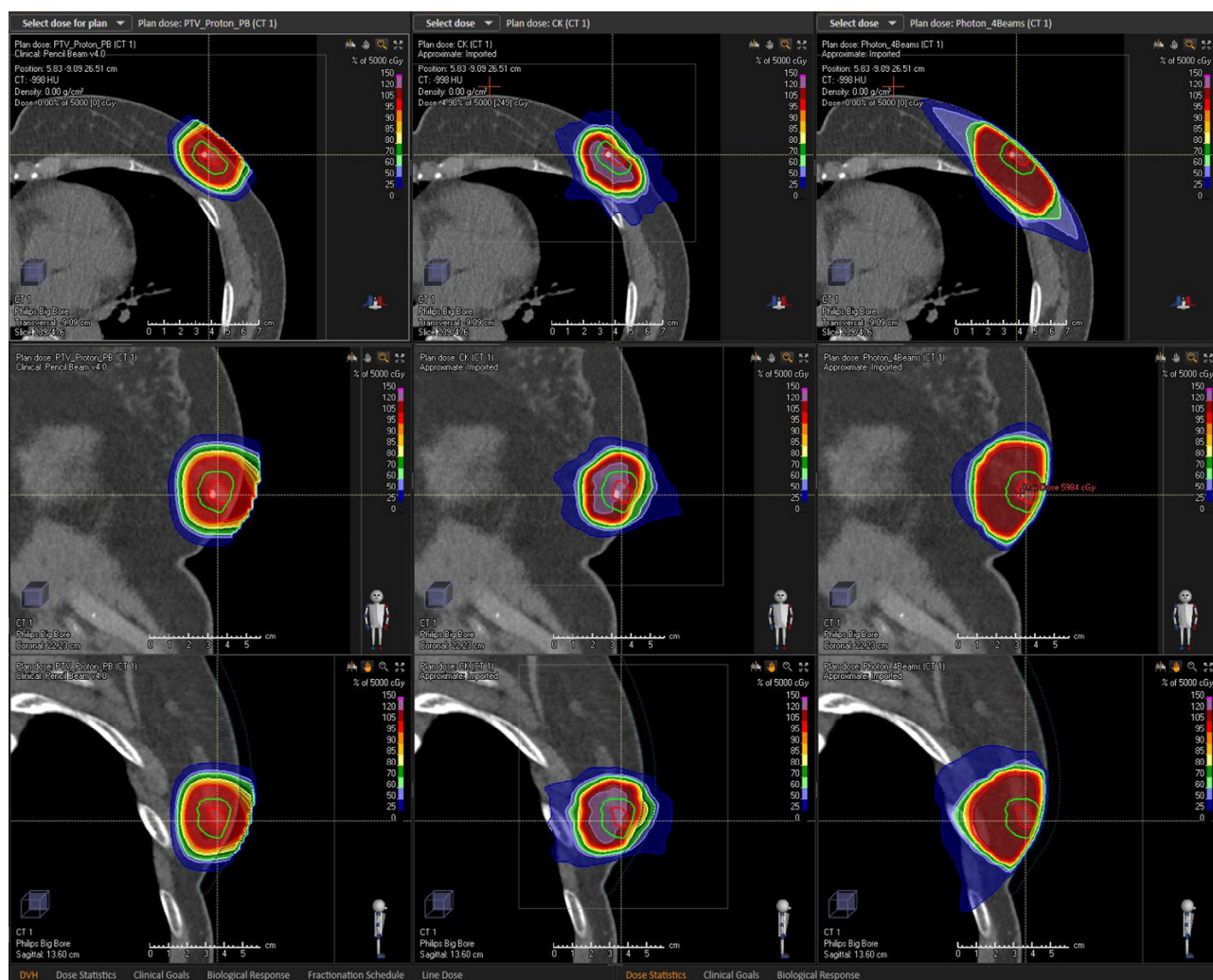


Figure 2 Tumor located in the left breast with gross tumor volume 15.8 mm away from the left chest wall and 1 mm away from the skin. Both proton beam therapy (PBT) and 3-dimensional conformal radiation therapy plans delivered moderately high skin doses relative to the stereotactic ablative radiotherapy plan that was able to achieve additional skin sparing. PBT plan (left), stereotactic ablative radiotherapy (middle), and 3-dimensional conformal radiation therapy plan (right); axial (top), sagittal (middle), and coronal (bottom) planes.

comparably high skin doses. From 5 mm to 10 mm, PBT plans seemed to deliver lower maximum skin doses relative to the other 2 modalities. Optimal skin sparing was achieved with SABR plans if the GTV lay ≥ 10 mm from the skin. PBT and 3-dimensional CRT plans achieved similar skin D_{max} doses after 15 to 20 mm.

