research article

Multicatheter interstitial brachytherapy versus stereotactic radiotherapy with CyberKnife for accelerated partial breast irradiation: a comparative treatment planning study with respect to dosimetry of organs at risk

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Background. The aim of the study was to dosimetrically compare multicatheter interstitial brachytherapy (MIBT) and stereotactic radiotherapy with CyberKnife (CK) for accelerated partial breast irradiation (APBI) especially concerning the dose of organs at risk (OAR-s).

Patients and methods. Treatment plans of thirty-two MIBT and CK patients were compared. The OAR-s included ipsilateral non-target and contralateral breast, ipsilateral and contralateral lung, skin, ribs, and heart for left-sided cases. The fractionation was identical (4 x 6.25 Gy) in both treatment groups. The relative volumes (e.g. V100, V90) receiving a given relative dose (100%, 90%), and the relative doses (e.g. D0.1cm^3, D1cm^3) delivered to the most exposed small volumes (0.1 cm^3, 1 cm^3) were calculated from dose-volume histograms. All dose values were related to the prescribed dose (25 Gy).

Results. Regarding non-target breast CK performed slightly better than MIBT (V100: 0.7% *vs.* 1.6%, V50: 10.5% *vs.* 12.9%). The mean dose of the ipsilateral lung was the same for both techniques (4.9%), but doses irradiated to volume of 1 cm^3 were lower with MIBT (36.1% *vs.* 45.4%). Protection of skin and rib was better with MIBT. There were no significant differences between the dose-volume parameters of the heart, but with MIBT, slightly larger volumes were irradiated by 5% dose (V5: 29.9% *vs.* 21.2%). Contralateral breast and lung received a somewhat higher dose with MIBT (D1cm^3: 2.6% *vs.* 1.8% and 3.6% *vs.* 2.5%).

Conclusions. The target volume can be properly irradiated by both techniques with similar dose distributions and high dose conformity. Regarding the dose to the non-target breast, heart, and contralateral organs the CK was superior, but the nearby organs (skin, ribs, ipsilateral lung) received less dose with MIBT. The observed dosimetric differences were small but significant in a few parameters at the examined patient number. More studies are needed to explore whether these dosimetric findings have clinical significance.

Key words: multicatheter interstitial brachytherapy; CyberKnife; APBI; dosimetric comparison

Introduction

Breast radiotherapy after breast-conserving surgery reduces the risk of breast cancer recurrence by half and related mortality by one-sixth in early-stage breast cancer patients.[1] Today, the accelerated partial breast irradiation (APBI) for treating early-stage breast cancer has been a widely accepted technique among radiation oncologists.[2] APBI can be used because most of the local recurrences develop near the tumour bed requiring irradiation of the surroundings of the removed tumour, only.[2] During APBI, a smaller volume needs to be irradiated compared to whole breast irradiation (WBI), so patients can tolerate an accelerated regimen of irradiation with higher fraction doses. In the case of APBI, the total treatment time is only 4–5 days instead of the few weeks of conventional WBI, and therefore, APBI is a preferred treatment option by patients. Because of the smaller irradiated volume, there are decreased doses to healthy tissues compared to WBI, which is another advantage of the APBI, and this is an important issue among long time survivors of breast cancer.[3,4] In planning studies, and also in phantom measurements, it was verified that with smaller target volume the adjacent organs received less dose.[5,6]

There are numerous techniques available for APBI.[7] The first one was the multicatheter interstitial brachytherapy (MIBT), having the longest patient follow-up with excellent clinical results.[8-15] Furthermore, recommendations for patient selection[16], target volume definition[17,18] have been published, and practical guidelines are also available for MIBT[19,20] ensuring appropriate quality assurance for this technique. Brachytherapy (BT) also performs well when it is used for boost irradiation following WBI.[21,22] Other BT modalities have also been introduced, such as single/multichannel balloon therapy, non-invasive BT, and seed implantation. The external beam radiotherapy (EBRT) methods include 3D conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT), volume modulated arc therapy (VMAT), CyberKnife therapy (CK), proton therapy and intraoperative methods with electrons or 50 kV photons.[23]

Dosimetric studies for APBI with CK are rare in the literature, and mainly focus on comparisons between different external beam techniques. CK dosimetry has been compared to 3D-CRT[24-31], IMRT[25,29,31], VMAT[28,29], and tomotherapy.[27] A dosimetric assessment of conformal and several different IMRT techniques for APBI is also available in the literature.[32] Treatment plans of MIBT were also as-

sessed against 3D-CRT[33], IMRT[34] and VMAT.[35] Three years ago, a CK was installed at our institution, and very soon we started using it for APBI. Since we had lots of experience in interstitial BT we were interested in seeing how much the CK can imitate the BT, and whether it can be an alternative to BT.

