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Dosimetric Plan Comparison of Accelerated Partial Breast Irradiation (APBI) Using CyberKnife

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Accelerated partial breast irradiation (APBI) is a new treatment delivery technique that decreases overall treatment time by using higher fractional doses than conventional fractionation. Here, a quantitative analysis study of CyberKnife-based APBI was performed on 10 patients with left-sided breast cancer who had already finished conventional treatment at the Inha University Hospital. Dosimetric parameters for four kinds of treatment plans (3D-CRT, IMRT, VMAT, and CyberKnife) were analyzed and compared with constraints in the NSABP B39/RTOG 0413 protocol and a published CyberKnife-based APBI study. For the 10 patients recruited in this study, all the dosimetric parameters, including target coverage and doses to normal structures, met the NSABP B39/RTOG 0413 protocol. Compared with other treatment plans, a more conformal dose to the target and better dose sparing of critical structures were observed in CyberKnife plans. Accelerated partial breast irradiation via CyberKnife is a suitable treatment delivery technique for partial breast irradiation and offers improvements over external beam APBI techniques.

Keywords: APBI, Cyberknife, Treatment planning

Introduction

Breast-conserving therapy (BCT) is the preferred treatment for early-stage breast cancer, and numerous published studies have shown that equivalent overall survival between patients who received breast-conserving surgery with whole breast irradiation (WBI) and patients treated by mastectomy alone. These studies demonstrate a 70% reduction in local recurrence, with the addition of adjuvant radiation after breast-conserving surgery.[1,2] However, researchers have estimated that up to 25% of patients have not received adjuvant radiation therapy after breast conservation surgery.[3] Prolonged treatment time, cost, distance to treatment facilities, and patient inconvenience have been implicated as possible deterrents to BCT.[4,5]

Accelerated partial breast irradiation (APBI) is a new treatment delivery technique that decreased overall treatment time by using higher fractional doses than conventional fractionation. As opposed to whole breast irradiation, the dose is only given to the resection volume. Various techniques have been tried and complete reviews of APBI techniques can be found in the literature.[6,7]

Applying to three-dimensional conformal radiation therapy (3D-CRT) and the NASBP B-39/RTOG0413 dose guidelines, Hepel et al.[8] found a severe late toxicity in six of 60 patients who were treated with APBI. Recht at el.[9] observed a higher risk of pneumonitis in patients with APBI who were treated with 3D-CRT. In other to reduce the dose to organs at risk (OAR), other treatment modalities have been used for APBI, including intensity modulated radia-

tion therapy (IMRT), tomotherapy, and proton therapy. IMRT showed improved ipsilateral breast and other normal tissue dose sparing compared with 3D-CRT, with very low acute toxicity.[10] Tomotherapy also reduced the dose to ipsilateral breast tissue, but at the cost of considerable increases in lung and heart doses. Protons have proven dosimetrically superior to all these techniques, but their availability is limited to a few centers globally.[11]

A frameless robotic stereotactic radiosurgery system, the CyberKnife (Accuray Incorporated, Sunnyvale, CA, USA) provides image-guidance for the continuous tracking of target motion during respiration and patient movement. In the context of APBI, the Cyberknife could spare non-target breast tissue volume (NTBTV) more efficiently and potentially, which allows more agreeable cosmetic outcomes due to the combination of non-coplanar fields with tracking of the target volume. Indeed, researchers at the University of Texas Southwestern Medical found that APBI treatment plans achieved highly conformal target coverage with sparing doses to OAR, relative to 3D-CRT plans.[12] Fox Chase's treatment planning study has come to a similar conclusion as improving the boost dose distribution produced by CyberKnife.[13] Here, a quantitative analysis study of CyberKnife-based APBI was performed on 10 patients with left-sided breast cancer who had already finished conventional treatment at the Inha University Hospital.

Materials and Methods

1. Patient selection

After Institutional Review Board (IRB) approval was obtained, 10 previously treated patients with left-sided breast cancer were selected for our retrospective study. Patients for CyberKnife-based APBI were selected over 50 years of age with stage I and II histologically-confirmed invasive non-lobular carcinoma or ductal carcinoma in situ (DCIS). All patients were treated with 50.4 Gy in 28 fractions, in a conventional fractionation. Further patient details are listed in Table 1.

