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CHAPTER 2

Treatment planning studies in
whole breast irradiation to reduce heart
and LAD dose

A heart sparing technique in women with left-sided breast cancer. Results of 4 years of experience in Radiotherapy Centre West

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Summary

The literature shows that, with the increasing survival of breast cancer patients after breast conserving therapy, the various therapies are associated with an increased risk of fatal cardiovascular events. Furthermore, the data also indicate that even today, recent techniques in left-sided breast cancer radiotherapy administer high doses radiation to the heart, and more specifically to the left anterior descending coronary artery.
A breathing adapted technique in left-sided breast cancer can be used to reduce the dose in the heart and in the coronary arteries. This technique is easy to use in daily practice. In Radiotherapy Centre West (RCWEST) the Active Breathing Control (ABC) method was used. We found that the preparation time increased once only by one hour; the time spent by the patient at the linear accelerator was not increased compared to the time without using the breathing adapted technique. The ABC method is well-suited to daily practice; 99% of the patients with clinical T1-2, N0-2, M0 left-sided breast cancer who were treated with the ABC technique, could complete the treatment. Until a threshold has been found to reduce heart damage after breast conserving radiation therapy, RCWEST administers the ABC method to all patients with left sided-breast cancer, as every reduction in heart dose is of importance.

Introduction

Breast cancer is the most common type of all cancers in The Netherlands. Breast-conserving therapy (BCT) is offered only if a good cosmetic result and optimal loco-regional tumour control can be achieved. In all other cases breast ablative surgery is opted for. Fractionated whole breast irradiation is seen as an integral part of breast conserving therapy [1]. Due to the improved survival probability of breast cancer patients, Darby et al. reported in 2005 that the probability of the occurrence heart diseases as caused by the various treatment modalities, is increased. The latter specifically applies to left-sided radiation, chemotherapy (including anthracyclines) and biologicals (trastuzumab). Due to improved irradiation techniques the increased risk of heart disease after irradiation clearly decreased over the years and is, after more than 10 years of follow-up, no longer present [2]. However, Taylor et al. stated that parts of the heart (the myocardium, but especially the Left Anterior Descending coronary artery (LAD) still receive high radiation doses with current radiation techniques [3]. The systematic review of Sardaro et al. shows that still much is unclear with respect to the resulting radiation-induced heart damage in breast cancer patients [4]. Various (preclinical and clinical) studies show the occurrence of atherosclerosis and arterial wall thickening after irradiation [5-7]. Decreasing the heart dose in breast cancer patients is, therefore, of (great) importance.
In recent years, several authors reported that a breathing-adapted irradiation technique could be used. This method, in which irradiation is applied only during a period of breath-hold, leads to a marked decrease of the heart dose. Breathing-adapted irradiation can be carried out by various methods. Active Breathing Control (ABC) is one of these methods (see Figure 1). In a recent article Swanson et al. described that the ABC method leads to a significantly lowered heart dose. They also showed that this method is well able to be sustained in patients with breast cancer. In the mean time, they have applied the ABC method for 6 years [8]. Breathing-adapted method appears to be feasible for loco-regional irradiation as well [9-11].

After an extensive literature study conducted by Van der Klein et al., we started an ABC pilot study in mid 2008 [12]. The aim of this study was to evaluate the feasibility of the routine implementation of the ABC method. In addition to providing support to the patient in the linear accelerator, the training of the patient on the computed tomography

(CT) -simulator and performing the CT scan differs from the routine procedure. The technique proved feasible for various patients [13]. From January 2010 onwards, the ABC method was implemented for all left-sided irradiation of breast cancer in our clinic. In The Netherlands (and outside of The Netherlands as well), little is known about the feasibility of the ABC method in a radiotherapy department. For this reason, we present our experiences.

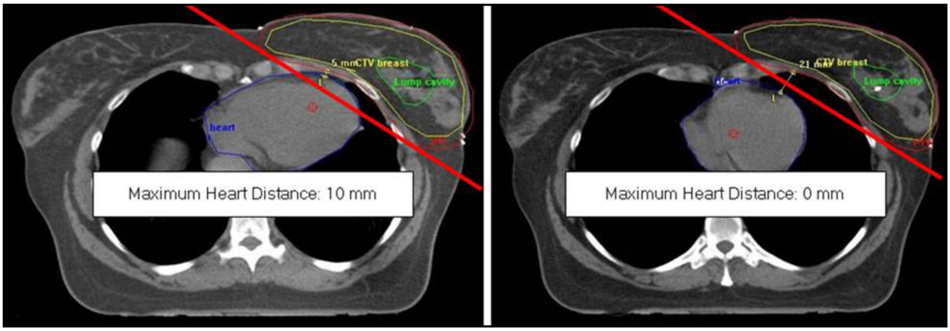

Figure 1. Example of a specific case planned to be irradiated in "Radiotherapiecentrum West" for left sided breast cancer with free-breathing (FB) (left) and with breath hold (BH) (right). These axial slides show that the cardiac dose is lower for the BH-case. In yellow the CTV breast; green: lumpectomy cavity; red: dorsal radiotherapy field border. The anatomy differs slightly between the left and right side of the Figure because of the performed breath-hold.

Materials and methods

First of all, a dedicated radiation therapist (RTT) informs the patient on the radiotherapy as well as on the necessary preparations. The latter is illustrated by a PowerPoint presentation. Then a training session takes place. In this training session, the patient practices with the Active Breathing Coordinator (ELEKTA, Crawley, United Kingdom) equipment. During this training session the lung volume of each patient and the threshold, above which she should inhale, is determined. For each patient, the number of seconds during which she is able to hold her breath, is registered. Once the patient understands the method well and can carry out the instructions of the radiation therapist (RTT), a CT scan in free-breathing (FB) and a CT scan breath-hold (BH) are performed.

If the patient, at a later time, is unexpectedly unable to follow the instructions of the ABC method correctly, the FB CT scan can be used. The glandular breast tissue is, using the ABC method, irradiated with two tangential opposing fields. A dose of 16 x 2.66 Gy is administered. Only on indication a boost dose was given. This boost dose was directed to the lumpectomy cavity. In this review on patients irradiated with BH at Radiotherapy Centre West (RCWEST) we limit ourselves to the period of January 1th in 2010 to December 31th in 2011. During this time, a total of 284 patients with left-sided breast cancer were irradiated. Forty of these patients were irradiated with another technique, e.g. irradiation of only the supraclavicular nodes or single dose radiotherapy during breast conserving surgery, the so-called intraoperative radiation therapy (IORT). A total of 52 patients (18%) was not irradiated with the ABC method due to a prior estimate of the radiation oncologist or because the method was not feasible. In Table 1 we summarised the reasons why the ABC method could not be carried out. Ultimately, 192 patients were irradiated with ABC. Of this group, only the patients with cT1-2;N0-2;M0 left-sided breast cancer, that were irradiated locally or loco-regionally, were included in this study. The following characteristics of each patient were registered: whether only a local or a locoregional radiation technique was applied; whether the ABC method could be completed by the patient or not; above which threshold (after the training) the patient ought to inhale; how long (in seconds) the patient could hold her breath; how many breath-holds had to be carried out during each session of irradiation; and whether the patient was familiar with pre-existing lung disease.