Having surveyed the literature on APBI, we observed that the target volume can be irradiated properly with any technique, but differences exist in dosimetric issues of the organs at risk (OAR-s). In another study we compared plans of patients treated by CK with virtual MIBT plans based on CT images and contours of CK plans.[36]

The goal of this study was to dosimetrically compare the multicatheter interstitial brachytherapy and stereotactic irradiation with CyberKnife for APBI using separate patient cohorts with a special focus on dose to OAR-s. We believe that our results provide radiation oncologists and physicists with information on dosimetric advantages and disadvantages of these two image guided treatment techniques.

Patients and methods

Treatment plans of thirty-two MIBT patients and thirty-two CK patients consecutively treated at our institute between June 2017 and May 2020 were selected for a dosimetric comparison. Mostly, all patients were candidate for both techniques, and the treatment option was primarily chosen by the patient. All the patients were treated according to our institutional protocol, and in this dosimetric study we retrospectively collected and evaluated the treatment planning data, so no ethical approval was needed.

Multicatheter interstitial brachytherapy

The patients were treated with a high-dose-rate afterloader (microSelectron V3, Elekta, Brachytherapy, Veenendaal, The Netherlands) with Ir-192 stepping source. For patient selection and target volume definitions the GEC-ESTRO guidelines were followed.[16,18] The number of implanted catheters ranged between 7 and 28, with a mean of 14. The catheters were placed into the breast with a template in a triangle pattern with 1.3 cm catheter separation, and the source step size was 2.5 mm. The positions of the catheters were planned with image guidance using pre-implant CT imaging.[37] The patients were treated according to plans made with an inverse planning method (Hybrid Planning

Optimization, HIPO). For treatment planning the Oncentra Brachy v4.3 planning system (Elekta, Brachytherapy, Veenendaal, The Netherlands) was used. The calculation algorithm was based on the TG-43 formalism.[38] After the catheter implantation, CT scans with a 3 mm slice distance were acquired. First, the lumpectomy cavity was outlined with the help of surgical clips placed into the cavity wall during the lumpectomy. To get the clinical target volume (CTV), a safety margin was added to the cavity according to the surgical tumour-free margin in all six main directions. The surgical and radiation margin together was always 20 mm.[18] The CTV was limited to skin, thoracic wall, and pectoral muscles. No additional margin was added to the CTV to create the planning target volume (PTV), so the PTV was always equal to the CTV. The outlined OAR-s were as follows: the ipsilateral and contralateral lungs and breasts, heart, skin, and ribs. The skin was defined as a 5 mm layer below the skin surface. The non-target ipsilateral breast was created from the ipsilateral breast and the PTV with a subtraction. After contouring all structures, the catheter reconstruction was carried out, and the dwell time optimization was performed. The source positions were activated within the PTV, and for selection an isodose line for prescription the aim was to achieve at least 90% target coverage by the prescribed dose (PD) while keeping the dose distribution relatively homogenous. A higher isodose line was selected if a proper dose homogeneity was maintained. Dose-nonuniformity ratio (DNR) was used to measure the dose homogeneity. DNR is the ratio of volumes irradiated by 1.5 times of PD and PD ($V_{1.5xPD}/V_{PD}$). The required value for DNR was less or equal to 0.35. When coverage and homogeneity constraints could not be fulfilled at the same time, the target coverage was prioritized. For the OAR-s no dose-volume constraints were used, the parameters were only recorded. The PD was 25 Gy with a fractionation of 4 x 6.25 Gy, which is an accepted fractionation regime in the GEC-ESTRO VAPBI study.[39] The treatment time of one fraction ranged between 5 and 15 minutes according to the volume of the PTV and the source strength.

CyberKnife treatments

The patients were treated with a CyberKnife M6 stereotactic system (Accuray, Sunnyvale, CA, USA) using InCise 2™ multileaf collimators (MLC-s) with step-and-shoot IMRT technique.[40] The patient selection was the same as for MIBT. The mean monitor unit number was 2498.8 (range, 1578.7–4142.2), and

the median segment number was 57 (range, 39–75). One week before the planning CT, four gold markers were implanted around the lumpectomy cavity with ultrasound guidance by an experienced interventional radiologist. The gold markers were used for real-time tracking during irradiation (Synchrony Respiration Tracking). Although surgical titanium clips were placed into the cavity wall during the lumpectomy, they do not provide enough contrast on X-ray images, and therefore they cannot be reliably tracked. That is why we used gold markers. The CT slice thickness for treatment planning was 1.25 mm, and the images were acquired in exhalation breath-hold. The CT scans included both breasts and both sides of the lung. Metal artifact reduction CT scans were obtained to decrease the scattering effect of gold markers. The contouring protocol for CK was the same as for MIBT. However, to generate the PTV, a 2 mm margin was added to the CTV in each direction. With frequent intra-fraction imaging and correction by the robotic arm, the 2 mm margin seems to be enough to account for the non-rigid components of composite errors.[41] For evaluation purpose, PTV_EVAL was created from PTV with the subtraction of the 5 mm skin layer. The prescribed dose was 25 Gy with fractionation of 4 x 6.25 Gy, exactly the same as in MIBT.