2. Acquisition and definition of treatment volumes

A radiotherapy treatment planning CT scan was acquired for each patient. Patients underwent standard CT simulation at 2.5 mm slice spacing, in the supine position, not using a breast board. The gross tumor volume (GTV) was identified on the planning CT based on clear visualization and/or with the help of surgical clips. The clinical target volume (CTV) was obtained by a uniform 10 mm expansion of the GTV. The planning target volume (PTV) was delineated as the CTV expanded by a margin of 2 mm, to account for setup uncertainties. All plans were calculated for each patient using same PTV margin for technique comparison purposes. This comparison allowed us to

Table 1. Patient and tumor characteristics for the ten patients with ten treated tumors.

Characteristic	Value
Age (years)	
Mean	60
Range	50~78
Tumor type	
DCIS	0
IDC	10
Tumor stage	
Tis	0
T1a	1
T1b	2
T1c	3
T2	4
GTV (cm^3)	
Mean	6.4
Range	3.5~11.2
PTV (cm^3)	
Mean	37.7
Range	21.3~65.1
Tumor laterality	
Right	0
Left	10
Quadrant	
UOQ	6
UIQ	3
Central	1
LOQ	0
LIQ	0

IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ; UOQ, upper outer quadrant; UIQ, upper inner quadrant, LIQ, lower inner quadrant.

Table 2. Constraints given by the NSABP B39/RTOG 0413 protocol for patients treated with CyberKnife SAPBI.

Structure	Constraint
Ipsilateral breast	$V_{30\,Gy}$<35%
	$V_{15\,Gy}$<60%
Contralateral breast	D_{max}<1 Gy
Ipsilateral lung	$V_{9\,Gy}$<15%
Contralateral lung	$V_{1.5\,Gy}$<15%
Heart (left breast)	$V_{1.5\,Gy}$<40%
Heart (right breast)	$V_{1.5\,Gy}$<5%
Thyroid	D_{max}<1 Gy
Skin	D_{max}<36 Gy
Chest wall	D_{max}<36 Gy

SAPBI, stereotactic accelerated partial breast irradiation; NSABP, National Surgical Adjuvant Breast and Bowel Project; RTOG, Radiation Therapy Oncology Group.

evaluate the dosimetric characteristics of both planning systems at the same target volume. The CTV and PTV were limited to 3 mm from the skin surface and the chest wall, and lungs were not included in the PTV and CTV volumes. The OAR considered in this study were ipsilateral, contralateral breast, ipsilateral, contralateral lung, heart, thyroid, chest wall, and skin.

3. Delineation and treatment planning

The CT images were exported to Eclipse treatment planning system (Version 8.6) and MultiPlan treatment planning system (Version 2.2.0). The Phase III NSABP B39/RTOG 0413 partial breast protocol was followed for structure delineation and planning. The structures contoured for planning were the lumpectomy cavity or GTV, CTV, PTV, ipsilateral, contralateral breast, ipsilateral, contralateral lung, and heart. The eclipse-planned technique were 3D-CRT, IMRT, and volumetric modulated arc therapy (VMAT). The 3D-CRT and IMRT plans were generated using a 5-field and 4-field coplanar technique, respectively. The VMAT plans were generated using RapidArc with anisotropic analytical algorithm (AAA). A double partial arc of 180° to 200° around the treated breast was used. The CyberKnife plans were generated using the iterative optimization mode to achieve the optimal dose to the target and normal structures. We used the fiducial marker tracking method. Prior to treatment, four 2-mm gold fiducials were implanted around the lumpectomy site under ultrasound guidance by a single board-certified radiologist. Depending on the size of the tumor, 1-2 fixed collimator ranging from 10 to 15 mm were chosen. Approximately, 95% of the PTV was to receive 100% of the prescription dose. All plans were generated to deliver 30 Gy in five fractions to the PTV over consecutive days.