Overall, SABR demonstrated maximum ipsilateral skin doses that were significantly lower than those of the 3-dimensional CRT plans (39.8 ± 12.2 Gy vs 46.5 ± 9.2 Gy; $P = .010$) and nominally but not significantly lower than those of the PBT plans (39.8 ± 12.2 Gy vs 42.9 ± 4.7 Gy; $P = .129$). There was a nonsignificant trend toward improvement with PBT versus 3-dimensional CRT in maximum skin doses ($P = .081$). Similar to the chest wall, the volumetric ipsilateral skin dose constraint ($V36.5$ Gy < 10 cm³) was achievable with all 3 treatment types with

significant improvements perceived in the SABR plans followed by the 3D-CRT and PBT plans.

Discussion

Herein, we report the dosimetric feasibility of SABR and PBT for the hypofractionated definitive treatment of early stage breast cancer. In this analysis, 3-dimensional CRT plans demonstrated lower PTV coverage and often delivered higher doses to normal structures relative to SABR and PBT plans, thus supporting the use of more advanced radiation delivery modalities. Intriguingly, SABR and PBT appeared to be feasible methods of dose delivery in the intact setting and allowed for significant minimization of normal tissue radiation, particularly for the lung, breast, and heart. Due

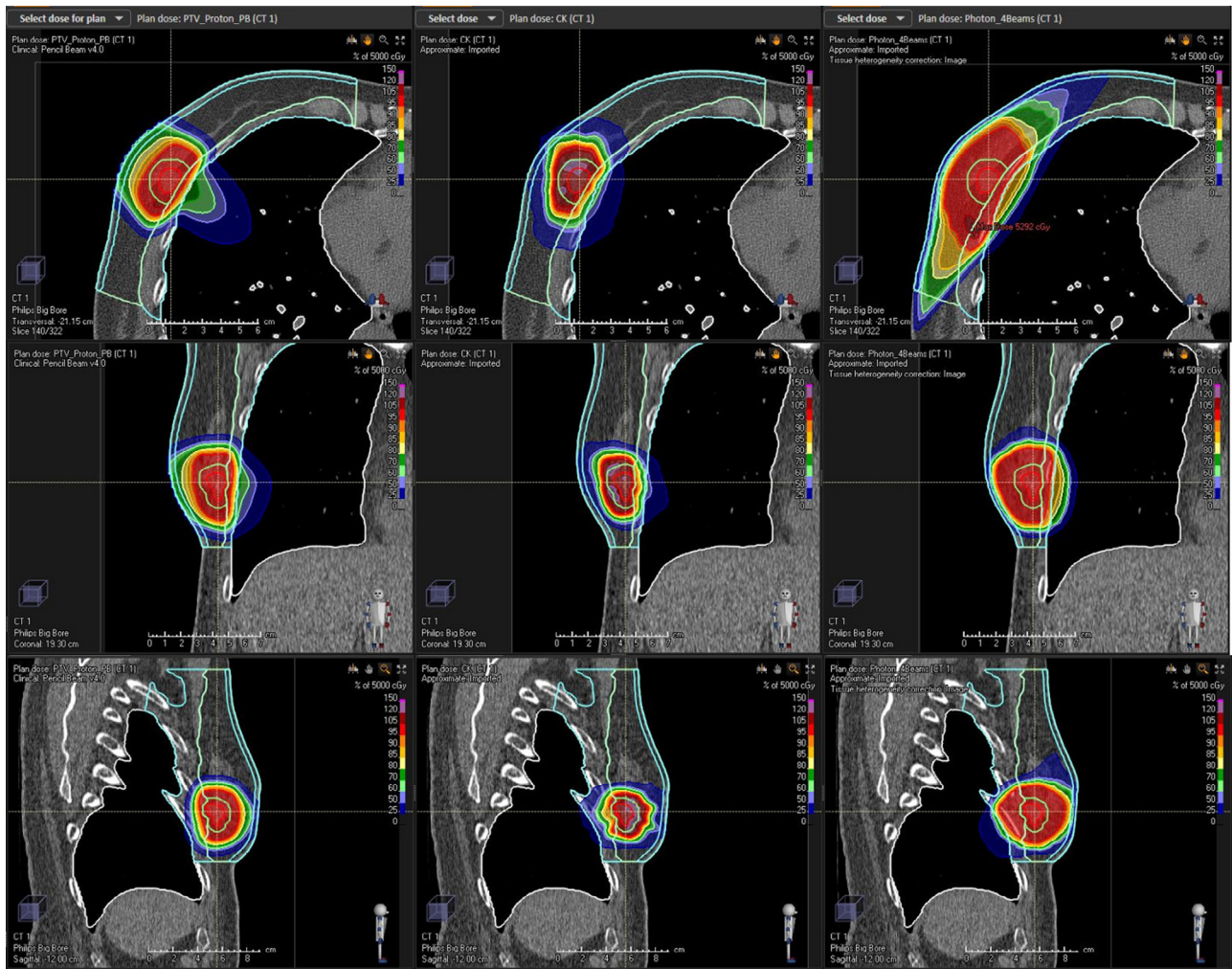


Figure 3 Tumor located in the right breast with gross tumor volume 1 mm away from the right chest wall and 16.3 mm away from the skin. Stereotactic ablative radiotherapy delivers a conformal treatment plan that minimizes intermediate dose fall off into the chest wall and lung relative to the proton beam therapy (PBT) plan. Again, the PBT plan delivers less integral dose to the ipsilateral breast, ipsilateral chest wall, and ipsilateral lung and no dose to the heart. PBT plan (left), stereotactic ablative radiotherapy (middle), and 3-dimensional conformal radiation therapy plan (right); axial (top), sagittal (middle), and coronal (bottom) planes.

to the unique properties of these radiation techniques, each modality offered target coverage and OAR dose reduction in a distinct manner.

However, the doses to the chest wall and skin frequently exceeded prespecified dose constraints and were intricately related to the anatomical location of the tumor. For tumors ≥ 1 cm away from the skin and chest wall, PBT was able to achieve outstanding and consistent target coverage while minimizing OAR doses, particularly integral doses to the lung, heart, and breast tissue. For more challenging tumors that sit closer to the skin, SABR offered target conformality and skin sparing that minimized the maximum doses. Although, maximum point doses to the skin and chest wall were both challenging to minimize in

certain anatomical locations, volumetric dose constraints were consistently achievable across platforms.

Nearly half of women aged ≥ 75 years will be diagnosed with breast cancer, and current trends indicate that standard-of-care treatment with breast-conserving surgery in this population is declining.² Historical data suggest very poor local control with hormone therapy alone and unacceptable toxicity with conventionally fractionated definitive whole-breast radiation therapy.^{7,8} The need for novel treatment modalities to achieve effective local control and reduce treatment-related toxicity is growing. Extrapolation of principles from the modern APBI realm offers a method of target volume reduction, dose escalation, and toxicity minimization in the definitive setting.²⁰ Contemporary methods of

