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Cardiac morbidity

Radiation exposure of the heart, lung and skin by radiation therapy for breast cancer: A dosimetric comparison between partial breast irradiation using multicatheter brachytherapy and whole breast teletherapy

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ABSTRACT

Background and purpose: Accelerated partial breast irradiation by means of multicatheter brachytherapy shows great promise in the modern treatment of early breast cancer combining high efficacy in preventing tumour recurrence with low levels of toxicity. The present work attempts a dosimetric comparison between this treatment modality and conventional whole breast external beam radiotherapy by looking at differences in risk organ exposure to radiation.

Patients and methods: The planning CT data sets of 16 consecutive patients with left-sided breast cancer who received external beam radiotherapy to the whole breast followed by a boost to the tumour bed using multicatheter interstitial brachytherapy after breast conserving surgery were used to create two independent physical treatment plans – one for an external radiotherapy, one for sole partial breast brachytherapy in each case assuming a total reference dose of 50 Gy for each patient. Dose–volume parameters $D_{0.1cc}$, $D_{0.5cc}$, D_{1cc}, D_{2cc}, D_{5cc}, D_{10cc}, D_{25cc}, D_{50cc}, V_{100}, V_{90}, V_{50}, V_{10}, V_5 for the ipsilateral lung, the heart and the adjacent skin were calculated and compared between the two treatment modalities.

Results: All organs at risk showed a substantially lower radiation exposure in the brachytherapy plan. This was most pronounced for the heart with values differing by a factor of four. Although somewhat less marked this was also true for the ipsilateral lung and the adjacent skin with exposure ratios of three and two, respectively.

Conclusions: With the use of multicatheter interstitial brachytherapy substantial reductions in the radiation exposure of risk organs can be achieved in comparison to whole breast external beam radiotherapy. These are likely to translate into profound clinical benefits.

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A breast conserving treatment approach consisting of local tumour excision followed by postoperative radiotherapy to the whole breast has become the standard of treatment for the majority of breast cancer cases diagnosed today. This marks a major improvement from the days when radical surgery involving the removal of the whole affected breast was considered inevitable to minimize the risk of local recurrence. It also serves as an encouraging example of how the addition of radiotherapy has turned an essentially mutilating treatment strategy into one that while causing much less collateral damage does not compromise the high potential for local disease control [1].

Even so, there still seems to be room for improvement. Whole breast irradiation by its very nature of homogenously treating the whole breast takes no account of the uneven pattern of in-breast recurrences with the majority occurring within or close to the tumour bed and only very few occurring at more distant locations of the same breast [2,3]. Neither does it give any regard to tumour stage and other factors known to affect the risk of local recurrence such as patient age and the state of the resection margins.

Irradiation of the whole breast to the same homogenous dose may therefore possibly not be the optimal adjuvant treatment for all breast cancer patients since it may lead to parts of the affected breast and even adjacent vital organs such as the heart and lungs being exposed to unnecessary ionizing radiation. Unnecessary radiation exposure of vital organs is bound to increase the risk of potentially life-threatening side effects that is not offset by a corresponding increase in local tumour control. Indeed, a meta-analysis of long-term toxicity and survival data on patients treated postoperatively with whole breast irradiation shows a significant increase in mortality from all causes except breast cancer that becomes more pronounced the longer the follow-up period and is particularly evident at 20 years' follow-up, and efforts have therefore been made for some time to shield the heart from unnecessary

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irradiation [4,5]. In this context vascular events stand out as the predominant cause of death. More recent work has shown a correlation between the radiation exposure of the left ventricle measured as the left ventricular volume receiving at least 50% of the prescription dose and the appearance of perfusion defects in the left ventricle in patients with left-sided breast cancer. There was a strong dependence on volume with hardly any defects occurring in patients where the left ventricle was outside the 50% isodose. Likewise even small errors in set up leading to accidental inclusion of the myocardium in such patients were associated with the occurrence of perfusion defects which suggests a clear dose–response relation in the clinically relevant range [6,7].