For planning, the Precision 1.1.1.1 (Accuray, Sunnyvale, CA, USA) software was used with a finite size pencil beam (FSPB) dose calculation algorithm for optimization and Monte Carlo algorithm with 0.5% uncertainty for plan evaluation. Regarding beam orientations, the contralateral breast and lung were allowed with "exit only" direction for optimization. Sequential optimization method was applied with the parameters of maximum 400 MU/segments, 650 MU/node, and for beam shaping all three types of segments (eroded, perimeter, random shape) were used with a 2.5 mm leaf margin. The aim was to achieve at least 99.5% of V95 for PTV_EVAL and keep the maximum point dose under 120% of the PD. Regarding doses to OAR-s no constraints were used, only the orientation of the beams was optimized. Time reduction was used to reach the optimal treatment time without compromising the optimal dose distribution. The mean estimated treatment time was 33.3 min (range, 27–40 min).

Dosimetric evaluation and statistical analysis

The treatment plan evaluation was performed using dose-volume histograms (DVH-s) (Figure 1).
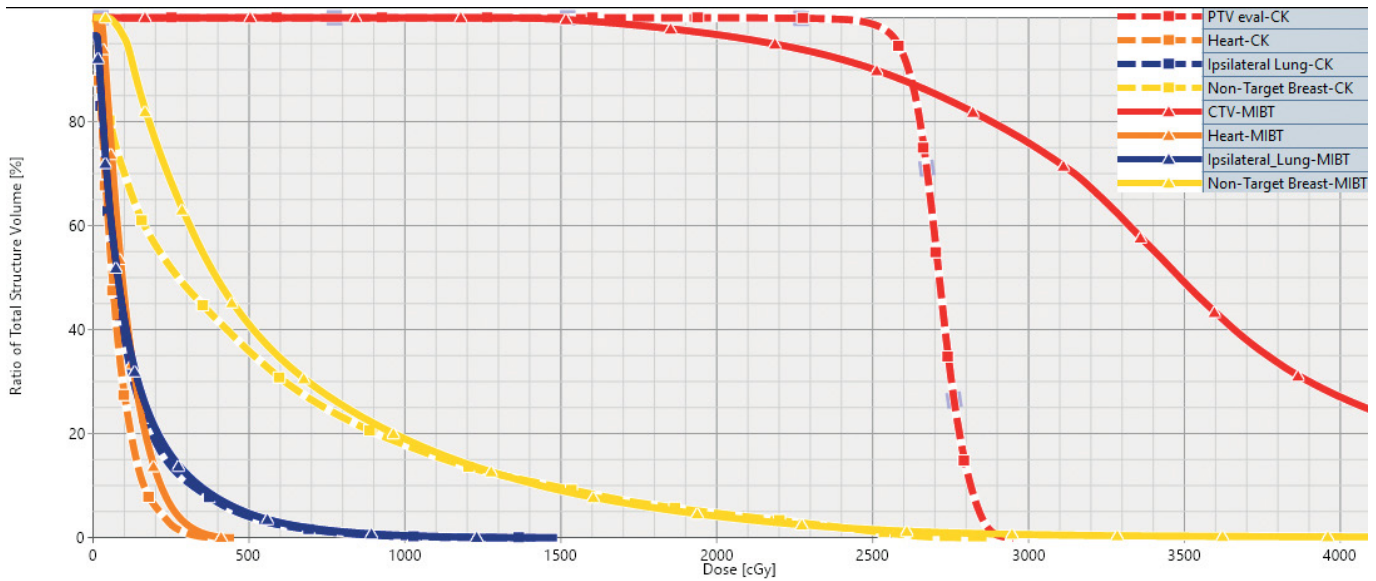
FIGURE 1. Representative dose-volume histograms (DVH-s) for multicatheter interstitial brachytherapy (MIBT) (solid line) and CyberKnife (CK) treatment (dashed line) for accelerated partial breast irradiation. The prescribed dose was 25 Gy. The target volume is indicated with red, the non-target breast with yellow, the ipsilateral lung with blue and the heart with orange. The solid red line clearly shows that with MIBT volumes irradiated by high doses (> 25 Gy) develop within the target volume.

All treatment plans and patient's data were anonymized for the dosimetric comparison. Quality parameters were derived as relative (e.g. V100, V90) or absolute volumes (e.g. V100 (cm³), V50 (cm³)) receiving a percentage of the PD. Relative doses in percentage of the PD to relative volumes (e.g. D5, D50) and to small absolute volumes (e.g. D0.1cm³, D1cm³) were calculated, too. The conformity of dose distribution was characterized by COIN.[42] Most of these parameters are published in dosimetric studies what makes the intercomparison possible. Descriptive statistics were calculated to describe the treatment plans. Shapiro-Wilk W test was used on the distribution of dose-volume parameters to test normality. Since almost none of the parameters followed Gaussian distribution, the Mann-Whitney U test was used for every comparison with the Statistica 10.0 software (StatSoft, Inc., Tulsa, OK, USA) and $p < 0.05$ was considered statistically significant.