4. Dosimetric parameters for plan comparison

For all treatment plans, dosimetric parameters calculated for the OARs are listed in Table 2. Here V_{30Gy}, V_{15Gy}, V_{9Gy}, and $V_{1.5Gy}$ represent the percentage volumes of the normal organs receiving 30 Gy, 15 Gy, 9 Gy, and 1.5 Gy doses, respectively. D_{max} is the maximum dose received by 1% of the evaluated OAR volumes. The dose conformity index (CI) for each plan was also calculated based on the Radiation Therapy Oncology Group (RTOG) definition[14]: $CI_{RTOG}=V_{RI}$ / TV

where V_{RI}=100% reference isodose volume (the volume receiving 100% prescription dose) and TV=target volume.

For the purpose of this study, cumulative dose-volume histograms of the normal structures were used for observation. Dosimetric parameters during these four treatment plans (3D-CRT, IMRT, VMAT, and CyberKnife) were analyzed and compared to constraints in the NSABP B39/RTOG 0413 protocol and a published CyberKnife-based APBI study. The total MUs for all plans were calculated and analyzed.

Results and Discussion

For the 10 patients recruited in this study, all the dosimetric parameters, including target coverage and doses to normal structures, met the NSABP B39/RTOG 0413 protocol, except for the contralateral breast maximum dose constraint as shown in Table 3. The PTV coverage requirement in the protocol is $V_{90\%}$>90%, which means that the percentage volume receiving 90% of the prescription dose should be greater than 90%. In our study, the mean percentage volume covering 100% of the prescription dose was 96.5±0.7%, which was more conformal than the target dose required in the protocol. The average CI for all

Table 3. Dosimetric parmeters from plans based on the NSABP B39/RTOG 0413 protocol.

Structure and dosimetric parameters	NSABP B39/ RTOG 0413 Protocol	Min (%)	Max (%)	Mean (%)	Std (%)
Ipsilateral breast	$V_{30\ Gy}$<35%	2	22	10	6.6
	$V_{15\ Gy}$<60%	5	48	24	12.9
Contralateral breast	D_{max}<1 Gy	1 Gy	8 Gy	3 Gy	3.1 Gy
Ipsilateral lung	$V_{9\ Gy}$<15%	0	9	3	2.6
Contralateral lung	$V_{1.5\ Gy}$<15%	0	20	9	5.7
Heart (left breast)	$V_{1.5\ Gy}$<40%	4	36	23	10.6
Thyroid	D_{max}<1 Gy	0 Gy	1.5 Gy	1 Gy	0.2 Gy
Skin	D_{max}<36 Gy	29 Gy	34 Gy	31 Gy	1.5 Gy
Chest wall	D_{max}<36 Gy	23 Gy	35 Gy	31 Gy	3.2 Gy
Coverage of PTV	>90%	95	97.6	96.5	0.7
CI		1.1	1.35	1.2	0.1

Table 4. Comparison of our dosimetric parameters to other CyberKnife studies.

Structure and dosimetric parameters	CyberKnife (mean, range)	Olusola et al (mean, range)	Sndra et al (mean, range)
Ipsilateral breast	10%, 2-22%	14%, 3-26%	11%, 8-13%
	24%, 5-48%	31%, 8-58%	23%, 16-30%
Contralateral breast	3 Gy, 1-8 Gy	3 Gy, 0-11 Gy	1 Gy, 1-2 Gy
Ipsilateral lung	3%, 0-9%	3%, 0-17%	5%, 0-10%
Contralateral lung	9%, 0-20%	8%, 0-21%	6%, 2-10%
Heart (left breast)	23%, 4-36%	31%, 7-43%	40%, 25-54%
Heart (right breast)	NA	18%, 0-37%	NA
Thyroid	<1 Gy, 0-1.5 Gy	<1 Gy, 0-1.4 Gy	<1 Gy, 0-1 Gy
Skin	31 Gy, 29-34 Gy	32 Gy, 28-36 Gy	33 Gy
Chest wall	31 Gy, 23-35 Gy	26 Gy, 13-33 Gy	30 Gy