These arguments have raised the concept of partial breast irradiation (PBI) for a subset of women who have breast tumours with favourable prognostic features and for whom a conventional course of postoperative whole breast radiotherapy would constitute an overtreatment [8]. If partial breast irradiation results in the same clinical success regarding local control, recurrence rate or overall survival, this modality will offer a chance for fewer side effects by reducing radiation dose to the skin and the thoracic organs by excluding from the target volume areas of the breast where the risk of recurrence is too low to warrant active treatment. In the case of accelerated partial breast irradiation (APBI), one more advantage is the reduction in treatment time to roughly 5 days. Currently, long-term results are available only from studies that have investigated partial breast irradiation using multicatheter brachytherapy as the mode of radiation delivery [9–14].

The data from these trials are very encouraging and we have therefore in this investigation attempted a quantitative intrapatient comparison of partial breast irradiation using multicatheter interstitial brachytherapy (BT) with external beam whole breast radiotherapy (WBRT) in terms of their associated differences in volume-dependent radiation exposure of adjacent organs such as the skin, heart and lungs.

Methods

The planning CT data sets of 16 consecutive patients with left-sided breast tumours, who had undergone breast conserving surgery and were scheduled to receive a course of postoperative whole breast external beam radiotherapy (EBRT) with a daily fraction dose of 1.8 Gy up to 50,4 Gy followed by an interstitial boost of 16 Gy encompassing the tumour bed using multicatheter brachytherapy, were used to perform a quantitative intrapatient comparison of the dose–volume parameters of the two different radiotherapy modalities.

For both the EBRT and the brachytherapy boost, patients underwent planning CT scans – first before the start of the EBRT and second after insertion of the interstitial catheters. As the implantation technique and the outlining procedure for the boost treatment volume are the same as for patients receiving interstitial partial breast therapy as their sole treatment, each patient's brachytherapy CT data set was used to create a hypothetical treatment plan for a course of accelerated partial breast interstitial brachytherapy to be virtually executed by a pulsed dose rate (PDR) technique with single doses of 0.6 Gy, 24 h per day up to a total dose of 50.0 Gy. Assuming first that a continuos low dose rate (LDR) regimen with dose rates around 50 cGy/h is biologically isoeffective to a fractionated irradiation regime with daily fractions between 1.8 Gy and 2 Gy and second, that PDR treatment performed at hourly intervals with doses per pulse of less than 1 Gy simulates a continuous LDR regime, both treatment modalities – the 50 Gy whole breast EBRT and the 50 Gy partial breast PDR interstitial brachytherapy (iBT) – were thought to be biologically equivalent. Using the LQ model with the correction for incomplete repair to calculate the BED for different tissue effects, described by α/β values between 1.8 Gy for late effects and 10 Gy for acute effects and tumour response, respectively, this equivalence can be partially verified [15]. On this assumption, dose–volume parameters can be directly compared using physical dose. Table 1 gives the BED values for both treatment modalities which have been calculated using the following equation: $\mathrm{BED} = D(1 + (1/(\alpha/\beta)) * d * (1 + \mathrm{Hm}))$, where [$D$: total dose, d: fraction dose, (α/β): tissue dependent fractionation sensitivity and Hm: repair half time $T_{1/2}$ dependent correction function for incomplete repair]. We have used α/β values ranging from 1.8 Gy to 10 Gy. This range includes also the α/β value of 3.6 Gy for breast appearance as calculated by Yarnold et al. [16]. The calculation confirms that the dose prescriptions for PDR brachytherapy and EBRT should have the same biological effect.

Table 1
Comparison of biological effectiveness of PDR-brachytherapy (PDR-BT) and EBRT for 50 Gy as total dose using the BED equation.