TABLE 1. Tumour localization according to breast quadrants in patients treated by multicatheter interstitial brachytherapy (MIBT) and CyberKnife (CK)

Method of treatment	Laterality	Upper outer	Lower outer	Upper inner	Lower inner	Central
MIBT	right	3	1	3	2	4
	left	3	3	4	1	8
CK	right	6	6	2	1	2
	left	2	4	1	3	5

TABLE 2. Absolute volumes of the body irradiated by 100%, 50% and 20% of the prescribed dose for multicatheter interstitial brachytherapy (MIBT) and CyberKnife (CK) treatments

Body	MIBT	CK	p-value*
V100 (cm³)	66.4 (28.9–193.8)	77.1 (18.3–141.5)	0.0356
V50 (cm³)	159.0 (73.4–444.2)	189.3 (58.6–397.6)	0.0184
V20 (cm³)	470.7 (253.4–1078.1)	609.1 (326.7–1160.8)	0.0013

*Mann-Whitney U test

Results

Thirteen MIBT patients (41%) had right-sided and nineteen (59%) left-sided tumours, and seventeen CK patients (53%) had right-sided and fifteen (47%) left-sided lesions. The distribution of tumour localization is shown in Table 1.

The mean volume of the ipsilateral breast was 825.7 cm³ (range, 386.9–2097.5 cm³) and 984.4 cm³ (range, 372.7–2437.1 cm³) for the MIBT and CK patients, respectively (p = 0.4400). The mean volume of the PTV was 58.2 cm³ (range, 26.6–173.6 cm³) for

MIBT patients and 71.7 cm^3 (range, 17.1−129.1 cm^3) for CK patients, which was significantly higher (p = 0.0101). The mean volume of the CTV was 51.9 cm^3 (range, 10.2−96.4 cm^3) for CK, which did not differ significantly from the volume of the CTV for MIBT (58.2 cm^3, p = 0.8456). For MIBT the V100 for PTV was 91.4% (range, 83.1−96.4%) meanwhile the DNR was 0.35 (range, 0.24−0.44). For PTV_EVAL of CK patients, the V100 and V95 were 97.5% (range, 95.2−99.3%) and 99.7% (range, 97.7−100%), respectively, and the mean of the maximum doses was 116.5% (range, 113.6−125%). Because of the smaller target volumes, the V100, V50, and the V20 absolute volume parameters calculated for the whole body were significantly smaller for MIBT than for CK as it is presented in Table 2.

But, by relating these mean volumes to mean PTV volumes, it can be observed that the CK irradiated relatively less normal tissues, especially at higher dose levels. For MIBT and CK, the ratio of $V100_{BODY}/V_{PTV}$ is 1.14 $vs.$ 1.08, and for $V50_{BODY}/V_{PTV}$ it is 2.73 $vs.$ 2.64. Only the $V20_{BODY}/V_{PTV}$ is smaller for MIBT (8.09 $vs.$ 8.5).

The conformity of the dose distributions was very high for both techniques (Figure 2), and the dosimetric parameters for ipsilateral breast were very similar (Table 3). Only the PD irradiated significantly less volume of the non-target breast at CK (0.7% $vs.$ 1.6%, p < 0.0001). For lower dose values, the CK resulted in slightly smaller volumes, but without statistical significance. Large conformity indices (COIN-s) demonstrate the high dose conformity for both techniques. The COIN was 0.74 for MIBT and 0.88 for CK patients (p < 0.001).

The mean dose of the ipsilateral lung was exactly the same (4.9%) for both techniques (Table 4). All other parameters were smaller for MIBT, and the doses to the most exposed low volumes (0.1 cm^3, 1 cm^3) were significantly less.

Heart dosimetry was examined only for left-sided cases. The results are shown in Table 5. For each parameter, larger values were obtained with MIBT, but none of the differences was significant.

The protection of skin and ribs was better with MIBT. The differences were significant for all parameters, as shown in Table 6. The maximal dose to the ribs never exceeded the PD in MIBT cases (V100(cm^3) = 0). The mean value for V100(cm^3) in CK patients was small, only 0.2 cm^3, and the maximal dose exceeded the PD in 11 cases.

