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A Dosimetric Comparison between Three Different External Photon Beam Techniques for Accelerated Partial Breast Irradiation

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Abstract

Objectives: To evaluate the advantages and limits of CyberKnife (CK) compared to the two external beams Radiotherapy (RT) Techniques, Three Dimensional Conformal Therapy and Volumetric Modulated Arc Therapy(3D-CRT and VMAT) for Accelerated Partial Breast Irradiation (APBI). A dosimetric study was conducted with special focus on dose to organs at risk (OAR), target coverage and technical features.

Methods: Ten consecutive early-stage breast cancer patients were selected and for each one of them, three treatment plans were generated for 3DCRT, VMAT and CK. Dosimetric parameters, extracted from the dose volume histograms, were used to evaluate the differences in terms of PTV coverage and OAR sparing among the irradiation techniques. Conformity Index (CI) and Homogeneity Index (HI) were also compared.

Results: VMAT and CK provided equivalent dose conformity, with CIs significantly higher compared to 3D-CRT technique. Besides, VMAT achieved the best results in terms of HI and target coverage ($p<0.05$). Significant differences were observed in the OAR dosimetric data, except for heart. 3DCRT achieved the best results in terms of the dose to the whole contra-lateral breast as regards technical features. The treatment session time is usually longer for CK (on average 60 min) than for VMAT and 3DCRT techniques (15 to 20 min).

Conclusion: In this dosimetric comparison, all RT techniques are feasible to deliver APBI.CK and VMAT provide higher conformity than 3D-CRT, although with 3D-CRT we observed a reduction of the dose to the OAR. In CK treatment organ motion is controlled and, despite the longer treatment times, the delivery accuracy is expected to be better than 3D-CRT and VMAT, especially if motion management systems are not used. Advances in Knowledge: 1) CK treatment allows to reduce safely the PTV margin, achieving both optimal PTV coverage and a better sparing OAR. 2) This study can provide an important guidance to select the right RT technique for APBI.

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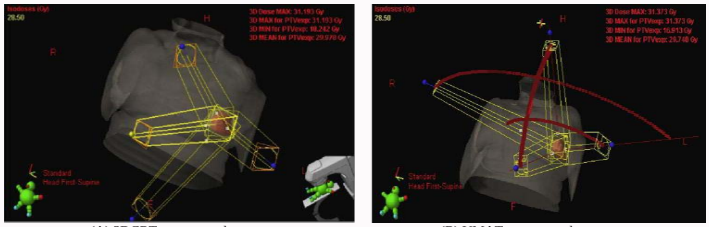
Introduction

Breast radiotherapy (RT) after breast-conserving surgery is known to reduce the risk of any breast cancer recurrence by a half and related mortality by a sixth in patients with early breast cancer [1]. While whole-breast RT actually remains the standard of care, consensus statement of the American Society for Radiation Oncology and the European Society for Radiotherapy and Oncology recommended partial breast RT for selected patients at low risk of recurrence because of age, small tumor size and early stage [2,3]. The rationale for investigating partialbreast RT is based on the evidence that the large majority of local recurrences in breast cancer after breast conserving treatment is close to the original tumor site [4,5]. This evidence suggested restricting the RT target to the surgical cavity in selected patients. With a reduced irradiation target volume, patients can tolerate an accelerated regimen of irradiation with an increased daily dose and a significant



(A) 3DCRT treatment plan (B) VMAT treatment plan

(C) CyberKnife treatment plan

Figure 1: Examples of (A) 3D-CRT with 4 beams (2 coplanar and 2 non-coplanar), (B) VMAT with partial coplanar and non-coplanar arcs, and (C).CK with non-isocentric non-coplanar beam arrangement.