	Not irradiated with the breath-hold technique
Age (>95 years)	1
Physical limitations:	
- pulmonary diseases: e.g. COPD	5
- other	4
Communicative limitations (language, deafness, etc.)	8
Psychological limitations	5
Other; estimation of the radiation oncologist, e.g. latex allergy	29

Table 1. Summary of limitations of patients with cT1-2; N0-2; M0 left-sided breast cancer prone to be irradiated with the ABC breath-hold technique.

Finally, in 20 consecutive patients of our study population we examined whether the dose in the heart and the left coronary artery (LAD) could be reduced when using the ABC method. For these analyses the following values were determined and compared to each other: (i) V50 %, the volume that receives 50% of the dose; (ii) D10, the dose that encompasses 10% of the volume; (iii) D50, the dose that encompasses 50% of the volume.

When performing the statistical analysis we used a 'Wilcoxon Signed Rank Test' and a p-value of <0.05 was considered as significant.

Results

Three (1.6 %) out of 192 patients were not able to complete the ABC procedure during their irradiation course. Retrospectively, we concluded that these patients had not completely understood the procedure.

A total of 175 patients, 174 women and 1 male, bearing a cT1-2;N0-2;M0 left sided breast cancer, had been included in the study. A total of 18 patients were affected by a restriction, but still were treated with the ABC-method (see Table 2). For example, a patient was irradiated who could only speak a foreign language. After defining a number of clear agreements the ABC-method could be completed. The mean age of the cohort was 56 years, ranging from 28 to 85 years. Twenty-five percent of the patients was irradiated loco-regionally.

The mean number of seconds that the patients could hold their breath was 26, ranging from 18 to 33. The mean of all lung volumes was 1.7 litres; with a range of 0.7 litres-2.5 litres. The limited lung volume of 0.7 litres for one particular patient appeared to place no restriction on completing her treatment sessions without any problem. We noted that a difference in lung volume of at least 0.2 litres must be achieved, because a smaller difference leads to a very limited chest wall extension and, hence, will result in a too small increase in the distance between the heart and the radiation fields. The total irradiation time takes about 2-3 minutes. For this reason the patient is asked to hold her breath over and over again. During each session of radiotherapy, on average 5 periods of breath-hold, with a range of 2-10 breath-holds, were necessary. The highest number of breath-holds was needed when irradiating loco-regionally. The same threshold values were used in patients receiving a boost dose (directed at the lumpectomy cavity). Again, on average 5 breathing-holds, with a range of 3-9 breath-holds, were needed.

Prematurely stopped with the ABC-breath-hold technique	Irradiated with the ABC-breath-hold technique	Prematurely stopped with the ABC-breath-hold techniqu
Age (>95 years)	0	0
Physical limitations:		
- pulmonary diseases: e.g COPD	13	0
- other	0	0
Communicative limitations (language, deafness, etc.)	4	0
Psychological limitations	1	1

Table 2. Summary of limitations of patients with cT1-2; N0-2; M0 left-sided breast cancer irradiated with and without the ABC breath-hold technique.

With the introduction of the ABC method the preparation time, when compared to the situation without using the ABC method, lasted about one hour longer; in one and a half hours, the patient has undergone the training and the two CT scans were made (FB and BH). After going through the learning curve of the radiation therapist, for which temporary extra time was given to accompany the patient on the radiation device to control the breathing, the time that is scheduled per patient lasts no longer than was previously the case (without the use of the ABC method), and is the same for a right-sided breast cancer irradiation. For local irradiation 10 minutes and for loco-regional irradiation 15 minutes is scheduled. Apart from the patients whose ABC method was not feasible in the long run, we noted no further challenges or emergency stops during the full course of the radiation therapy.

The analyses of the radiation treatment plans show that the ABC-method results in a significantly lower dose in the heart and the heart vessels and at the same time appear to have a comparable coverage of the irradiated target volume (see Table 3).

Mean; n=20	BH	FB	p-value
Heart V50 (%)	1,4	4,9	<0,01
Heart D10 (Gy)	3,0	7,3	<0,01
Heart D50 (Gy)	0,8	1,0	<0,01
LAD V50 (%)	16,9	41,6	<0,01
LAD D10 (Gy)	20,9	33,0	<0,01
LAD D50 (Gy)	7,3	19,7	<0,01

Table 3. Dose volume values for the heart and the 'Left Anterior Descending coronary artery' (LAD): For the 'breath-hold'(BH) technique and in 'Free-breathing'(FB).

Discussion

The breathing-adapted irradiation is well enforceable in daily practice; of patients with cT1-2;N0-2;M0 left-sided breast cancer, and being irradiated with the ABC-method, 99% can completely sustain the treatment. Little is known about the feasibility of the ABC method. Massaccesi et al. indicated that 90% of the patients the method can insist, however, they have examined a group of only 20 patients [14].

But data are available on another method of heart sparing: the 'Gating' technique. Irradiation with this technique is administered only when the breathing cycle of the patient is within a certain predefined phase. In their institute, Berson et al. noted beforehand that 20% of their patients (n=136) were not suitable to undergo the 'Gating'-technique [15]. The latter was partly due to reasons other than not being able to perform the technique. They reported that 97% of the patients who started the treatment with the "Gating" method could sustain it till the end [15].

Our study showed that 29 patients (15%) were irradiated without the ABC method. The radiation oncologist had judged beforehand that these patients were not suitable to undergo the ABC method. This assessment did not only take place in the start-up phase, but was kept up regularly in the past 2 years. For example, patients have been irradiated without ABC. One of the considerations was a latex allergy. But the ABC-respiratory equipment contains no latex, so in that respect, this patients could have undergone the irradiation with the ABC method. Thus, eventually more patients could have been irradiated with the ABC method. We recommend that radiation therapists perform an assessment to judge whether (yes/no) the patient is able to complete irradiation combined with the ABC method. The radiation oncologist decides on medical grounds whether (yes/no) the patient is eligible for the ABC method.