BED in $T_{1/2}$ interval	α/β = 1.8 Gy	α/β = 3 Gy	α/β = 5 Gy	α/β = 10 Gy
$\mathrm{BED}_{\mathrm{EBRT\ 28*1.8Gy=50.40Gy}}$/Gy	100.80	80.64	68.54	59.47
$\mathrm{BED}_{\mathrm{PDR\text{-}BT\ 83*0.6Gy=49.80Gy}}$/Gy (0.75–1.5) h	101.73	80.96	68.50	59.15

Treatment planning

External beam radiotherapy

All patients underwent a CT scan of their chest prior to WBRT for 3D conformal radiotherapy planning. Patients were scanned from the tip of the mandible down to the lower border of diaphragm including both costophrenic angles. Scans were performed with the patient breathing at rest. For whole breast irradiation the planning target volume (PTV) was defined as the left breast including its whole thickness extending from the sternal notch superiorly to two centimetres below the lower clinical border of the breast inferiorly. Medially and laterally the edge of the sternum and the mid axillary line were used as landmarks, respectively. Both the defined PTV and the organs at risk (OAR) – ipsilateral lung, heart and adjacent skin (skin thickness was taken to be 5 mm as a standard value for all patients) – were contoured. The heart, lungs and skin were contoured by marking their surfaces as seen at the moment of the CT scan with the patient breathing normally.

For the irradiation with 6 MV photons from a linear accelerator, individual 3D conformal physical treatment plans were generated using either tangential opposing beams or a rotational technique. A dose of 50.4 Gy was prescribed and specified according to ICRU 50 [17]. DVH parameters were calculated and the plan was accepted if the following constraints for coverage, homogeneity and lung dose were fulfilled: $D_{\max} < 115\%\ D_{\mathrm{ref}}$, D90 > 100% and dose to 20% of the lung volume should not exceed 20 Gy.

Treatment planning was performed using the Pinnacle software (Phillips version 8.0 m). An example of an EBRT treatment plan is shown in Fig. 1.

Partial breast irradiation using multicatheter brachytherapy

Prior to the implantation of 6 french flexible plastic afterloading catheters, the location of the tumour bed was identified using intraoperative X-ray imaging to visualize the titanium clips. Implantation was then performed in a geometrically uniform way by use of a template and a sufficient number of catheters were used to cover the tumour bed with a safety margin of at least two to three centimetres in all directions [18].

After catheter insertion all patients underwent a CT scan with slice thickness of 2 or 3 mm in which the boost volume (for the real treatment) or the PTV for APBI (for the purposes of this study) was defined as follows.

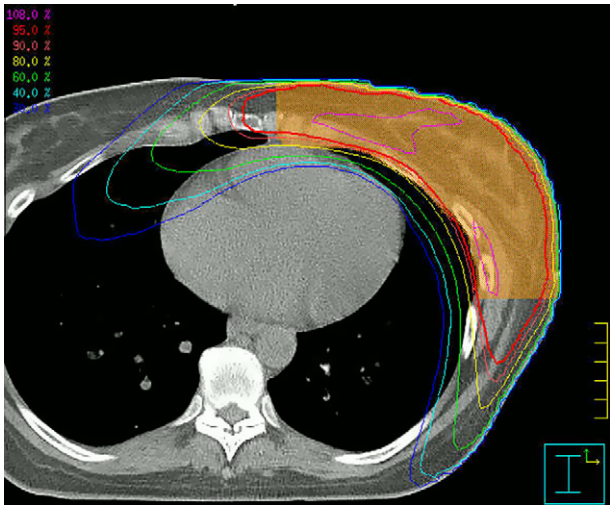

Fig. 1. Example of dose distribution of external beam whole breast irradiation.

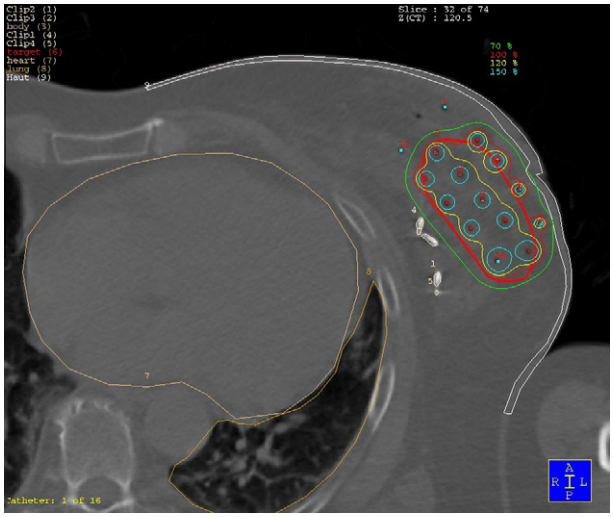

Fig. 2. Example of dose distribution of APBI using multicatheter brachytherapy.