For contralateral breast and lung, volumetric dose parameters were very low for both techniques, but CK resulted in significantly lower values in each parameter, as it is shown in Table 7.
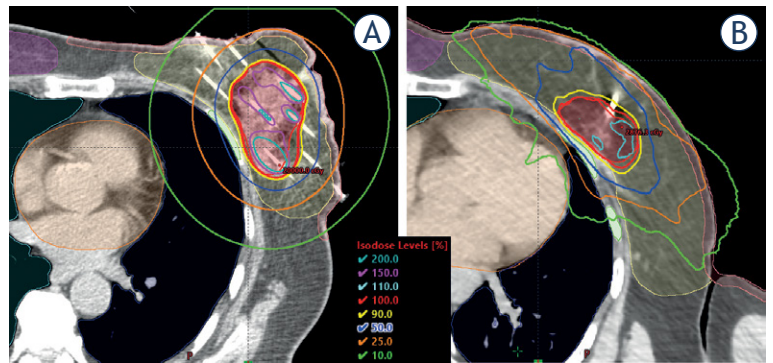

FIGURE 2. Representative dose distribution for multicatheter interstitial brachytherapy (MIBT) **(A)** and CyberKnife (CK) treatment **(B)**. PTV: red, ipsilateral breast: yellow, contralateral breast: pink, ribs: green, heart: orange, ipsilateral lung: dark blue, contralateral lung: light blue.

Discussion

As a result of the technological development during the last decade, a number of new techniques have been introduced for APBI, and the question

TABLE 3. Dosimetry of ipsilateral breast for multicatheter interstitial brachytherapy (MIBT) and CyberKnife (CK) treatments. The values are given in percentages

	MIBT	**CK**	**p-value***
Whole breast			
V100	9.7 (2.2−29.7)	9.6 (0.9−20.4)	0.9381
V50	23.2 (5.1−68.0)	23.3 (2.7−47.1)	0.9822
Non-target breast			
V100	1.6 (0.4−4.2)	0.7 (0.0−2.0)	< 0.0001
V90	2.8 (0.6−8.1)	2.3 (0.0−4.4)	0.7019
V50	12.9 (3.1−35.4)	10.5 (1.7−18.9)	0.5501
V25	31.8 (9.4−68.4)	29.9 (7.6−55.2)	0.8772

*Mann-Whitney U test

TABLE 4. Dosimetry of ipsilateral lung for multicatheter interstitial brachytherapy (MIBT) and CyberKnife (CK) treatments. The values are given in percentages

Ipsilateral lung	**MIBT**	**CK**	**p-value***
Mean lung dose	4.9 (1.9−11.1)	4.9 (1.6−11.8)	0.9946
D0.1cm^3	41.0 (10.1−61.5)	52.2 (15.6−90.5)	0.0068
D1cm^3	36.1 (8.7−55.8)	45.4 (14.4−84.5)	0.0162
D2cm^3	33.6 (8−52.5)	42.2 (13.7−80.5)	0.0198
D2	21.2 (7.4−32.9)	24 (8.8−46.4)	0.2454
V5	30.6 (5.1−50.0)	30.7 (5.8−63.2)	0.9357

*Mann-Whitney U test

now arises whether which technique is the most advantageous for the patients. Based on large trials, at selected patients, the non-inferiority of APBI against WBI was confirmed, but between the various APBI techniques, only minor differences exist.[11] Dosimetric analysis can explore these differences providing some guidance for clinicians in selecting the appropriate method for a patient. Papers have been published on dosimetric comparisons between different APBI techniques[24,43-46]; and a few papers are available about the comparison of CyberKnife and other external beam techniques.[26-29] However, to our knowledge, this analysis is the first one which compares the dosimetric differences between the multicatheter interstitial brachytherapy and CyberKnife treatments for partial breast irradiation using clinical plans.

A couple of studies have investigated the feasibility of APBI with CK. The treatment characteristics with the dosimetric data from the literature are shown in Table 8. In most of the studies, cones or the Iris applicator were used, and the most frequent fractionation scheme was 5 x 6 Gy, but clinical results of dose escalation up to 5 x 8 Gy are also available now.[47] In the studies, the CTV-PTV margin ranged between 0 and 5 mm. With the introduction of the MLC, the treatment time remarkably decreased, compared to using cones or the Iris applicator. It is difficult to make quantitative dosimetric comparisons between studies because the reported parameters are too diverse. The first report on using stereotactic radiotherapy for breast tumours was published in 2009.[48] The study showed the feasibility of irradiation with CK, but dosimetric details were not reported. The earliest study with dosimetry was performed by Vermeulen et al.[49], and based on their results, the authors recommend the CK as a suitable treatment method for APBI.

They compared their dosimetric data with the constraints of 3D-CRT used in the NSABP-39/RTOG 0413 protocol.[50] On average, 11% of the ipsilateral breast received the PD (V100), and 23% (for two patients) and 26% (for seven patients) were irradiated by the half of the PD (V50). These values are well below the constraints of the NSABP-39/RTOG 0413 protocol and are in good agreement with our CK results (V100 = 9.6%, V50 = 23.3%). We note that for MIBT patients, we obtained practically the same values (V100 = 9.7%, V50 = 23.2%). In 2014, the same group published dosimetric data of twenty-one patients, but those basically did not differ from the previous ones.[51] In a retrospective planning study published by Xu et al.[25] for fourteen