Since RCWEST is located in the centre of The Hague, relatively a large number of patients of foreign origin is referred for treatment to RCWEST (patients living in the 'Schilderswijk', patients working at the embassies). Many of them do not speak the Dutch language properly. We did not explicitly investigate this item. Despite the observed language barrier, we observed that the ABC method could successfully be carried out regularly in this group. Massaccesi et al. noted in their feasibility study that the workload increased [14]. However, we noticed that when the ABC method is administered to all patients with left-sided breast cancer, this technique is no longer an exception and, hence, the radiation therapists feel familiar with this method. For this reason, there is no need anymore to schedule extra time on the linear accelerator. The preparation time, though, remained increased by about one hour. This extra time is required to prepare the patient in a proper manner for the breathing adapted irradiation. Based on these findings, we plan to pass the FB scan, thus reducing the preparation time.

To handle a maximum age to propose (or not to propose) the option with ABC is a matter of opinion and grounds for debate. However, a paper by Van Schoor et al. makes clear that the expected mean median survival duration of women aged 75 years is 10 years [16]. Also, Louwman et al. indicate that the relative survival (taking into account the risk of mortality due to causes other than breast cancer) of a 70-year old patient with breast cancer lasts 3-10 years after breast cancer diagnosis. This is similar to the relative survival duration of breast cancer patients aged 40-70 years. The relative survival 3-5 years after diagnosis of breast cancer of 80-year old female breast cancer patients is 5% lower than breast cancer patients of 40-70 years; it should be kept in mind that the stage distribution in this 80-year old group was often worse and that this group of patients was regularly undertreated [17].

Since the effects of irradiation for cardiovascular damage may become manifest after 10 years, using the ABC method of patients over 70 years of age can be justified [2]. In RCWEST, no age limit is used when proposing the ABC method. Wang et al. indicate that, by means of an automatic planning process, insight is obtained into which patients may benefit from a breathing adapted irradiation technique [18]. They opt for a dose reduction at the heart of a small group of patients (the threshold V50> 10 cm^3), which implies that only in 15-20% of all left-sided breast cancer patients the ABC method would useful [18]. Taylor et al., however, do not expect that the dose of the current irradiation techniques, when compared to those of the older techniques, is reduced. And a threshold dose is not yet determined [19]. For this reason, the aim of RCWEST is to reduce the dose to the heart and the heart vessels to zero.

Qi et al. indicated that because of the intrinsic motion the position of the heart and the heart vessels on the CT scan varies and appears to be only a snapshot in time. On a 4D-CT, this is a CT scan in which the patients were scanned in several phases of respiration; the location of both varies over a short period of time. They reconfirm that the lowest dose in the heart and the LAD was found at the end of the normal inspiration. In RCWEST, when using the ABC method, the patient is irradiated at a level of 75% of the patient's deep inspiration [20]. Wang et al. have also investigated the displacement of the heart and the coronary arteries, which shows that during the deep inspiration, the LAD was displaced around 2.3 mm. For this reason, they suggest to implement an extra safety margin of ≥5 mm between the LAD and the radiation field edge [21]. Follow-up studies to examine further reduction of the dose in the heart and the cardiac vessels (to compensate for the displacement of the heart) will take place in RCWEST.

Conclusion

The Active Breathing Control method appeared to be feasible in daily practice; in 99% of the left-sided breast cancer patients (cT1-2;N0-2;M0), treated with the ABC method, it can be sustained. Until it becomes clear which threshold dose should be used for evaluating the risk of reducing heart damage, in RCWEST the breathing adapted irradiation technique is offered to all patients with left-sided breast cancer. Furthermore, any reduction in heart dose is judged to be of importance, especially in patients who are prone to receive cardio toxic chemotherapy (e.g., adriamycin and trastuzumab).

Recommendations

1. We advice to combine the breath-hold technique with irradiation for all women bearing left-sided breast cancer, because this technique is easy to implement into daily practice.
2. More research is needed to assess the threshold dose.

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Left-sided breast cancer radiotherapy with and without breath-hold: Does IMRT reduce the cardiac dose even further?

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Abstract

Purpose

In radiotherapy for left-sided breast cancer, Active Breathing Control enables a decrease of cardiac and Left Anterior Descending (LAD) coronary artery dose. We compared 3D-Conformal (3D-CRT) to Intensity Modulated Radiotherapy (IMRT) treatment plans based on free-breathing (FB) and breath-hold (BH). We investigated whether IMRT enables an additional decrease of cardiac dose in radiotherapy plans with and without BH.

Materials and methods

Twenty patients referred for whole breast irradiation were included. The whole breast, heart and LAD-region were contoured. Four treatment plans were generated: FB_3D-CRT; FB_IMRT; BH_3D-CRT; BH_IMRT. Several doses were obtained from Dose Volume Histograms and compared. Results were compared statistically using the Wilcoxin Signed Rank Test.

Results

For heart and LAD-region, a significant dose reduction was found in BH ($p < 0.01$). For both BH and FB, a significant dose reduction was found using IMRT ($p < 0.01$). By using IMRT an average reduction of 5% was noted in the LAD-region for the volume receiving 20 Gy.

In 5 cases, the LAD-region remained situated in the vicinity of the radiation portals even in BH. Nevertheless, with IMRT the LAD dose was reduced in these cases.

Conclusion

IMRT results in a significant additional decrease of dose in the heart and LAD-region in both breath-hold and free-breathing.

Introduction

Left-sided breast cancer radiotherapy has been associated with an increased risk of fatal cardiovascular events [1]. These findings were confirmed in population-based studies carried out in Denmark, Sweden and The Netherlands. In these series, the risk of developing ischemic heart disease, pericarditis and valvular disease was increased [2,3]. Several (pre)clinical studies established that a higher risk on atherosclerotic lesions was found after radiation treatment [4,5]. Nilsson et al. and Correa et al. described the effect of radiotherapy on the development of stenosis after several years [6,7]. Recently, Darby et al. found that the incidence of ischemic heart disease was proportional to the mean dose to the heart and started to increase within a few years to at least 20 years after exposure [8]. Patients with pre-existing cardiac risk factors had higher absolute risks after radiotherapy than those without [8]. Correa et al. described that, in modern radiotherapy, a reduction in risk of coronary damage was noticed [7]. However, Taylor et al. found that, even in modern radiotherapy techniques, the anterior part of the heart, including the LAD, still receives doses of over 20 Gy [9]. These findings confirm the importance of taking the coronary arteries (i.e. the Left Anterior Descending coronary artery (LAD)) into account as an "Organ At Risk" when defining a radiation treatment plan.
Therefore, sparing the heart and the coronary arteries, specifically, the LAD, seems highly relevant to reduce cardiac morbidity risk in contemporary radiotherapy.