reduction in overall times. An additional theoretical advantage of accelerated partial breast irradiation (APBI) is a decreased dose to normal tissue. This way, APBI should allow reducing RT morbidity without compromising its ability to cure the cancer. There are a number of approaches now available for the implementation of APBI, i.e.: multi-catheter interstitial brachytherapy [6-9], balloon catheter brachytherapy [10-12], external beam radiation therapy (EBRT) [13-15] and intraoperative radiation therapy [16]. All these techniques show different and peculiar characteristics in terms of degree of invasiveness, radiation delivery, operator proficiency, acceptance between radiation oncologists and length of treatment [17]. Specifically, EBRT has potential advantages over brachytherapy, among which being non-invasive, less operator dependent, and having acceptable cosmetic outcome. The main techniques in use for EBRT are 3- dimensional conformal radiation therapy (3D-CRT) [13,18] and intensity-modulated radiation therapy (IMRT) [19], the latter being frequently delivered as Volumetric Modulated Arc Therapy (VMAT) [20]. CyberKnife (CK) has emerged as a possible alternative to conventional techniques for APBI, although there is still a reduced experience with this technique up to now [21-23]. Since June 2013, a prospective non-randomized trial, designed to assess the toxicity, cosmesis and the feasibility of CK treatments for APBI, started as cooperation between two Institutes in Milan. To evaluate the advantages and limits of CK compared to the two EBRT techniques (3D-CRT and VMAT) normally employed for APBI, a dosimetric study was conducted with special focus on dose to normal breast tissue and (OAR), and on target coverage and technical.

Materials and Methods

Ten consecutive patients with stage I-IIA histologically confirmed breast carcinoma, with tumorfree inked histologic margins at surgical resection and enrolled in the clinical trial NCT02896322 [24] were selected for the study. For each patient, a planning CT scan (1.5 mm slice thickness) was obtained, from the skull base to the diaphragm, in supine position with the arms lying along the body to ensure a comfortable position during CK treatment. Three gold fiducials were placed in the walls of the surgical cavity at the time of lumpectomy to allow CK to track respiratory motion. The clinical target volume (CTV) was defined as tumor bed (GTV, gross target volume) plus a 15 mm margin to take into account subclinical disease extension; CTV was limited to 5mm below the body surface, muscles and chest wall. The planning target volume (PTV) was obtained as a CTV isotropic expansion of 5 mm to take into account organ motion and setup errors, clipped 5 mm into body surface anteriorly and bounded by posterior breast extent. Heart, bilateral lungs, thyroid, ipsi- and contra-lateral breasts were separately contoured as OAR according to RTOG guidelines [25]. The non-target breast volume was then obtained by subtracting the PTV from the ipsi-lateral breast volume. The skin volume was created with an 3mm contraction of the external body contour resulting in a shell with 3 mm thickness. The prescription dose (PD) to the PTV was 30Gy in 5 consecutive daily fractions (6 Gy per fraction). The planning objectives for PTV coverage and the OAR dose constraints are summarized in Table 1.Furthermore, hot spots had to be kept within the PTV and not exceed 115% of PD, whereas OAR dose-volume constraints should be fulfilled within a 5% tolerance with respect to the values inTable 1.

Three treatment plans were generated for each patient: 3D-CRT and VMAT plans were designed using Varian Eclipse (version 11.0.30, Varian Medical Systems, Palo Alto, CA) treatment planning system (TPS), while CK plans were optimized using Multiplan (Accuray Incorporated, Sunnyvale, CA) TPS. In particular, 2 coplanar fields plus 2 fields with the treatment couch rotated by 90° were set for 3D-CRT plans. Two partial coplanar arcs were set for VMAT: a clockwise gantry rotation from 260-290° to 50° with the corresponding counterclockwise rotation for right breast treatments, and from 300-310° to 85-100° for left breast treatments. In the most challenging cases, two additional arcs were added with the treatment couch rotated by 90°. Collimator angles were set different from zero in order to reduce the tongue and groove effect. The dose calculation algorithm used by Eclipse TPS was the anisotropic analytical algorithm with a 2-mm calculation grid and heterogeneity correction. All 3D-CRT and VMAT plans were performed with a 6 MV photon beam produced by a Varian Clinac equipped with a Millennium Multi Leaf Collimator with 120 leaves.

CK treatment plans were optimized using the variable aperture Iris collimator to deliver a set of multiple non-isocentric non-coplanar beams: the entry angles and the total number of beams were fully managed by the TPS. The dose distribution calculations