patients previously treated with 3D-CRT, additional CK plans were created and compared with 3D-CRT and IMRT plans. Since in CK plans very homogenous dose distributions were created, the mean V100 parameter was 95.7%, which is lower than the value in our study (97.5%). The maximum dose in PTV was kept on 104% which is much lower than presented in this study (116.5%). The mean V100 and V50 parameters of the uninvolved normal breast were 9% and 23.1%, which are much higher than our values (0.7% and 10.5%). Probably, because of the relatively homogenous dose distribution, the dose gradient was not steep enough to achieve very low V100 parameters for the breast. Another explanation for our better dose conformity can be the use of MLC-s with step-and-shoot IMRT technique. For the median V5 parameter of ipsilateral lung, their analysis resulted in 31.4%, which is very similar to our 30.7%. In another retrospective study, Obayomi et al.[52] analyzed the dosimetric results of 10 CK treated patients. The mean PTV volume was 70 cm³, very similar to ours (71.7 cm³). The fractionation was 5 x 6 Gy (30 Gy), and the authors reported the maximum doses of skin and ribs as 32 Gy (107% of PD) and 26 Gy (87% of PD), consecutively. In our assessment, for skin and ribs, the D0.1cm³ value was 88.8% and 78.9%. In the paper of Lozza et al.[53], mainly the clinical results from 20 CK treated patients were reported. Among 20 patients, the mean volume of PTV was 88.1 cm³, and the V5 value of heart for left-sided cases was 14.0%, which is lower than in our study (21.2%). For skin, they examined the Dmax parameter, which was 98.2% of the PD. In our study, the D0.1cm³ was 88.8%. In a recent paper, Lee et al.[54] published their first experience in Korea of partial breast irradiation with CK. In their study, on average, 35.5% of ipsilateral breast volume received 50% of the PD, while in our case, only 23.3%. The mean volume of PTV was similar (73.6 cm³ *vs.* 71.7 cm³), although they did not use any CTV-PTV margin. But, the ipsilateral breast volume of their patients was less than half compared to ours (481.1 cm³ *vs.* 984.4 cm³). Despite the fact, that Korean women have smaller breast the authors consider the CK technique as a feasible method for APBI. They found that the mean maximal skin dose was 89%, while in our case, the D0.1cm³ was 89%. The mean dose to heart for left-sided lesions was also similar (2.3% *vs.* 3.3%).

APBI treatment with CyberKnife is feasible and compared to other external beam techniques the CK plans produce better dosimetric parameters regarding the OAR-s. Xu et al.[25] found CK plans more

conformal and observed better dose sparing of the critical structure except for the extremely low dose region (for example, V1 for ipsilateral lung) compared to IMRT and 3D-CRT. In a quantitative analysis with ten patients, Lee at al.[29] compared CK with 3D-CRT, IMRT and VMAT for APBI. They only examined patients with left-sided lesions and had a very similar conclusion about conformity of dose distribution as Xu et al. 25.[25] Rault et al.[27] examined the dosimetric effect of respiratory tracking at CK treatments against Tomotherapy and 3D-CRT. The authors stated that the non-coplanarity of the CK resulted in significantly less dose to the normal tissue of ipsilateral breast, in case of the 2 mm CTV-PTV margin. A very profound analysis was performed by Goggin et al.[26] in comparing different CK treatment plans (Iris, MLC) with 3D-CRT ones. Based on the analysis of nine patients, they found that CK-MLC technique resulted in lower dose to the ipsilateral lung than CK-Iris and comparable treatment time with 3D-CRT. In an examination with ten patients, Bonfantini et al.[28] compared CK with 3D-CRT and VMAT. Based on their analysis, 3D-CRT gives a reduction of the dose to OAR-s except for ipsilateral breast.

Major et al.[34] reported results of MIBT against co-planar IMRT. They found that MIBT generally spares normal tissues and organs at risk (except for heart) better than IMRT. They found significant differences in non-target breast dosimetry parameters in favour of MIBT. Inverse planning can improve the plan quality of breast implants, better homogeneity and a few percent less dose to OAR-s can be achieved at identical target coverage.[55,56] In this way we made a comparison between the treatment plans of the most advanced inverse optimized BT and a high-tech stereotactic EBRT technique.

In a recent publication our group reported a comparative dosimetry between CK and MIBT, but in that work ideal implant geometry was assumed in the hypothetical BT plans.[36] Therefore, the strength of the conclusion is weaker than in case of comparison between real clinical plans. Anyway, the findings regarding the dose to OAR-s are very similar to the ones observed in current study.