the plans was 1.2±0.1%. The mean $V_{15\ Gy}$ and mean $V_{30\ Gy}$ to the ipsilatearal breast were 24.0±12.9% and 10.0±6.6%, which were well below 60% and 35% of the total volume, as required in the protocol. The maximum dose to the contralateral breast was relatively difficult to meet, depending on the distance between the tumor and the contralateral breast. The maximum doses to the contralateral breast for all 10 patients varied from 1.0 Gy to 8.0 Gy. The mean $V_{1.5\ Gy}$ and mean $V_{9\ Gy}$ to the contralateral and ipsilateral lungs were 9.0±5.7% and 3.0±2.6%, respectively. The means of $V_{1.5\ Gy}$ to the heart was 23.0±10.6%. The CyberKnife plan was designed to deliver a multiple, non-isocentric, non-coplanar beam set. For this reason, the CyberKnife plan is more likely to pass through the contralateral breast than other plan techniques. The CyberKnife has the function of arbitrarily limiting the beam intersection to the tumor or OAR. If this function is used well without reducing target coverage, it may be possible to control maximum doses of contralateral breast.

We also compared our planning results to the published data from the studies of Olusola et al. and Sndra et al., which followed a similar protocol. We extracted all the corresponding dosimetric parameters for our 10 patients and compared these parameters to the data of Olusola et al. and Sndra et al. as shown in Table 4. Dosimetric data from CyberKnife studies were very close for the ipsilateral and contralateral breast and the ipsilateral and contralateral lungs. However, in our planning study, the mean $V_{1.5\ Gy}$ doses to the heart were lower than those of the published data.

Our quantitative analysis study results is superior to the previously published work from Xu et al.,[15] who showed the feasibility of using the CyberKnife for APBI. Their work proposed the dosimetric comparison of treatment plans

Table 5. Comparison of our dosimetric parameters to 3D-CRT, IMRT, and VMAT plan.

Structure and dosimetric parameters	Constraint	CyberKnife (mean, range)
Ipsilateral breast	$V_{30\ Gy}$<35%	10%, 2-22%
	$V_{15\ Gy}$<60%	24%, 5-48%
Contralateral breast	D_{max}<1 Gy	3 Gy, 1-8 Gy
Ipsilateral lung	$V_{9\ Gy}$<15%	3%, 0-9%
Contralateral lung	$V_{1.5\ Gy}$<15%	9%, 0-20%
Heart (left breast)	$V_{1.5\ Gy}$<40%	23%, 4-36%
Thyroid	D_{max}<1 Gy	<1 Gy, 0-1.5 Gy
Skin	D_{max}<36 Gy	31 Gy, 29-34 Gy
Chest wall	D_{max}<36 Gy	31 Gy, 23-35 Gy
CI		1.2
MU		12138

Structure and dosimetric parameters	3DCRT (mean, range)	IMRT (mean, range)	VMAT (mean, range)
Ipsilateral breast	16%, 4-33%	12%, 5-24%	12%, 2-25%
	33%, 9-67%	33%, 8-59%	25%, 5-57%
Contralateral breast	3 Gy, 0-12 Gy	5 Gy, 3-13 Gy	2 Gy, 2-5 Gy
Ipsilateral lung	8%, 1-12%	2%, 0-9%	6%, 0-14%
Contralateral lung	26%, 17-36%	10%, 0-23%	13%, 1-41%
Heart (left breast)	58%, 32-94%	29%, 11-65%	43%, 28-59%
Thyroid	<1 Gy, 0-0.1 Gy	<1 Gy, 0-0.1 Gy	<1 Gy, 0-0.1 Gy
Skin	30 Gy, 27-32 Gy	31 Gy, 29-33 Gy	31 Gy, 26-36 Gy
Chest wall	31 Gy, 21-36 Gy	30 Gy, 10-33 Gy	32 Gy, 19-38 Gy
CI	1.8	1.3	1.3
MU	749	1285	2433

that were calculated for 14 patients to previously published results obtained using 3D-CRT and IMRT. However, the results were somewhat limited because the authors compared their planning results to published data that was based on IMRT and 3D-CRT. Using different plans calculated for the same patients, we were able to compare mean DVHs for a better evaluation of the differences between techniques.