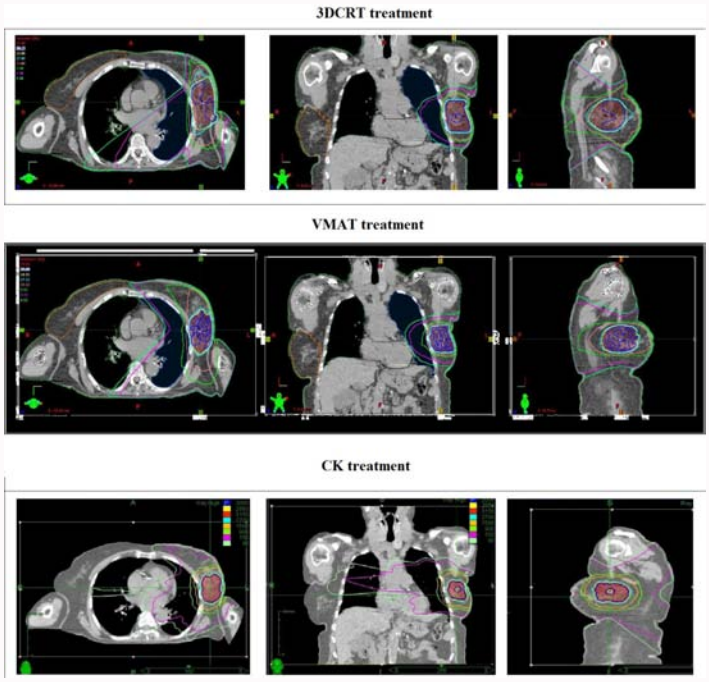


Figure 2: Example of dose distribution obtained with the three techniques for the same left-sided breast cancer patient, in the axial, coronal and sagittal views (red, 31.5 Gy; blue, 30 Gy; yellow, 28.5 Gy; cyan, 27 Gy; orange, 15 Gy; green, 9 Gy; magenta, 1.5 Gy; light green 0.9 Gy).

were performed using the ray-tracing algorithms with heterogeneity correction and a high-resolution grid of 1-pixel size. An example of the beam setup for each of the three RT techniques is shown in Figure 1.

All treatment plans were optimized to achieve optimal PTV coverage without exceeding OAR constraints. In addition, all generated plans were acceptable for a treatment delivery.

Treatment plans were evaluated from a technical and dosimetric point of view. In particular, dosimetric parameters, extracted from the dose volume histograms (DVHs), were used to evaluate PTV coverage and OAR sparing for the different irradiation techniques.

For PTV coverage, minimum (Dmin), maximum (Dmax) and mean dose (Dmean), and the percentage of PTV receiving 90%, 95% and 105% of the PD (i.e.: V27Gy, V28.5Gy and V31.5Gy, respectively) were considered.

To evaluate the overall quality of treatment plans, their conformity, homogeneity, number of monitor units (MU) and delivery treatment times were also compared. Conformity index (CI) and homogeneity index (HI) were calculated according to the reported formula [26]. CI=!"!"!"# x !"!"#!"# HI =! !!"!"#.

Where TVPVI is the target volume covered by the prescription isodose volume, TV is the target volume and PIV is the prescription isodose volume; Dmax is the maximum point dose and PD is the prescribed dose to the target volume. CI ranges from 0 to 1, the last being the ideal case while a value close to 0 indicates a total absence of conformation [27].

Data were also analyzed dividing the patients into 2 subgroups based on PTV laterality.

The differences among the three RT techniques were analyzed by paired Student's t-test, considering a p-value <0.05 (2-tailed) as statistically significant. Statistical analysis was performed by using the MedCalc software (MedCalc® Version 12.1.3.0, MedCalc Software BVBA 2011, Belgium).

Results

Five patients received RT to the right breast and five to the left breast. The tumors were located as follows: 3 in the upper outer quadrant, 3 in the lower inner quadrant, 2 in the lower outer quadrant and 2 in the upper inner quadrant of the breast. The average PTV volume was 121.6 ± 68.2 cc (range: 31.8 – 259.0 cc).

All the planning objectives required by the APBI protocol were achieved with all techniques.

The results for PTV coverage, CI, HI and the OAR dosimetric data obtained for each treatment modality are summarized in Table 2.

VMAT and CK provided equivalent dose conformity, with CIs significantly higher compared to 3D-CRT technique. Besides, VMAT

Table 1: Parameters used for treatment planning optimization.

Structure	Planning objectives and dose constraints
PTV	$V_{27Gy} \geq 90\%$
Ipsi-lateral Breast	$V_{15\,Gy} \leq 40\%$
(PTV-excluded)	$V_{30\,Gy} \leq 20\%$
Contra-lateral Breast	$V_{0.9\,Gy} \leq 100\%$
Ipsi-lateral Lung	$V_{9Gy} \leq 10\%$
Contra-lateral Lung	$V_{1.5Gy} \leq 10\%$
Heart	$V_{1.5Gy} \leq 5\%$ (right breast)
	$V_{1.5Gy} \leq 40\%$ (left breast)
Thyroid	D_{max} <0.9Gy
Skin	D_{max} <34.5Gy

VxxGy: Volume of the Structure (PTV or organ) Receiving at least XX Dose (Gy); Dmax: Maximum Dose

Table 2: Comparison of PTV and OAR dosimetric data for the three RT approaches. For each variable was reported the mean value ± standard deviation. For each comparison, only the statistically significant differences are reported (p-values <0.05).