For the definition of the target volume (PTV = CTV) the tumour bed was first identified with the help of titanium clips which had been left as markers on the chest wall at the time of surgery as well as information from preoperative mammography or ultrasound images. The CTV was then defined as the tumour bed plus a minimum margin of 20 mm in all directions [18] while keeping a minimum distance of 5 mm from the skin surface. Posteriorly, the CTV did not extend beyond the fascia of the chest wall muscles. The OAR were contoured in the PLATO planning software in the same way as for EBRT in the Pinnacle planning software. All contouring for EBRT and BT were done by the same physician in each case.

For the physical treatment plan, after catheter reconstruction and definition of the dwell positions, the dose distribution was optimised; starting with a geometrical optimisation followed by manual modification of the dwell times, to get a CTV adapted homogenous dose distribution. The dose was prescribed and specified according to ICRU 58 resulting in reference doses being 80–90% of the MCD [19]. The plan was accepted if the following constraints were met:

$V_{100} > 90\%$, DNR = $V(1.5 * D_{ref})/V(D_{ref}) < 0.30$ and the dose to the skin surface is smaller than 70% of D_{ref}.

Treatment planning for brachytherapy was performed using the PLATO software (Nucletron, version 14.2.6). An example of a brachytherapy treatment plan is shown in Fig. 2.

Table 2
Quality parameters of interstitial implants.

	Number of tubes	Number of implant planes	DNR	V_{ref}	V_{150}
Value (median)	16	3	0.22	89.3 cc	21 cc

DNR = dose non-uniformity ratio V_{ref} = volume of the reference isodose.

Plan evaluation

Dose–volume parameters for each OAR were calculated for each patient for both the external beam whole breast treatment plan and the partial breast brachytherapy treatment plan. In particular the dose to a certain absolute tissue volume $D_{V/cc}$ – parameters $D_{0.1cc}$, $D_{0.5cc}$, D_{1cc}, D_{2cc}, D_{5cc}, D_{10cc}, D_{25cc}, D_{50cc}, and the volume that is exposed to a certain percentage part of the reference dose $V_{\%Dref}$ – V_{100}, V_{90}, V_{50}, V_{10} and V_5 for the heart, the ipsilateral lung and adjacent skin were used to compare risk organ exposure to radiation.

Statistical analysis

For each of the dose–volume parameters the mean was calculated by summing the values obtained for all patients. Differences in the means of the dose–volume parameters for brachytherapy and for external beam radiotherapy were tested for statistical significance using the paired two-tailed Student's *t*-test as well as the rank test. The paired *t*-test was used because each patient served as her own control with the same CT data set being used for both the brachytherapy and the external beam plan.

Results

Looking at the maximum doses received by different volumes of the heart, the lungs and the skin, dose values for all OAR are consistently lower for partial breast irradiation using brachytherapy than those for whole breast irradiation with EBRT. An example of parameters describing interstitial implant characteristics and quality are given in Table 2.

In the case of the heart, the $D_{0.1cc}$, (which represents the dose received by the most highly exposed 0.1 cc of the risk organ, i.e. the dose peak) is only 12.59 Gy for partial breast brachytherapy whereas for external beam whole breast irradiation values in excess of 45 Gy are reached. The situation for the ipsilateral lung and the adjacent skin is similar with much higher peak doses occurring in the external beam treatment plans as compared to the brachytherapy plans (lung: 51.99 Gy vs 19.61 Gy, skin: 54.58 Gy vs 35.15 Gy). A corresponding pattern is found for the $D_{0.5cc}$, D_{1cc}, D_{2cc}, D_{5cc}, D_{10cc}, D_{25cc}, D_{50cc} which are progressively less sensitive to dose peaks and representative of the dose received by progressively larger volumes of the risk organ in question (see Tables 3–5).