Table 5 shows mean dosimetric data computed for each treatment technique, and the corresponding mean DVHs are displayed in Fig. 1 for all treatment techniques. Dosimetric data for the contralateral breast and contralateral lung between techniques are very similar. In contrast, as shown in Fig. 1a, 1c, 1e, and 1f, DVHs of theses OARs show significant differences between techniques. These differences could relate to the more conformal beam arrangement in CyberKnife treatment, since the beams could enter the patient body from many angles. Significant differences were found between CyberKnife and all other techniques for the volumes receiving 15 Gy ($V_{15\ Gy}$) and 25 Gy ($V_{25\ Gy}$) of the ipsilateral breast and chest wall. Also, significant differences in the volume of the heart and ipsilateral lung receiving less than 5 Gy were observed.

The mean total MUs and standard deviations are 12138±3121 for CyberKnife plans, 749.3±32.7 for 3D-CRT plans, 1284.6±181.8 for IMRT plans, and 2432.5±1580.8 VMAT plans. The total MU with 3D-CRT plans was significantly lower than that of IMRT (mean total MU reduction ratio of 41.7%), VMAT (mean total MU reduction ratio of 69.2%), and CyberKnife (mean total MU reduction ratio of 93.8%) plans. Using the CyberKnife system with fixed collimator, treatment time including patient set-up on treatment couch was approximately 60 min, with a range from ~40 min to ~90 min. The longer time (90 min) was limited to the initial treatments and was a consequence of the inexperience of the team, especially in the patient setup