Structure	Variable	3DCRT	VMAT	Cyber	p Value		
					3D vs. VMAT	CK vs. 3D	CK vs. VMAT
Contra-lateral lung	**V1.5Gy (%)**	1.1 ± 1.5	4.1 ± 2.4	2.7 ± 5.2	0.02	-	-
	Dmean (Gy)	0.2 ± 0.5	0.4 ± 0.2	0.4 ± 0.2	-	-	-
Ipsi-lateral lung	**V_{9Gy} (%)**	2.0 ± 2.1	3.6 ± 2.7	2.1 ± 2.0	0.01	-	-
	Dmean (Gy)	1.3 ± 0.7	2.1 ± 0.7	1.8 ± 0.9	-	-	-
Thyroid	**Dmax (Gy)**	0.08 ± 0.04	0.06 ± 0.04	0.4 ± 0.3	0.03	0.01	< 0.01
Heart *(right breast)*	**$V_{1.5Gy}$ (%)!**	1.7 ± 1.3	1.4 ± 1.4	2.3 ± 2.2	-	-	-
	Dmean (Gy)	0.4 ± 0.4	0.40 ± 0.19	0.38 ± 0.24	-	-	-
Heart *(left breast)*	**$V_{1.5Gy}$ (%)!**	12.9 ± 13.4	22.0 ± 14.3	23.2 ± 8.8	-	-	-
	Dmean (Gy)	0.7 ± 0.5	1.1 ± 0.6	0.9 ± 0.3	-	-	-
Skin	**Dmean (Gy)**	0.8 ± 0.2	0.7 ± 0.2	0.8 ± 0.3	0.02	-	-
	Dmax (Gy)	27.5 ± 4.1	29.6 ± 2.8	28.4 ± 2.9	< 0.01	-	0.01
Ipsi-lateral breast	**V15Gy (%)**	26.0 ± 7.8	18.4 ± 5.2	16.3 ± 6.4	< 0.01	< 0.01	-
(excluded PTV)	**V30Gy (%)**	4.2 ± 1.7	1.2 ± 0.5	1.7 ± 4.1	< 0.01	-	-
Contra-lateral	**Dmean (Gy)**	0.2 ± 0.2	0.3 ± 0.3	0.2 ± 0.2	-	-	-
breast	**$D_{100\%}$ (Gy)**	0.01 ± 0.02	0.04 ± 0.08	0.1 ± 0.1	-	< 0.01	< 0.01
PTV	**V_{27Gy} (%)!**	99.9 ± 0.2	99.9 ± 0.01	96.5 ± 3.0	0.02	0.01	< 0.01
	V28.5Gy (%)!	98.9 ± 1.2	99.9 ± 0.2	84.1 ± 10.0	0.01	< 0.01	< 0.01
	V31.5Gy (%)	0.2 ± 0.3	0.1 ± 0.1	39.3 ± 23.8	-	< 0.01	< 0.01
	Dmin (Gy)	24.8 ± 2.8	26.0 ± 1.7	24.9 ± 1.7	-	-	-
	Dmean (Gy)	30.4 ± 0.2	30.1 ± 0.1	30.7 ± 1.0	< 0.01	-	-
	D max (Gy)	31.5 ± 0.2	31.8 ± 0.2	34.2 ± 1.3	0.02	< 0.01	< 0.01
	HI	1.05 ± 0.01	1.05 ± 0.01	1.14 ± 0.04	0.02	< 0.01	< 0.01
	CI	0.47 ± 0.07	0.64 ± 0.05	0.63 ± 0.16	< 0.01	0.01	-

achieved the best results in terms of HI and target coverage (V27Gy and V28.5Gy).

An example of representative dose distributions for each treatment technique is shown in figure 2.

As shown in Table 2, significant differences were observed in dosimetric data of lungs, thyroid, skin and breast. Concerning heart, similar dose values were obtained in each right-sided breast cancer treatments, while low doses were reduced with 3D-CRT compared to CK and VMAT in left-sided breast cancer treatment. For all techniques, mean heart dose for right and left-sided breast cancer were less than 0.5 and 1.1Gy, respectively.