Various techniques are available to decrease the cardiac dose; the Active Breathing Control (ABC) method is one of these techniques. When using the ABC method the patient holds her breath during the administration of radiotherapy for left-sided breast cancer patients. In doing so, the distance between the heart and the radiation fields is enlarged. The use of ABC results in a significant decrease of the dose applied to the heart as well as of the dose applied to the LAD [10,11]. Intensity Modulated Radiotherapy (IMRT) is successfully used as a class solution for various tumor sites. Subsequently, several authors described the use of IMRT for the dose reduction in the heart during breast cancer irradiation. Coon et al. showed that the dose to the heart can be lowered in patients with unfavorable cardiac anatomy, when using an IMRT technique. And Schubert et al. found that inversely planned IMRT, when compared to a 3D-CRT technique, resulted in a lower dose to the heart without compromising the dose in the target volume [12,13].

In the present study, we examined whether the use of IMRT enabled an additional decrease of the cardiac dose as well as a further decrease of the dose to the LAD, in cases with and without the use of the ABC breath-hold technique. Therefore, we compared 3D-Conformal Radiotherapy (3D-CRT) treatment plans to IMRT treatment plans based on either a free-breathing or a breath-hold CT scan. In this way we were able to distinguish between the contributions of the breath-hold technique and those of the IMRT technique in lowering the cardiac dose and the dose to the LAD.

Materials and methods

Twenty consecutive patients, diagnosed with left-sided ductal carcinoma in situ or infiltrative breast cancer, were included in this planning study. All patients underwent breast-conserving surgery (and axillary staging). Thereafter, they were treated with whole breast radiotherapy using the breath-hold technique. No regional radiotherapy was given. All patients underwent a free-breathing CT scan and a breath-hold CT scan in the same treatment position, i.e. they were placed on a carbon fiber breast board (Sinmed B.V., Reeuwijk, The Netherlands) with both arms abducted above the head. A copper wire was placed around the palpable breast tissue as an aid for Clinical Target Volume (CTV) delineation.

Single-slice CT images (AcQSim Inc., Philips Medical Systems, Cleveland, OH, United States) were obtained using 3-mm inter-slice thickness from lung apices to the diaphragm. The breath-hold CT scan was executed using the ELEKTA Active Breathing Coordinator™ device (ELEKTA, Crawley, United Kingdom), the threshold was determined at 75% of the moderate deep inspiration as described by Remouchamps et al. [10]. Patients were trained on the CT-simulator to hold their breath for a maximum duration of 30 s, using a mouth piece, nose clip and prism glasses. The duration of the breath-hold was defined for each patient individually. The method described above has been the standard procedure in our department since October 1st, 2010 for all left-sided breast cancer radiotherapy patients [14].

Target delineation and organs at risk

To avoid inter-observer-based differences, the glandular breast tissue, heart and the LAD-region were delineated for each breath-hold- and free-breathing-scan by one observer only (by MLKH). All delineations were performed in the Pinnacle^3 planning system (version 8.0m, Philips Medical Systems, United States). The glandular breast tissue was contoured according to RTOG delineation guidelines [15] and was defined as the CTV. PTV was created by expanding the CTV 5 mm in the transversely, 6 mm cranially, and 9 mm caudally. The PTV was retracted 5 mm from the patient surface to minimize high-dose levels in the build-up regions for IMRT plans (PTV_{trim}).

The heart was delineated according to the University of Michigan cardiac atlas of Feng et al., from the cranial border of the left atrium to the apex of the heart [16]. As no contrast was used during the planning-CT scan, the LAD was in some slices difficult to visualize and, therefore, the LAD-region was contoured instead [9,16]. To contour this region we followed the anatomic borders of the pericardium, which served as the anterior border. The superior border was defined as the origin of the LAD from the left main coronary artery and followed the anterior-interventricular groove; the caudal border was situated at the apex cordis. When, in some slices the LAD was difficult to visualize, its location was inferred from the course of the interventricular groove and interpolated between slices. Delineations of the heart and LAD-region were reviewed by the radiologist (MH).

Our 3D-CRT technique consisted of two opposing wedged tangential fields. If optimal dose homogeneity was not achieved an additional field was added. With our IMRT technique, 60% of the dose was given with two open tangential fields and 40% with four inversely planned IMRT fields, with a 'Step-and-Shoot' technique. For the optimization a Direct Machine Parameter Optimization (DMPO) was used with the following criteria: the maximum number of segments was constricted to 12; the minimum segment area was set to 9 cm^2; and the threshold for the minimum number of monitor units (MUs) per segment was 4 MUs. For the heart we started to define a maximum equivalent dose of 20 Gy after weights for the heart and the LAD-region were set individually for each individual patient to enable a maximum sparing of these structures. For the PTV_{trim} several constraints were used: uniform dose (42.56 Gy), maximum dose (45.5 Gy) and minimum dose (40.6 Gy).

All plans were calculated with a Collapsed Cone algorithm using heterogeneity correction (Philips Medical Systems 2006 Pinnacle[3]. Physics REFERENCE GUIDE Release 8.0). For 3D-CRT as well as for IMRT plans identical gantry angles and beam energies were used. In this way a more reliable comparison of the two techniques could be obtained. Moreover, the dose to the contralateral breast was not biased due to the use of identical gantry angles. All treatment plans had to meet the criterion that 97% of the PTV_{trim} was covered by at least of the 95% isodose (and <108% isodose). The plans were judged and approved by one radiation oncologist (HS).

The prescribed dose was 42.56 Gy in 16 fractions in all cases. For both techniques (3D-CRT and IMRT), the treatment plans based on the breath-hold and free-breathing scans were compared for all patients. For PTV_{trim}, the percentages of volumes receiving 95% and 107% of the prescribed dose (V95%; V107%) were determined and compared. Furthermore, for the heart and the LAD-region, various dose volume parameters were generated and evaluated; the choice was based on those published in the literature. As far as the lung tissue was concerned, the mean lung dose and the volume receiving 20 Gy (V20 Gy) (averaged over both lungs) were analyzed for both techniques. And finally, the total body dose, the volume receiving 5% of the prescribed dose (V5%), and the number of monitor units were compared.

Statistics

A Wilcoxon Signed Rank Test was performed to compare doses and volume differences since the number of eligible cases was less than 30. For analysis, we used SPSS Statistics version 17.0 (IBM Corporation, Armonk, NY, United States). The level of statistical significance was considered at a p-value of <0.05 for all tests.