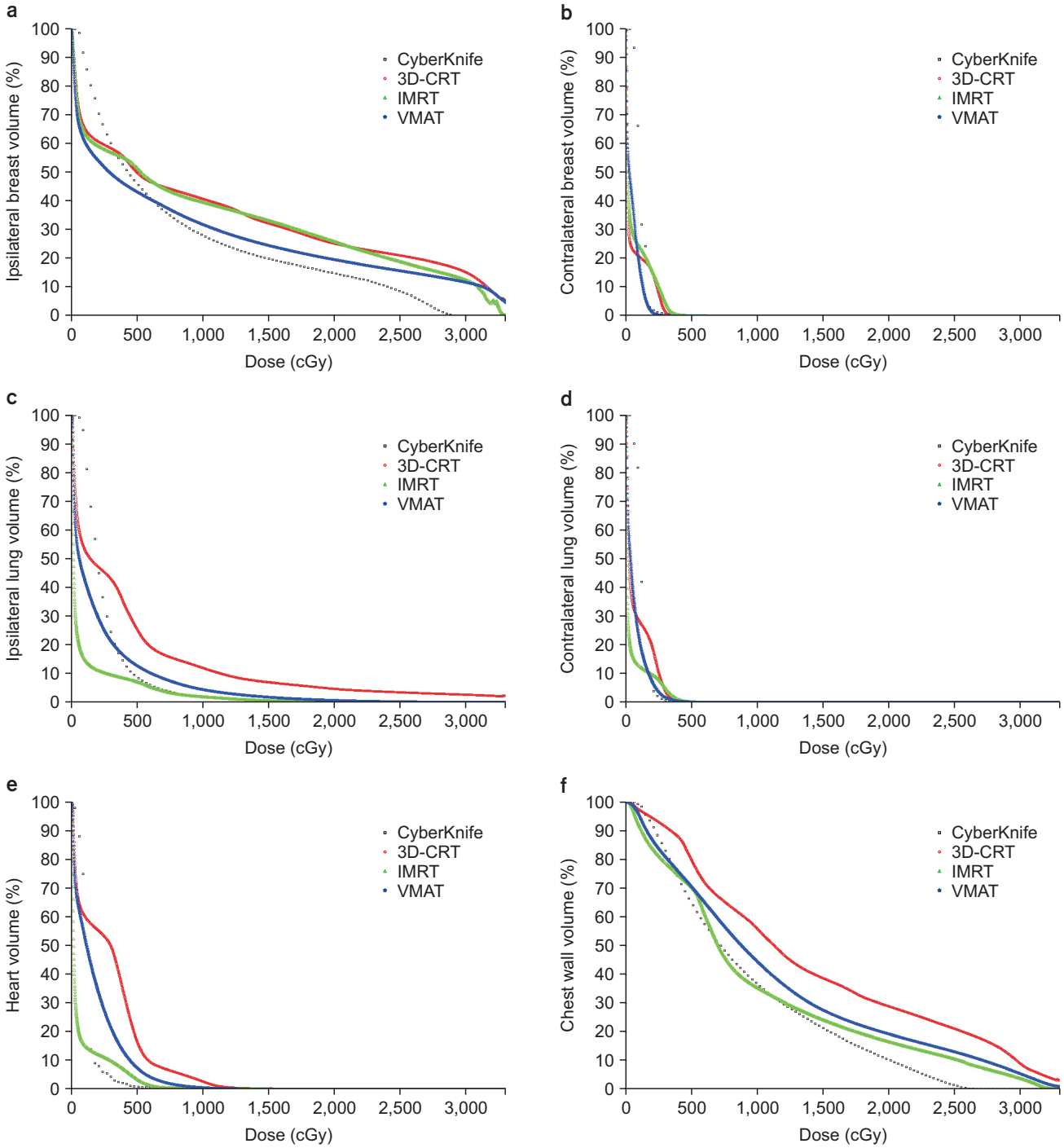

Fig. 1. Mean DVH data for ipsilateral breast (a), contralateral breast (b), ipsilateral lung (c), contralateral lung (d), heart (e), cheat wall (f).

and fiducial alignment phase. In general, larger breasts were associated with increased mobility, requiring longer patient set-up time. Time is important for the efficiency of treatment, but it is more meaningful when accuracy is involved. Although the treatment time of the CyberKnife is longer than other plan techniques, the PTV margin is unnecessary because the CyberKnife is tracked target volume considering the respiration of the patient. Therefore, the CyberKnife plan can save NTBTV and improve the accuracy of treatment over other plan techniques.

For a fairer comparison, it would have been interesting to compute doses using the same algorithm for each of the two modalities. However, we believe that the results obtained on NTBTV are too important to be a result of the dose calculation algorithm. It would also be interesting to calculate dose distributions on four-dimensional computed tomography (4DCT), to further investigate the benefit of tracking. Unfortunately, 4DCTs were not available for the selected patients.

Using Synchrony to track respiratory motions could reduce PTV margins and thus reduce the dose delivered to the NTBTV. However, the fiducial markers must follow the target volume shift inside the patient. Titanium surgical clips are used for delineating the excision volume after surgery. Surgical clip tracking has the advantage of not requiring additional implantation of fiducial markers. Implantation of fiducial markers is an additional invasive act for a patient. If these clips are visible in CyberKnife's tracking system, the implantation of fiducial markers is no longer necessary. On the other hand, there may be no surgical clip depending on the surgery protocol of institution.

The CyberKnife does not require the extra margin to compensate for treatment set-up and breathing motion. As such, we believe that the steep dose gradients that are characteristic of CyberKnife APBI will allow more than acceptable cosmetic results and low toxicity over the long-term.

Conclusion

For the 10 patients who were recruited in this study, all the dosimetric parameters, including target coverage, and doses to normal structures, met the NSABP B39/RTOG 0413 protocol. Compared to other treatment plans, a more conformal dose to the target and better dose sparing of critical structures were observed in CyberKnife plans. Accelerated partial breast irradiation via CyberKnife is a suitable tretment delivery technique for partial breast irradiation and offers improvements over external beam APBI techniques.

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Conflicts of Interest

The authors have nothing to disclose.

Availability of Data and Materials

All relevant data are within the paper and its Supporting Information files.

Ethics Approval and Consent to Participate

The study was approved by the institutional review board [IRB approval number; 2017-11-002-003].

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