Analyzing the subgroups of patients treated for right and left breast cancer, the results for PTV coverage proved to be very similar to those for the whole group of patients, as shown in Table 3. For both subgroups, the mean percentage of PTV receiving 95% of the PD (V28.5Gy) was significantly lower for CK compared to 3D-CRT and VMAT technique, while V31.5Gy and Dmax were significantly higher in CK plans.

In table 3 was also reported the only significant results for the OARs.

Comparing right- and left-sided breast treatments for each RT technique, no significant differences for OARs were observed, although the doses delivered to thyroid, ipsi-lateral lung and ipsi-lateral breast were higher in left breast treatments. Besides, in order to reduce the heart dose, a small increase of dose to ipsi-lateral lung and breast was sometimes allowed, slightly increasing the weight of the beams directed toward these organs.

As to PTV: HI, V31.5Gy and Dmax of VMAT treatments resulted significantly higher in left-sided than right-sided breast cancer ($p<0.01$).

The CK plans, with an average of 122 beams (range: 89-187), delivered on average approximately 13-18 times more MU over the course of the treatment than the other two techniques (15229 MU per fraction for CK *vs.* 851 MU and 1151 MU per fraction for 3D-CRT and VMAT, respectively).

The average beam-on time to deliver the 3D-CRT and VMAT plans was approximately less than 5 and 2 min, respectively. Using the CyberKnife system with Iris, the treatment time including patient set-up on treatment couch was approximately 60 min, ranging from ~35 min to ~120 min (beam delivery time: 33.5 ± 9.7 min).

Discussion

The National Surgical Adjuvant Breast and Bowel Project B-06 trial reported that 75% of local recurrences were found at or in proximity to the lumpectomy cavity [28]. This evidence suggested to restrict the RT target to the lumpectomy cavity in selected patients with low recurrence rate risk, using an approach of APBI [2,3]. Moreover, in a context of a modern vision of personalized treatments, it does not always seem suitable to apply the same radiotherapy to all

the patients.

Multicatheter brachytherapy was the most widely used technique in APBI and with the largest follow up [9,29-32], although it never gained wide acceptance because of the complexity and invasiveness of the procedure and treatment initiation based on the final pathology. Furthermore, tumor size and location may preclude patients from receiving APBI with the brachytherapy technique. 3D-CRT offers a more homogenous dose distribution than brachytherapy-based APBI does, but could give a higher dose to lung, heart, or the remaining normal breast. However, the limits of 3D-CRT concern dosimetry, motion, and cosmesis. Usually, a larger margin is used with this technique, potentially increasing toxicity and decreasing cosmesis outcomes. Two recent reports investigating 3D-CRT using conventional linear accelerators for APBI have raised concerns for unacceptable cosmesis [14,33]. The authors illustrated that in patients developing unacceptable cosmesis, the mean volume of breast receiving 50% and 100% of the prescribed dose was significantly higher than in patients with acceptable cosmesis [33].

Several studies have investigated the use of 3D-CRT and the modern RT techniques, including IMRT [15,34], VMAT [20] and CyberKnife [21-23,35] for APBI. Recently we have published our results, in terms of acute/subacute toxicity, of a pilot study for APBI by CK. In particular we showed as, by using CK and a fractionation of 30 Gy in 5 fractions, very good cosmetic results were achievable [24].

In this study, we performed a technical and dosimetric comparison among 3D-CRT, VMAT and CK for an APBI clinical protocol using 10 patients treated by CK as reported in the study of Lozza et al. [24].

We evaluated the plans considering different dosimetric parameters for the PTV, such as target coverage, conformity and homogeneity indexes, and the doses delivered to the OARs, and technical aspects of dose delivery, such as the total number of MUs and the treatment delivery time. All the planning objectives required by the APBI protocol were achieved by all techniques.

VMAT and CK provided equivalent dose conformity, significantly better than 3D-CRT, with a consequent better sparing of the non-PTV ipsi-lateral breast. Besides, VMAT achieved the best results in terms of HI and percentage of target volume receiving 90% of PD.

Our results confirm those reported by Qiu et al., who demonstrated that VMAT can improve dose conformity and reduce the beam delivery time, as compared with 3D-CRT.