Results

Heart and LAD-region
For both the heart and the LAD-region a significant dose reduction ($p < 0.01$) was found when comparing the treatment plans based on breath-hold to those based on the free-breathing scans. In the LAD-region an average volume reduction for the 20 Gy (V20 Gy) of 20% was achieved by using the breath-hold technique.

Another 5% reduction in irradiated volume for the 20 Gy (V20 Gy) could be achieved by using an IMRT technique. Furthermore, for the IMRT technique when compared to the 3D-CRT technique, a significant dose reduction ($p < 0.01$) was found (Table 1).

However, in 6 out of 20 patients over 30% of the LAD-region still received 20 Gy in 3D-CRT, even when using the breath-hold technique. In these cases, IMRT resulted in a reduction of the V20 Gy with an average of 15%.

Figure 2 shows that the caudal part of the heart in particular, and thus the LAD-region, is situated in the vicinity of the radiation portals, even in the breath-hold treatment plans. With IMRT, a lower dose was attained in the LAD-region, and in doing so, in all patients a decrease of the dose in the caudal part of the LAD-region was found. This was attained by the fact that the multileaves enclosed the PTV_{trim} better by rotating the collimator angle (Figure 3). Nevertheless, in five patients the caudal part of the LAD-region, i.e. around 45 mm from the apex cordis, still received doses between 21 and 34 Gy.

		Mean (SD) (n=20)				p-value	
		Breath-hold (BH)		Free-breathing (FB)		BH compared to FB, for both 3D-CRT and IMRT	3D-CRT compared to IMRT, for both BH and FB
Table 1.		3D-CRT	IMRT	3D-CRT	IMRT		
Heart	**Mean (Gy)**	1.8 (0.8)	1.5 (0.5)	3.3 (1.6)	2.7 (1.3)	p < 0.01	p < 0.01
	Dmax (Gy)	15.8 (13.0)	8.6 (6.2)	29.2 (14.6)	24.7 (14.7)	p < 0.01	p < 0.01
	V5Gy (%)	3.8 (3.0)	2.5 (2.1)	8.9 (5.0)	7.4 (4.7)	p < 0.01	p < 0.01
	V20Gy (%)	1.5 (1.5)	0.6 (0.8)	5.0 (3.5)	3.5 (3.0)	p < 0.01	p < 0.01
	V30Gy (%)	1.0 (1.1)	0.3 (0.4)	4.0 (3.1)	2.4 (2.3)	p < 0.01	p < 0.01
LAD-region	**Mean (Gy)**	9.6 (6.9)	6.7 (5.1)	18.6 (9.3)	14.9 (9.3)	p < 0.01	p < 0.01
	Dmax (Gy)	25.2 (15.3)	18.8 (13.6)	35.5 (11.6)	31.4 (13.0)	p < 0.01	p < 0.01
	V5Gy (%)	39.4 (26.4)	30.3 (25.9)	62.6 (23.0)	54.9 (25.1)	p < 0.01	p < 0.01
	V10Gy (%)	25.0 (23.8)	18.2 (21.5)	49.9 (25.2)	42.9 (26.6)	p < 0.01	p < 0.01
	V20Gy (%)	17.8 (20.1)	9.7 (15.1)	42.5 (25.6)	32.8 (27.1)	p < 0.01	p < 0.01
Lung	**Mean (Gy)**	3.0 (1.0)	2.6 (0.9)	3.3 (1.1)	2.9(1.1)	p < 0.02	p < 0.01
	Dmax (Gy)	36.1 (8.0)	33.4 (5.7)	18.0 (6.9)	35.5 (5.0)	p < 0.01	p < 0.01
	V5Gy (%)	11.4 (3.3)	10.1 (3.1)	11.3 (3.3)	10.1 (3.3)	3D-CRT: p = 0.94 / IMRT: p = 0.90	p < 0.01
	V20Gy (%)	6.2 (2.4)	5.1 (2.2)	6.8 (2.8)	5.7 (2.6)	3D-CRT: p < 0.01 / IMRT: p = 0.06	p < 0.01
Total body	**V5% (%)**	18.3 (5.0)	16.2 (4.8)	20.0 (5.2)	17.4 (5.2)	P < 0.02	p < 0.01
Monitor Units		462	340	467	342	p > 0.7	p < 0.01

Table 1. Overview of mean doses and volumes, including the p-value. Abbreviations: BH: Breath-hold. FB: Free-breathing. V5 Gy, 10 Gy, 20 Gy, 30 Gy: volume receiving 5 Gy, 10 Gy, 20 Gy, 30 Gy respectively. Dmax: dose encompassing 2% of the volume. V95%, V107%: volume receiving ≥95% and 107% of the prescribed dose respectively. V5%: volume receiving ≥5% of the prescribed dose.

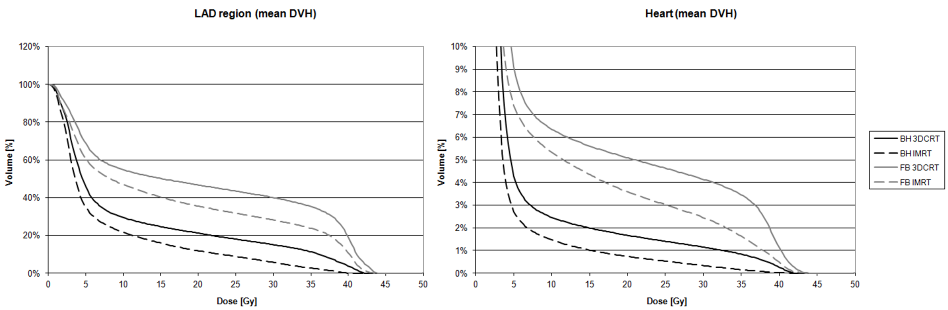

Figure 1. Mean Dose Volume Histograms of the 20 patients of the study; Left: the Left Anterior Descending coronary artery region; Right: the heart. In black the breath-hold technique; in grey the free-breathing technique. The dotted lines represent the Intensity Modulated Radiotherapy technique. Note that the y-scale is different for he left and right graphs.

The mean doses and volumes, averaged over 20 patients, are presented in Table 1. In Figure 1, mean Dose Volume Histograms (DVHs) of the LAD-region and the heart were reproduced for both breath-hold and free-breathing, as well as for the 3D-CRT and IMRT technique.