When looking at the V_{10} and V_5 which measure the volume of the risk organ exposed to relatively low doses of radiation there was a considerable difference for all risk organs in favour of brachytherapy. Taking the V_{10} as an example, the brachytherapy value is about a quarter of the WBRT value in the case of the heart (64.11 cc vs 242.05 cc) as well as the ipsilateral lung (138.41 cc vs 645.21 cc). For the skin the V_{10} for brachytherapy is still less than one-third of the WBRT value (39.2 cc vs 142.74 cc) (see Tables 3–5).

Discussion

Assuming that APBI is equivalent to EBRT in terms of local tumour control rates, the presented results show that partial breast irradiation using multicatheter brachytherapy is clearly superior

Table 3
Dose parameters characterizing radiation exposure of the heart using partial breast brachytherapy vs whole breast external beam radiotherapy.

Heart	D_{50cc}	D_{25cc}	D_{10cc}	D_{5cc}	D_{2cc}	D_{1cc}	$D_{0.5cc}$	$D_{0.1cc}$	
Mean external beam	18.17 ± 8.83 (36.35)	27.49 ± 9.60 (54.98)	35.86 ± 8.61 (71.72)	39.39 ± 7.98 (78.78)	41.91 ± 7.63 (83.82)	43.11 ± 7.30 (86.21)	44.06 ± 6.88 (88.12)	45.60 ± 5.79 (91.20)	Gy ± SD (%of 50 Gy)
Mean brachytherapy	5.60 ± 2.40 (11.20)	7.01 ± 3.13 (14.01)	8.64 ± 4.00 (17.28)	9.65 ± 4.53 (19.31)	10.72 ± 5.10 (21.44)	11.34 ± 5.43 (22.68)	11.82 ± 5.67 (23.64)	12.59 ± 6.01 (24.19)	Gy ± SD (%of 50 Gy)
p-Value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	

Heart	V_{100}	V_{90}	V_{50}	V_{10}	V_5	
Mean external beam	0.02 ± 0.06	0.76 ± 1.73	51.07 ± 88.38	242.05 ± 218.77	416.00 ± 226.91	cm^3 ± SD
Mean brachytherapy	0.00 ± 0.00	0.00 ± 0.00	0.18 ± 0.12	64.11 ± 62.37	208.89 ± 90.86	cm^3 ± SD
p-Value	<0.01	<0.01	<0.01	<0.01	<0.01	

Table 4
Dose parameters characterizing radiation exposure of the ipsilateral lung using partial breast brachytherapy vs whole breast external beam radiotherapy.

Lung	D_{50cc}	D_{25cc}	D_{10cc}	D_{5cc}	D_{2cc}	D_{1cc}	$D_{0.5cc}$	$D_{0.1cc}$	
Mean external beam	43.38 ± 3.37 (86.77)	46.03 ± 2.32 (92.06)	48.28 ± 1.57 (96.57)	49.33 ± 1.50 (98.67)	50.30 ± 1.48 (100.59)	50.83 ± 1.48 (101.66)	51.26 ± 1.47 (102.52)	51.99 ± 1.49 (103.98)	Gy ± SD (%of 50 Gy)
Mean brachytherapy	8.19 ± 2.83 (16.38)	10.53 ± 3.39 (21.07)	13.32 ± 4.12 (26.65)	15.03 ± 4.65 (30.07)	16.74 ± 5.19 (33.48)	17.70 ± 5.52 (35.40)	18.44 ± 5.78 (36.88)	19.61 ± 6.19 (39.23)	Gy ± SD (%of 50 Gy)
p-Value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	

Lung	V_{100}	V_{90}	V_{50}	V_{10}	V_5	
Mean external beam	2.65 ± 3.36	16.97 ± 11.80	219.52 ± 62.80	645.21 ± 179.73	1062.05 ± 226.45	cm^3 ± SD
Mean brachytherapy	0.00 ± 0.00	0.00 ± 0.00	0.33 ± 0.79	138.41 ± 85.66	345.22 ± 159.84	cm^3 ± SD
p-Value	<0.01	<0.01	<0.01	<0.01	<0.01	

Table 5
Dose parameters characterizing radiation exposure of the adjacent skin using partial breast brachytherapy vs whole breast external beam radiotherapy.