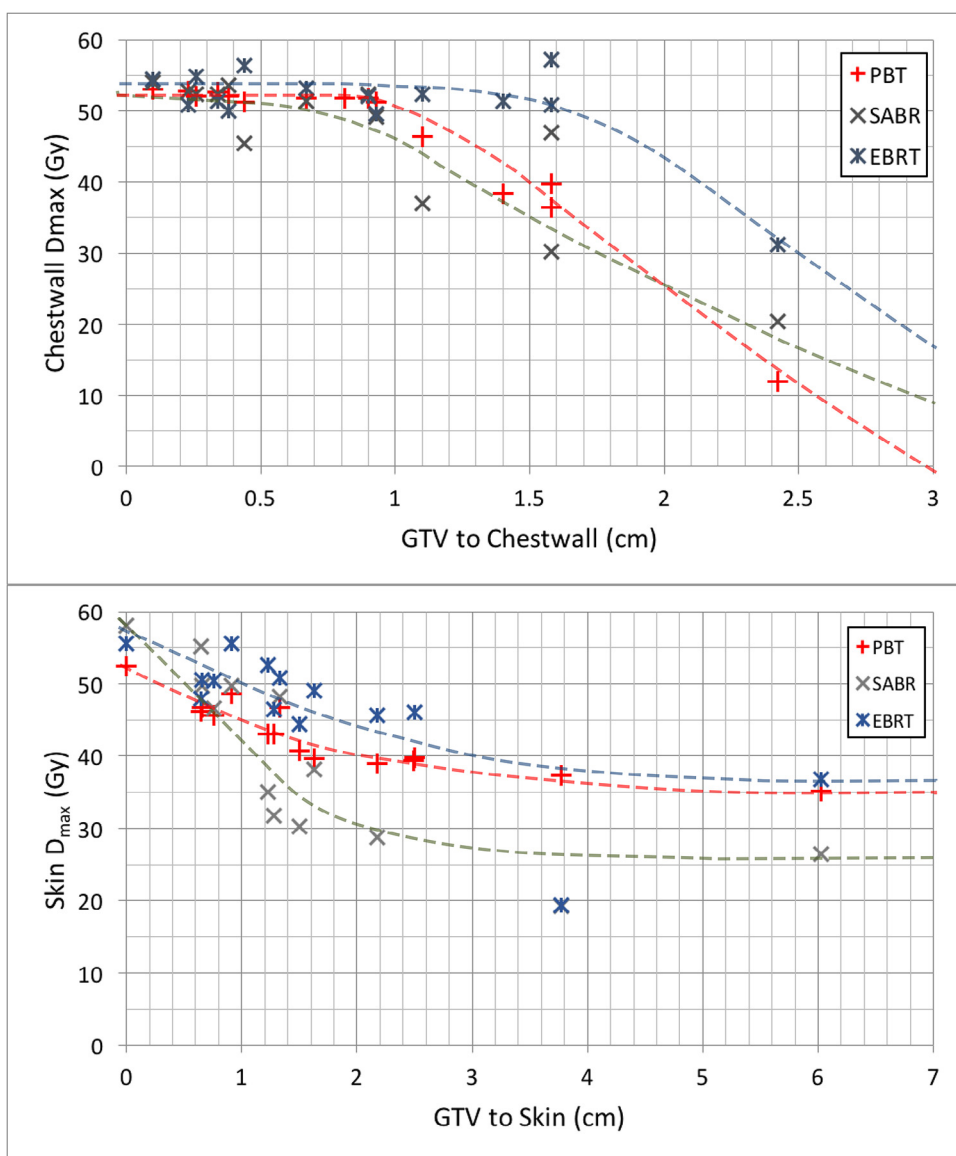


Figure 4 Gross tumor volume distance to the chest wall (top) and skin (bottom) versus chest wall and skin maximum organ-at-risk dose (Gy), respectively. Line of best fit is illustrated for each radiation modality 3-dimensional conformal radiation therapy (✖), proton beam therapy (+), and stereotactic ablative radiation surgery (x).

APBI delivery include SABR and PBT, both of which are used for an expanding variety of malignancies and are becoming more ubiquitous forms of radiation treatment in the United States.

Definitive radiation therapy for breast cancer in the operable patient population has been investigated by Van Limbergen et al., who reported on the 15.5-year follow-up of 221 patients with operable breast cancer treated with definitive radiation therapy.¹⁶ The most common fractionation schedules were 40 Gy in 4 weeks and 60 to 65 Gy in 8 to 10 weeks to the whole breast, with nearly half of these patients receiving a boost to the tumor site (most commonly 20 Gy in 10 fractions). They reported excellent 10-year rates of local control in tumors ≤ 1.0 cm and 1.1 to 3.0 cm of 96%

and 83%, respectively. Of note, each 1 cm increase in tumor diameter led to an 8% decrease in local control.

When compared with surgery plus adjuvant radiation in patients treated in the same era they found equivalent local control required a definitive radiation therapy dose of approximately 75 Gy to the tumor site. Arriagada et al. also reported a retrospective review of 463 patients with more advanced breast tumors treated with definitive radiation therapy. They analogously reported that improved local control was significantly associated with higher radiation dose and smaller tumor size.²¹ These data lend credence to the notion that long-term local control can be achieved with definitive radiation therapy and ablation is in fact dose-dependent and related to the primary tumor size.