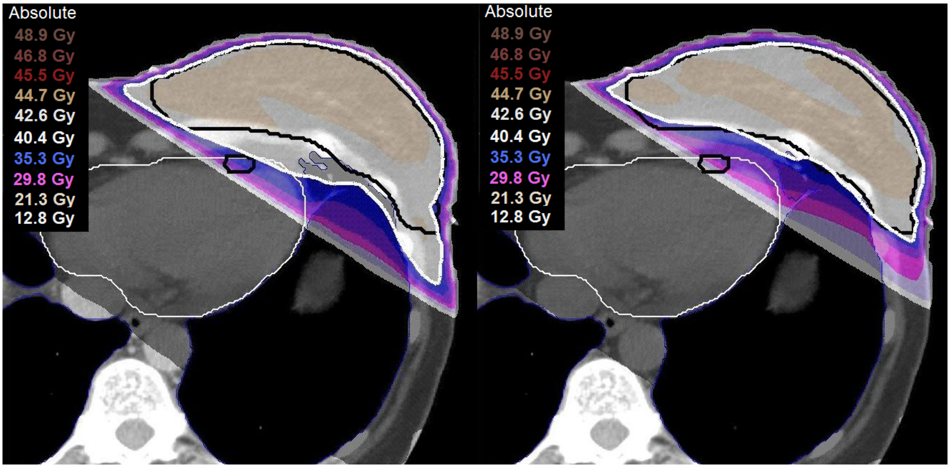

Figure 2. Comparison of the 95% isodose (white line) in the caudal part of the radiation fields for the 3D-Conformal Radiotherapy (left) and the Intensity Modulated Radiotherapy (right) technique on the breath-hold scan. Black line = PTV_{trim}.

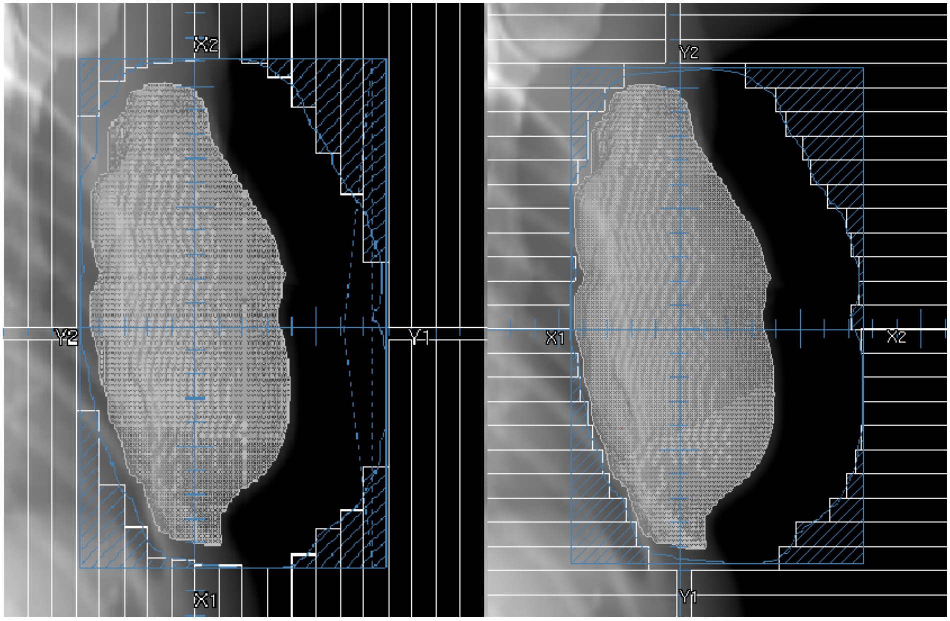

Figure 3. Beams Eye View of the left anterior oblique treatment field; Left: the 3D-Conformal Radiotherapy technique; Right: the Intensity Modulated Radiotherapy technique. The collimator was turned to adapt the treatment field as much as possible to the PTV_{trim}. This collimator adaption is not possible for 3D-Conformal radiotherapy because of the wedge. In grey PTV_{trim} was visualized.

Lung
For the 3D-CRT plans, the lung volume receiving 20 Gy was significantly reduced in breath-hold ($p < 0.01$). In the IMRT plans, a borderline significant reduction was found for the lung volume that received 20 Gy in breath-hold ($p = 0.06$). For the mean lung dose a significant reduction was found in breath-hold ($p < 0.02$).

Total body
The volume of the total body receiving 5% of the prescribed dose was significantly reduced when using the breath-hold technique ($p < 0.02$). Also, a significant reduction of irradiated volume ($p < 0.01$) was found when 3D-CRT and IMRT techniques were compared (Table 1).

Delineated volumes
For the delineated volume of the LAD-region no significant differences ($p = 0.15$) were found in treatment plans in breath-hold (mean 10.5 cm^3, range 6.3–19.2) when compared to those in free-breathing (mean 10.9 cm^3, range 6.8–14.2). The delineated heart volumes in breath-hold treatment plans appeared to be significantly smaller compared to free-breathing; mean of 682 cm^3 (range 516–884) and 741 cm^3 (range 561–883) respectively ($p < 0.01$). Significantly larger lung volumes were found in breath-hold than in free-breathing ($p < 0.01$); mean lung volume in breath-hold was 5506 cm^3 (range 4681–6476) and in free-breathing 3049 cm^3 (range 1341-4718).

Monitor units
Significantly less monitor units ($p < 0.01$) were needed using the IMRT technique when compared to the amount of monitor units used in the 3D-CRT technique. We found an average of 465 monitor units versus 341 respectively (Table 1).

Discussion

In general, we found that the breath-hold technique resulted in a significant dose reduction in the heart and of the dose in the LAD-region. Furthermore, with IMRT a significant further dose reduction could be attained. IMRT enables a decrease in the dose in the LAD-region in the caudal part of the radiation fields as well. Even when using the breath-hold technique, the LAD-region is situated close to the radiation fields, because of the position of the heart, and more specifically of the LAD, in the thorax. Sparing the caudal part of the LAD seems to be of great (clinical) relevance, since Nilsson et al. found a four- to sevenfold increase of high-grade coronary artery stenosis after radiation therapy in the mid- and distal LAD when comparing women with left- and right-sided breast cancer [6]. In our study we defined the caudal part of the LAD-region, comparable to the distal branch of the LAD Nilsson et al. described [6]. However, the cranial border of the distal branch was difficult to define, therefore we chose the cranial border of the distal branch arbitrarily at a distance of 15 slices (3 mm/slice) on the planning CT scan, starting from the apex cordis in cranial direction.

Kirby et al. delineated the LAD itself without using contrast, they made use of the course of the anterior-interventricular groove, when the LAD was difficult to find and added an isotropic 10 mm margin around the defined LAD to take delineation uncertainties and heart/respiratory motion into account [17]. In our cases, the pericardium was defined as the border of the LAD-region [16], and in this way the LAD-region could remain at a somewhat larger distance from the high-dose areas of the radiation fields. Because of these delineation differences between the two investigations the LAD doses were difficult to compare. As for the significantly smaller volumes of the heart in the breath-hold scan, the breath-hold probably influences the heart volume as well. No studies were identified to confirm this finding.