Similarly, Heinzerling et al. [36] found that the CK treatment planning for PBI allows achieving very conformal target coverage while significantly reducing dose to OARs, as ipsi-lateral lung and heart, compared to 3D-CRT. Also, Goggin et al. [37] showed that CK offers both a higher conformity than 3D-CRT due to the higher number of non-coplanar beams, and a less normal breast tissue exposure attributable to image-guided tracking.

The maximum doses and HIs of PTV for our CK plans are higher than the other two techniques: these results are expected considering the inherent property of CK to create heterogeneous dose distributions inside the PTV. This explains also the significantly higher values of V27Gy and V28.5Gy obtained with3D-CRT and VMAT.

Significant differences were observed in the OAR dosimetric data, except for heart. However, low doses to heart were in general reduced with 3D-CRT in left-sided breast patients and this is expected to reduce the risk of radiation-related cardiac disease.

Lung doses were significantly lower for 3D-CRT than for VMAT. This result is opposed to what obtained by Qui et al. [20]. This discrepancy is probably due to the different planning approach: Qui et al. optimized VMAT plans using specific avoidance sectors to avoid entry angles directed toward the lungs and heart, thus reducing their absorbed dose.

3DCRT achieved the best results in terms of the dose to the whole contra-lateral breast thanks to the beam arrangement; however, the mean doses were very low for all three techniques.

The localization (position and depth) and shape of the PTV and its relative position with respect to the OARs can significantly influence the treatment plan optimization and, consequently, the treatment results [38-40]. Moreover, the planning CT scans used in this study were acquired in supine position with the arms lying along the body to ensure a comfortable position during the long lasting treatments performed with CK. This setup necessarily limits the available degrees of freedom for the beam angles and the arc rotations in the 3DCRT and VMAT planning, respectively. In particular, to avoid arm irradiation and to keep the dose to the heart as low as possible a small increase in the dose to the ipsi-lateral lung and the contra-lateral breast is expected. The patient position should be choice in an appropriate manner to ensure a certain comfort in order to get a reproducible and stable position during irradiation. Anyway, all the 3DCRT and VMAT treatment plans fully fulfilled the dosimetric objectives, proving that this kind of patient setup can be managed with a proper treatment plan optimization.

The treatment session time is usually longer for CK (on average 60 min) than for VMAT and 3DCRT techniques (15 to 20 min dependently if non-coplanar beams are used), both because of longer time needs for dose delivery and for patient setup and fiducials alignment phase. In general, larger breasts were associated with an increased mobility, requiring longer patient set-up times with CK. Furthermore, CK delivered on average approximately 13-18 times more MU over the course of the treatment than the other two techniques, which may lead to increased total body scattered dose, as described by Hermando et al. [41] and Vallis et al. [42].

However, VMAT minor delivery time potentially reduces the inaccuracy that maybe caused by respiratory motion or errors in patient setup, although in many cases the use of a respiratory management system is recommended if a proper expansion of PTV margin is used. Different studies [43-45] showed the efficiency both of 3D-CRT and VMAT delivery using breath-hold techniques or respiratory-gating systems for APBI. In fact, in EBRT difficulties in set up reproducibility and organ motion result in larger expansion margins to make up for target localization uncertainties [46-47]. Unfortunately, this larger margin can result in greater normal breast tissue volume receiving high dose irradiation. Furthermore, even by using wider margins the interplay effect (interplay between respiration-induced tumor motion and the dynamic dose delivery) can be not negligible in VMAT treatment, especially if delivered in hypo fractionated regime [48-49].

Between the three RT modalities analyzed in this study, the CyberKnife offers meaningful technical improvements to existing PBI techniques using real time tracking, respiratory motion management with Synchrony system [50] and sub-millimeter accuracy. This could allow reducing the margins of PTV in CK treatment, minimizing the doses at the OARs without compromising the target coverage.

Conclusion

In this dosimetric comparison, all RT techniques are feasible to delivery APBI.CK and VMAT provide higher conformity than 3D-CRT, although with 3D-CRTwe observed a reduction of the dose to the OARs except ipsi-lateral breast.

In CK treatment organ motion is controlled and, despite the longer treatment times, the delivery accuracy is expected to be better than 3D-CRT and VMAT, especially if motion management systems are not used. The results of this study can provide certain guidance for clinicians that want to apply a clinical protocol for ABPI taking into account the specific technologies available in their own hospital. Clinical considerations about the impact of the dosimetric difference on patients' toxicity are necessary to select the optimal RT technique for each patient treated with APBI.

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