Skin	D_{50cc}	D_{25cc}	D_{10cc}	D_{5cc}	D_{2cc}	D_{1cc}	$D_{0.5cc}$	$D_{0.1cc}$	
Mean external beam	46.82 ± 5.59 (93.65)	49.96 ± 2.99 (99.92)	51.66 ± 2.22 (103.31)	52.45 ± 1.98 (104.89)	53.18 ± 1.78 (106.36)	53.61 ± 1.67 (107.22)	53.97 ± 1.59(107.95)	54.58 ± 1.48 (109.16)	Gy ± SD (%of 50 Gy)
Mean brachytherapy	2.38 ± 3.63 (10.88)	9.60 ± 3.98 (19.19)	21.24 ± 2.73 (42.59)	24.93 ± 3.21 (49.86)	28.05 ± 3.97 (55.10)	30.02 ± 4.49 (60.04)	31.75 ± 5.04 (63.50)	35.15 ± 6.45 (70.31)	Gy ± SD (%of 50 Gy)
p-Value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	

Skin	V_{100}	V_{90}	V_{50}	V_{10}	V_5	
Mean external beam	39.92 ± 31.79	74.75 ± 49.92	139.37 ± 63.13	142.74 ± 63.32	143.03 ± 63.08	cm^3 ± SD
Mean brachytherapy	0.01 ± 0.01	0.01 ± 0.03	3.88 ± 3.34	39.20 ± 16.83	48.56 ± 24.43	cm^3 ± SD
p-Value	<0.01	<0.01	<0.01	<0.01	<0.01	

to whole breast irradiation when parameters derived from the DVHs for the adjacent risk organs are used as a basis for comparison. As a rough guide our results show that the dose parameters differ most for the heart where APBI outperforms whole breast external beam radiotherapy by a factor of 4, followed by the lungs and the skin where APBI leads by a factor of 3 and 2, respectively.

To assess the clinical significance of improvements in the physical parameters characterizing the exposure of risk organs to ionizing radiation it is necessary to know how normal tissue side effects and complications depend on radiation dose. Unfortunately data that throw light on this question are very hard to obtain and are scattered sparsely throughout the literature [20]. In view of this lack attempts have been made to develop theoretical models that establish a connection between the physical radiation dose, the irradiated volume and the likelihood of complications arising in the irradiated tissues as a result of the exposure [21]. The complexity of the dose–response relation for the whole organ is considered a result of the complex ways in which damaged subunits interact to cause functional impairment at the organ level [22]. Broadly speaking, interactions can be either serial or parallel. When the mechanism is serial, damage to a single subunit may be sufficient to cause loss of function of the whole organ. With a parallel mechanism there is redundancy and loss of a single subunit may not be clinically apparent. With this in mind it is now worth taking a look at the different risk structures one by one.

Considering the case of the heart, coronary artery disease arising as a result of or being exacerbated by exposure to ionizing radiation must be seen as a potential late complication of radiotherapy that has great clinical significance. In western countries it rivals cancer as the single most common cause of death and even small increases in relative risk must therefore be taken very seriously. The vasculature of the heart is known to have little to no built-in redundancy with the occlusion of a single vessel or branch thereof often having catastrophic consequences. The underlying mechanism is therefore essentially serial and confining a high dose to a small volume may therefore not do much to reduce the risk that results from the same dose given to a larger volume. In this context the fact that the doses received by the most exposed small subvolumes of the heart (i.e. $D_{0.1}$ 45.6 Gy vs 12.59 Gy) are a lot less for partial breast brachytherapy than for whole breast external beam radiotherapy is an important finding of the present work because it suggests that this would reduce the probability of late complications. The finding that the volume exposed to low doses of radiation is also less (V_{10}, V_5) would further reduce risk if exposure to

low radiation doses, i.e. less than 10 Gy, is also atherogenic. For the end point of coronary events all the DVH parameters considered therefore suggest a risk reduction.