Neither for the dose in the heart nor for the dose in the LAD any specific thresholds could be defined according to several authors, summarized in the systematic review performed by Sardaro et al. [18]. Since no threshold doses for the heart and LAD are available and the clinical effect of low doses is not completely clear, we think it would be best clinical practice to keep the dose in the heart and LAD as low as achievable. Therefore, we decided to use the breath-hold technique for all left-sided breast cancer patients. It is a simple method, which has been completely implemented in our clinic. Other breathing adapted radiation techniques could be useful as well, such as the fluoroscopy-guided Deep Inspiration Breath-hold (DIBH) irradiation technique [19], the gated technique [20] and the voluntary inspiration breath-hold [21].

No significant differences were found according to the PTV_{trim} coverage for both the breath-hold and free-breathing scans; however, a significantly lower dose outside the PTV_{trim} was observed for IMRT in comparison to 3D-CRT. Since Remouchamps et al. and Schubert et al. reported that, with IMRT, generally a more homogeneous dose distribution will be achieved in comparison to a 3D-CRT technique, dose homogeneity was not involved in our study [10,13]. According to Cao et al. the influence of breathing motion should be considered and thus the choice for an optimal treatment technique should be made. Using IMRT and a breathing adapted radiation treatment technique, the dosimetric coverage may be more optimal [22]. Furthermore, significantly less monitor units were determined for the IMRT technique compared to 3DCRT; this was also found in the study of Remouchamps et al. [10]. The significant reduction in mean lung dose, found for both lungs, was confirmed in the study by Borst et al. [19].

Finally, the ABC method in our experience is a simple and well-tolerated technique. Also, Swanson et al. report 6 years of experience in their clinic with this method [10]. In the evaluation study of Mast et al. it was stated that 99% of the patients with clinical T1–2, N0–2, M0 left-sided breast cancer who were treated with the ABC technique, completed the treatment without any problem [14].

Conclusion

We confirmed that the breath-hold technique in left-sided breast cancer radiotherapy leads to a significant dose reduction in the heart and the LAD-region. IMRT enables an additional dose reduction in these critical organs in both free-breathing and breath-hold. Applying an IMRT technique can reduce the dose in the caudal part of the radiation fields in both free-breathing and breath-hold as well.

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Whole breast proton irradiation for maximal reduction of heart dose in breast cancer patients

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Abstract

Purpose
In left-sided breast cancer radiotherapy, tangential intensity modulated radiotherapy combined with breath-hold enables a dose reduction to the heart and left anterior descending (LAD) coronary artery. Aim of this study was to investigate the added value of intensity modulated proton therapy (IMPT) with regard to decreasing the radiation dose to these structures.

Materials and methods
In this comparative planning study, four treatment plans were generated in 20 patients: an IMPT plan and a tangential IMRT plan, both with breath-hold and free-breathing. At least 97 % of the target volume had to be covered by at least 95 % of the prescribed dose in all cases. Specifically with respect to the heart, the LAD, and the target volumes, we analyzed the maximum doses, the mean doses, and the volumes receiving 5–30 Gy.

Results
As compared to IMRT, IMPT resulted in significant dose reductions to the heart and LAD-region even without breath-hold. In the majority of the IMPT cases, a reduction to almost zero to the heart and LAD-region was obtained. IMPT treatment plans yielded the lowest dose to the lungs.

Conclusions
With IMPT the dose to the heart and LAD-region could be significantly decreased compared to tangential IMRT with breath-hold. The clinical relevance should be assessed individually based on the baseline risk of cardiac complications in combination with the dose to organs at risk. However, as IMPT for breast cancer is currently not widely available, IMPT should be reserved for patients remaining at high risk for major coronary events.

Introduction

Postoperative radiotherapy is considered standard of care after breast-conserving surgery for breast cancer [1]. After mastectomy, radiotherapy is required in case of intermediate or high risk of locoregional failure [2,3]. Previous studies [4,5] have shown that radiotherapy is associated with an increased rate ofmajor coronary events, especially in patients treated for left-sided breast cancer. However, it should be noted that the follow-up period in these studies is relatively short [4, 5].With improved survival, more patients will be at risk for long-term radiation-induced toxicity, thus making it even more important to reduce the dose to all organs at risk (OARs).

Recently, Darby et al. found that the rate of major coronary events was proportional to the mean dose to the heart starting within a few years after exposure. Patients with pre-existing cardiac risk factors had higher absolute risks after radiotherapy than those without [6]. Given its anatomical location, the left anterior descending (LAD) coronary artery is most at risk for developing atherosclerosis after left-sided breast-conserving radiotherapy [7]. Taylor et al. showed that even with contemporarily delivered tangential fields, the mean dose to the LAD was considerable: 7.6 Gy. Furthermore, half of the patients appeared to receive more than 20 Gy in the ventral part of the heart [8]. As the rate of ischemic heart disease is proportional to the mean heart dose, Darby et al. advised to reduce the dose to the heart as much as possible. In order to reduce the dose to the heart and the LAD using photons, intensity modulated radiotherapy (IMRT), either combined or not combined with breath-hold techniques, has been investigated [9–11] and compared to 3D-conformal radiotherapy (3D-CRT) with and without breath-hold [11].

A commonly used IMRT technique for breast cancer treatment is an IMRT technique based on the standard tangential fields with additional smaller subfields in order to improve dose homogeneity [12]. The advantage of this technique, compared to the full inversed planned multiple beam IMRT, is, that the dose redistribution is confined to the same area as the tangential fields, thus avoiding an excessive low dose to surrounding OARs. In addition, breath-hold techniques can be used to decrease the heart dose. With a breath-hold technique, a patient holds her breath during 25–30 s intervals in which radiation is administered. In doing so, the distance between the heart and the radiation fields increases and, consequently, the dose to the heart decreases [10].