Comparing the dose distributions between MIBT and EBRT techniques, the CK seems most similar to the MIBT regarding the shapes of the isodose lines between 50–100% of PD. The explanation can be the use of lots of non-isocentric beams entering from different directions, not limited from one plane, which results in more focused 3D dose delivery to the PTV. This is presented in Figure 2, where the isodose lines between 50–100% of PD

following the shape of the PTV are very similar for both techniques. But, differences exist because volumes irradiated by high doses always develop in BT, which is shown in Figure 2 by the 150 and 200% isodose lines. However, the low isodoses around BT implant become nearly circular, while in CK case, they are irregular due to the multiple

TABLE 5. Dosimetry of heart for multicatheter interstitial brachytherapy (MIBT) and CyberKnife (CK) treatments. The values are given in percentages

Heart	MIBT	CK	p-value*
Mean heart dose	4.1 (1.0–7.7)	3.3 (1.3–6.9)	0.1706
D0.1cm³	21.4 (4.0–47.2)	18.9 (8.4–43.2)	0.2822
D1cm³	18.2 (3.2–42.3)	16.6 (7.3–40.3)	0.4878
D2cm³	17 (3.0–40.0)	15.6 (6.8–38.3)	0.5324
D2	13.3 (4.3–26.4)	12.5 (5.2–31.5)	0.5098
V5	29.9 (0.0–62.5)	21.2 (6.1–41.0)	0.1653

*Mann-Whitney U test

TABLE 6. Dosimetry of skin and ribs for multicatheter interstitial brachytherapy (MIBT) and CyberKnife (CK) treatments. The values are given in percentages except for V100 and V50

Skin	MIBT	CK	p-value*
D0.1cm³	75.3 (18.0–164.2)	88.8 (27.6–112.4)	0.0080
D0.2cm³	70.3 (17.4–140.7)	86.8 (21.1–111.1)	0.0053
D1cm³	58.4 (15.0–97.1)	79 (22.8–106.0)	0.0007
Ribs			
D0.1cm³	53.7 (8.1–92.7)	78.9 (17.6–108.4)	0.0003
D1cm³	43.1 (5.3–76.4)	69.1 (16.4–105)	0.0004
V100 (cm³)	0 (0–0)	0.2 (0.0–3.0)	0.0101
V50 (cm³)	2 (0.0–16.4)	4.2 (0.0–13.4)	0.0105

*Mann-Whitney U test

TABLE 7. Dosimetry of contralateral breast and lung for multicatheter interstitial brachytherapy (MIBT) and CyberKnife (CK) treatments. The values are given in percentages

Contralateral breast	MIBT	CK	p-value*
D0.1cm³	4 (0.0–9.8)	2.1 (0.3–11.2)	0.0039
D1cm³	2.6 (0.0–6.4)	1.8 (0.3–9.9)	0.0378
Contralateral lung			
D0.1cm³	5.5 (0.0–11.7)	3 (1.0–5.6)	0.0000
D1cm³	3.6 (0.0–8.3)	2.5 (0.6–4.8)	0.0228

*Mann-Whitney U test

TABLE 8. Treatment characteristics and mean dosimetric parameters in publications for accelerated partial breast irradiation (APBI) with CyberKnife

Publication	Xu 2012[25]	Vermeulen 2014[51]	Goggin 2015[26]	Rault 2016[27]	Obayomi 2016[52]	Lozza 2018[53]	Bonfantini 2018[28]	Lee 2018[29]	Lee 2020[54]	Fröhlich 2020[36]	Current study
Patient number	14	21	9	10	10	20	10	10	103	25	32
Applicator	Cones	-	Iris, MLC	Iris	-	Iris	Iris	Cones	-	MLC	MLC
Beam number	-	151	- , -	-	155	180	122	-	-	-	40 (57)[@]
Fractionation	10 x 3.85 Gy	10 x 3.4 Gy	5 x 6 Gy	10 x 4 Gy	5 x 6 Gy	5 x 6 Gy	5 x 6 Gy	5 x 6 Gy	5 x 6 Gy	4 x 6.25 Gy	4 x 6.25 Gy
Treatment Time (min)	-	46	28, 14.7	40	-	60	60	60	33[#]	-	33.3
CTV-PTV margin (mm)	2	2	2	3	5	5	5	2	0	2	2
Mean PTV volume (cm^3)	-	114	-	-	70	88.1	121.6	37.7	73.6	71.6	71.7
Ipsilateral breast											
V100 (%)	7[#]	12	12.5, 12.2	-	14	28.7	-	10	-	-	9.6
V50 (%)	22.4[#]	26	25.8, 24.2	-	31	75	-	24	35.5[#]	-	23.3
Ipsilateral non-target breast											
V100 (%)	9	-	-	-	-	-	1.7	-	-	-	0.7
V50 (%)	23.1	-	-	17.6	-	-	16.3	-	-	10.5	10.5
Ipsilateral lung											
V30 (%)	1.3	3	1.9, 1.6	-	3	2.3	2.1	3	2.2[#]	-	1.0
V5 (%)	31.4[#]	-	39.4, 17.9	-	-	-	-	-	-	-	30.7
mean dose (%)	-	-	-	-	-	-	6	-	-	-	4.9
D0.1cm^3	-	-	-	-	-	-	-	-	-	57.5	52.2
D1cm^3	-	-	-	-	-	-	-	-	-	45	45.4
Heart											
V5 (%)	9.4	10	-	3.9	31	14	23.2	23	-	-	21.2
mean dose (%)	-	-	-	-	-	-	-	-	2.3[#]	-	3.3
D0.1cm^3	-	-	-	-	-	-	-	-	-	12.1	18.9
D1cm^3	-	-	-	-	-	-	-	-	-	10.5	16.6
Skin											
Dmax (%)	-	108.8	-	-	106.6	98.2	94.7	103.3	88.7[#]	99.6*	88.8*
Contralateral breast											
Dmax (%)	1.6	3	-	-	10	-	-	10	2.7[#]	3.8*	2.1*