The ipsilateral lung is another organ that can develop complications as a result of breast radiotherapy. The main acute problem is radiation pneumonitis the mechanism of which is not well understood and which has a complex relation to dose and volume. Although in mild cases it usually responds well to treatment and leaves no lasting impairment it causes a temporary reduction in quality of life and in its chronic stages causes a localized fibrotic reaction which may be relevant in patients with preexisting lung disease The question of how differences in the distribution of radiation dose that leave the mean dose unchanged influence side effects has been hotly debated in the literature and has been poignantly referred to as "the debate of a lot to a little vs a little to a lot" [23]. Our data show that both in terms of the highly exposed small volumes ("a lot to a little", e.g. $D_{0.1}$ 51.99 Gy vs 19.61 Gy) and in terms of the larger volumes exposed to low doses ("a little to a lot", e.g. V_{10} 645.21 cc vs 138.41 cc) partial breast brachytherapy is superior to external beam whole breast radiotherapy and therefore suggest that while the above-mentioned debate is ongoing the resulting complication probability for the lung should be less for patients treated with brachytherapy.

Last but not least the skin and cosmetic considerations must also be looked at when comparing the side effect profiles of the two treatments. In the case of whole breast external beam radiotherapy the skin is considered part of the target volume and therefore receives the whole treatment dose. Partial breast brachytherapy constitutes a means whereby the skin can be spared effectively. This is borne out by our data which show much better values for the brachytherapy plans (e.g. $D_{0.1}$ 54.58 vs 35.15 Gy) Because the skin is easily inspected its response to radiation is much more thoroughly researched than for the heart and lungs, and there are data from the literature which show that the dose reductions resulting from the use of brachytherapy have clinical relevance in terms of reducing fibrosis and improving cosmesis. There are in fact several current phase II trials with long-term follow-up to support the relevance of this effect [12,24–27].

It is interesting to compare our data to those from other work evaluating EBRT against APBI using the MammoSite balloon [28,29]. While the DVH parameters for the MammoSite balloon show strong similarity to our results over the higher dose range this is not true for exposure to low doses, i.e. V_5 or less. Over this dose range the MammoSite balloon was found to perform worse than EBRT when looking at the heart as the organ-at-risk [29]. Importantly, this phenomenon is not seen with multicatheter APBI as demonstrated in our study, probably because of its ability to individually shape the dose distribution and may be considered a reason for preferring the multicatheter technique over the MammoSite balloon while the clinical relevance of exposure to low doses is not adequately known.

Another interesting comparison can be made with data from a dosimetric study looking at tomotherapy as an alternative tool for dose delivery in partial breast irradiation. Although in this study PTV coverage from tomotherapy was found to be very good as would be expected for this modality this was at the expense of an increase in radiation dose to the heart and ipsilateral lung compared to EBRT which would suggest that tomotherapy is not a good alternative to multicatheter brachytherapy for partial breast irradiation [30].

Conclusion

Our data show that accelerated partial breast irradiation (APBI) using multicatheter brachytherapy effectively reduces radiation exposure of organs-at-risk in comparison to whole breast irradiation using EBRT.

Dose parameters are most discrepant for the heart where APBI outperforms whole breast external beam radiotherapy by a factor of 4, followed by the lungs and the skin where APBI leads by a factor of 3 and 2, respectively. Importantly, this is true for the low as well as the high-end of the dose spectrum. From theoretical considerations this should lead to a reduction in the risk of important clinical endpoints such as cardiovascular events. Large scale clinical trials with very long periods of follow-up will be needed to prove this expected risk reduction in the clinical setting.

Conflict of interest statement

None of the authors has any financial and personal relationships with other people or organisations that could inappropriately influence (bias) our work.

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