Several factors have been established as affecting the late normal tissue toxicity after breast radiation, including smoking, breast size, surgical complications, radiation dose, hot spots, systemic therapy, and use of boost irradiation.²⁰ Clinical data now exist suggesting decreased volume of irradiated breast is correlated with a reduction in late toxicity consistent with what would be radiobiologically expected. Hepel et al. reported that large target to breast volume ratios in 3-dimensional CRT partial breast irradiation correlated with fair-to-poor cosmetic outcomes and grade 2-4 subcutaneous fibrosis.²²

The mean proportion of breast volume receiving prescription dose after partial breast irradiation was also correlated with poor cosmesis according to Jagsi et al.²³ As a result, there is growing clinical evidence that volumetric reduction of irradiated breast tissue may lead to improved cosmetic results. A recent report by Rahimi et al. in which 75 patients underwent partial mastectomy followed by stereotactic partial breast irradiation, up to 40 Gy in 5 fractions, reported physician-evaluated cosmetic outcomes as excellent or good in >95% of patients at all evaluated time points (up to 24 months).¹⁴ Additional research is required to determine whether small-volume breast radiation in tumors that are adjacent to the skin and chest wall and treated with ablative radiation doses also lead to acceptable cosmetic outcomes.

An additional investigation into nonsurgical modalities of treatment for high-risk surgical candidates with early stage breast cancer includes the use of radiofrequency ablation (RFA). Leylek et al. describe this novel technique, which utilizes percutaneously placed electrodes to produce local heat and ideally tumor ablation.²⁴ This procedure requires adequate tumor visualization on ultrasound and/or MRI targeting equipment and is limited to small tumors with a minimum distance of 1 cm between the treatment margin and the skin, nipple, and muscle.²⁴

This treatment is not without side effects, including skin burns, fat necrosis, bleeding, and needle tumor seeding. Skin burns appear to be the most common treatment-related side effect with an incidence that ranges from 4% to 33% in the literature.²⁴ Palussiere et al. published the results of a cohort of 21 inoperable patients with early stage breast cancer (tumor size ≤ 3 cm) who were treated with neoadjuvant endocrine therapy followed by RFA.²⁵ Although RFA achieved promising ablative outcomes in this group at 1 year, with a longer follow-up the 5-year local recurrence rate rose to 19%.²⁵ Improved local control may be possible to achieve with definitive radiation therapy but radiation may be limited similarly by tumor distance to the skin.

Neoadjuvant, single-fraction, partial breast irradiation has been studied as a means to reduce the large postoperative volumes that are required for 3D-CRT partial breast irradiation. Horton et al. recently published data on a cohort of 32 patients with favorable early stage breast cancer (size ≤ 2 cm) treated with preoperative single-fraction intensity

modulated radiation therapy.¹² Single-fraction doses of 15 Gy, 18 Gy, and 21 Gy were delivered to tumors with a 1.5 cm margin and lumpectomy was performed 10 days later. At a median follow-up of 23 months, the authors noted no local recurrences or dose-limiting toxicities. Cosmetic outcomes were all good/excellent and late toxicities included grade 1 to 2 hyperpigmentation and fibrosis. Continued investigation into preoperative radiation may identify a favorable subset of patients who can achieve pathologic complete responses with high-dose preoperative radiation.

Limitations of the present study include the finite number of patients and tumor locations (particularly relative to the skin and chest wall) that were used for dosimetric analysis. The utilization of this technique is also dependent on the accurate identification of tumor GTV on preoperative imaging, which could theoretically be nebulous in some cases but was not our institutional experience. In fact, CT-based tumor size correlated well with actual pathological tumor dimensions. In addition, institutional variations in set-up uncertainty and image guidance capabilities dictate PTV margins necessary for treatment and have important implications on comparative dosimetry among the three modalities of treatment that are explored in this report.

Finally, future PBT dosimetric studies should include dose differences as a consequence of variations in linear energy transfer as a function of spot location. Future research should evaluate a larger cohort of patients with a more heterogeneous group of tumor sizes and locations. Additional trials should also explore the clinical outcomes of well-selected nonsurgical patients with small breast tumors treated with definitive SABR and PBT, particularly with respect to clinical skin and chest wall toxicity.

Conclusions

This dosimetric analysis supports the feasibility of SABR and PBT hypofractionated, definitive treatment for early stage breast cancer. On the basis of these results, significant normal tissue sparing appears to be achievable, especially for the breast, lung, and heart. Nevertheless, careful attention must be paid to the location of the tumor relative to the skin and chest wall to determine patient eligibility and toxicity risk. In an era when surgical resection of early stage breast cancer in elderly patients seems to be in decline, the exploration of minimally toxic, noninvasive treatment alternatives are important in cases of medical inoperability or patient refusal of surgery. Prospective clinical trials will be crucial to explore the safety and efficacy of definitive SABR and PBT in the future.

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