* = D0.1cm^3; [#] = median value; [@] = segment number in parentheses; CTV = clinical target volume; MLC = multileaf collimator; PTV = planning target volume

non-coplanar beam entries. The absolute volumes encompassed by 100%, 50%, and 20% isodose surfaces are 16%, 19%, and 29% larger at CK compared to MIBT (Table 2). The volume of the ipsilateral breast was slightly larger in the CK group (984.4 cm^3 vs. 825.7 cm^3), but the PTV was also bigger (71.7 cm^3 vs. 58.2 cm^3), and this explains why the relative volumes of ipsilateral breast irradiated by the 100% and 50% dose for the two techniques were nearly identical (Table 3). There was no difference between the mean lung doses and the volumes irradiated by low dose (V5) for the two techniques (Table 4). However, the other examined dose parameters were significantly smaller with MIBT (D0.1cm^3: 41.0% vs. 52.2%, D1cm^3: 36.1% vs. 45.4%). The heart was better protected with CK, since all dosimetric parameters were smaller, but without statistical significance (Table 5). This observation is similar to the findings of Major et al.[34] when MIBT was compared to IMRT. In our CK group, almost half of the tumours located in one of the

upper quadrants, and in these cases, the heart protection was better maintained because the beams could avoid the heart directly. In most cases, the skin and ribs are close to the PTV, sometimes they are contacting, and that is why the MIBT performs better for these two organs. In close proximity to the implant, due to inverse square law, the dose gradient is high resulting in proper protection of adjoining organs. In our study, all dose parameters for skin and ribs were significantly lower for MIBT than for CK (Table 6). We note that the TG-43 formalism overestimates the skin dose because it assumes a full scattering condition, which is not fulfilled at all in breast BT.[34,57] From this follows that the real differences are even higher in favour of MIBT. The contralateral breast and lung receive low doses at both techniques, but the values were smaller with CK (Table 7). These organs are usually far from the PTV, and therefore in MIBT there is no way to lessen the dose without compromising the target coverage. In contrast, with proper selection

of beam orientations, such as choosing 'exit only' option for these volumes at optimization, the dose can be kept lower at CK. Both techniques require invasive intervention, but with different degrees of invasiveness. At MIBT sometimes quite a lot of catheters are implanted, but at CK the gold markers are inserted with 2–3 needles, only. The overall treatment times of CK and MIBT treatments were similar, every patient finished the therapy in four days.

The limitation of our study is that the dosimetric evaluation was performed on two separate patient populations. However, the patient selection, target volume definition, and organ delineations in the two patient cohorts were performed using the same rules by three experienced radiotherapists providing appropriate consistency. The volumes of ipsilateral breasts and CTV-s were similar in the two groups meaning a proper balance with respect to base-line dosimetry. The differences in patient characteristics and individual anatomy in two patient cohorts may cause some uncertainties regarding dosimetric comparison. However, this serves the purpose of assessment of real treatments. Using the same CT-data with identical contours to compare the two treatment techniques would decrease the uncertainties, but in that case real treatments are compared with hypothetical ones which can never be realized.[36] In contrast, the advantage of our current analysis is that both investigated treatment methods reflect reality, as in the study of Weed et al.[24], in which MIBT against MammoSite™ and 3D-CRT techniques was compared for three different patient cohorts. Our investigated two techniques are routinely used in our clinical practice, therefore the obtained results are realistic. However, whether the observed small dosimetric differences translate into different clinical outcomes requires further investigations with an assessment of more data.

Conclusions

In APBI, the dose distributions of MIBT and CK are similar with high dose conformity and comparable isodose lines between 50–100 % of PD, but at MIBT regions in the target volume irradiated by very high doses develop due to unique feature of the BT. The low dose isodose lines are nearly circular at MIBT and irregular at CK cases. Regarding the PD the CK treatments mimic well the BT irradiation with taking advantage of non-coplanar beam entries and management of organ motion. OAR-s

close to tumour bed (skin, ribs, ipsilateral lung) can be better protected with MIBT, but CK performs better for other organs (heart, contralateral breast, and lung). The advantage of CK is its less invasiveness, but its accessibility is very limited. BT is an easily accessible technique in almost all radiotherapy departments, but it demands proper skills with good dexterity.

Acknowledgements

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