However, due to anatomical variations in some patients, the radiation dose to the heart remains relatively high, even with the use of advanced photon-based techniques. Due to its physical characteristics, proton therapy may eventually enable a further decrease of dose to the heart. In contrast to a photon beam, a proton beam is characterized by a very narrow width of a relatively high peak of maximum dose administration: the Bragg peak. In other words, a proton beam is characterized by a dose distribution that is finite and adjustable in depth depending on the energy of the proton beam. Theoretically, these characteristics of protons enable a very precise irradiation of the target volume, while at the same time better sparing of the surrounding normal tissue can be obtained [13].
Therefore, we assumed that proton therapy may enable an improved sparing of the heart and LAD in left-sided breast cancer patients, especially in cases where the heart dose remains (relatively) high with advanced photon techniques [14–16]. In a previous paper, we found that tangential IMRT in combination with a breath-hold procedure resulted in a significant decrease of the dose to the heart and LAD-region compared to 3D-CRT in breathhold, while retaining optimal target volume coverage [11]. Furthermore, compared to standard photon 3D-CRT, tangential IMRT improves overall cosmesis and reduces the risk of skin telangiectasia [17]. However, to the best of our knowledge, planning compar-

ative studies are lacking, which focus on the additional value of protons for whole breast irradiation compared to that of tangential IMRT (both with and without breath-hold).

Therefore, the aim of this planning comparative study was to determine whether a further dose reduction to the heart and LAD could be obtained with proton therapy (either with or without breath-hold).

Materials and methods

We used the same methods as described in our previous planning comparative study comparing conformal photon radiotherapy (3D-CRT) and tangential IMRT (with and without breath-hold) [11]. The current study population consisted of 20 consecutive female breast cancer patients (pT1-2; pN0-1; M0). All patients underwent breast-conserving surgery and axillary staging with a sentinel node procedure.

To avoid interobserver-based delineation differences, the glandular breast tissue was contoured by one experienced radiation oncologist (LKH), according to RTOG delineation guidelines [18], and defined as the CTV. The PTV was created by expanding the CTV with 5 mm in transverse directions, 6 mm cranially, and 9 mm caudally according to the guidelines of our department for 3D-CRT and IMRT. The PTV was retracted 5 mm from the patient surface (PTV_{trim}) to minimize high-dose levels in the buildup regions for IMRT plans. No adaptations for PTV_{trim} were performed in the direction of the lungs, in doing so the thoracic wall may be included in PTV_{trim}. In order to be able to compare the same volumes, we applied the same margins to the proton plans. Furthermore, the heart and the LAD-region were delineated by one experienced radiation oncologist (LKH) and were subsequently reviewed by an experienced cardiac radiologist (MH). All volumes were delineated on each breath-hold scan and free-breathing scan. For the breath-hold scan, the Active Breathing Control (ABC) method was used (ELEKTA Active Breathing CoordinatorTM device, Crawley, United Kingdom) [19]. A high feasibility rate was reported when using the ABC method [10,20]. Details concerning the ABC method were described by Mast et al. [11].

Treatment planning techniques

Tangential IMRT-planning
All IMRT plans were produced by one experienced dosimetrist (HR), who was blinded for the IMPT plans. The applied IMRT technique was a tangential IMRT technique. According to this technique, approximately 60 % of the dose was given with two tangential open fields, and 40 % with four inversely planned tangential IMRT fields using the same gantry angles, with a 'step-and-shoot' technique [11,12]. The nominal energy used was 6 MV in most of the cases, and occasionally 10 MV.

Proton planning
Spot scanning intensity modulated proton therapy (IMPT) plans were planned by two experienced IMPT dosimetrists (HC, PK) using a research version of the Pinnacle3 planning system (version 9.1, Philips Medical Systems, Cleveland, OH, United States). Both were blinded for the IMRT plans. With spot scanning, a pencil beam of protons is regulated in a highdose spot. This spot can be positioned for a specified period of time; by superimposing several spots, the desired radiation dose can be composed. Generally, for protons a RBE of 1.1 is used over the full depth of the proton beam, and the dose is represented as CGE (Cobalt Gray Equivalent, which is Relative Biological Effectiveness (RBE) 9 physical dose in Gy) [15]. In the doses we report here, this RBE has been taken into account.

IMPT dose calculations and field configurations were planned according to Ares et al. [21]. In all plans, the gantry angles were 345° (-15°), 27°, and 75°. The different beams were set to distribute the spots in such a way that no spot was more than 0.2 cm outside the PTV_{trim}. Spots were placed over the PTV_{trim} with 8 mm separation in the plane perpendicular to the beam direction; while in depth, spot layers were positioned and interspaced with 5 mm between each spot.

Energy layers ranged from 7.7 to 23.0 g/cm2 (representing the depth of the Bragg peak location) or 100–185 MeV. Corresponding lateral spot sizes ranged approximately from 15 to 8 mm full-width-at-half-maximum at the isocenter in air and without range shifter. A range shifter of 75 mm water equivalent thickness was used so that the spot positions ranged from 2 to 155 mm water equivalent depth. Note that the range shifter and air gap between range shifter and patient skin increase the spot size.

All plans were adapted to the individual target volumes and critical organs, using the "trial-and-error" method.

IMRT and IMPT treatment plan optimization
The prescribed dose was 42.56 Gy in 16 fractions in all cases. For all IMRT and IMPT plans, 97 % of the PTV_{trim} had to be covered by at least 95 % of the prescribed dose with a maximum of 2 % receiving more than 107 % of the prescribed dose [22]. No compromises on the PTV coverage with either of the techniques were made to ensure a fair comparison. For the PTV_{trim}, the following constraints were used: uniform dose (42.56 Gy), maximum dose (45.5 Gy, point dose), and minimum dose (40.6 Gy). The maximum dose (Dmax) was defined as the maximal dose to a volume of at least 2 % of that specific volume; according to the ICRU 83. All further planning objectives used were similar again to obtain fair dosimetric comparisons between the two techniques. For the purposes of our study, IMRT and IMPT treatment plans based on the breath-hold and free-breathing scans were compared in all patients.
Furthermore, various dose volume parameters of PTV_{trim}, heart, LAD-region, and lung (both lungs as well as the left lung separately) were generated and evaluated. The choice of these dose volume parameters (Dmax; mean; V5–V30 Gy) was based on those published in the literature [10,22,23]. Finally, all plans were evaluated and approved by two experienced breast cancer radiation oncologists (HS and JM).

Statistics

A Wilcoxon signed-rank test was performed to compare dose and volume differences since the number of eligible cases was less than 30. For this analysis, we used SPSS Statistics version 20.0. The level of statistical significance was defined by a p value of 0.05 (two-sided) for all tests. (IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.)

Results

Heart and LAD-region
The mean doses for the heart and LAD-region, for IMRT and IMPT, in breath-hold and free-breathing, in all cases are presented in Figure 1.
Despite the use of tangential IMRT with breath-hold in some patients, the dose to the LAD-region remained relatively high (Table 1; Figure 1). With breath-hold IMRT, still 9 out of 20 patients received a mean dose to the LAD-region exceeding 5 Gy, while in 4 out of 20 patients the dose remained beyond 10 Gy. In 3 patients, the mean heart dose was more than 2 Gy (Figure 1).

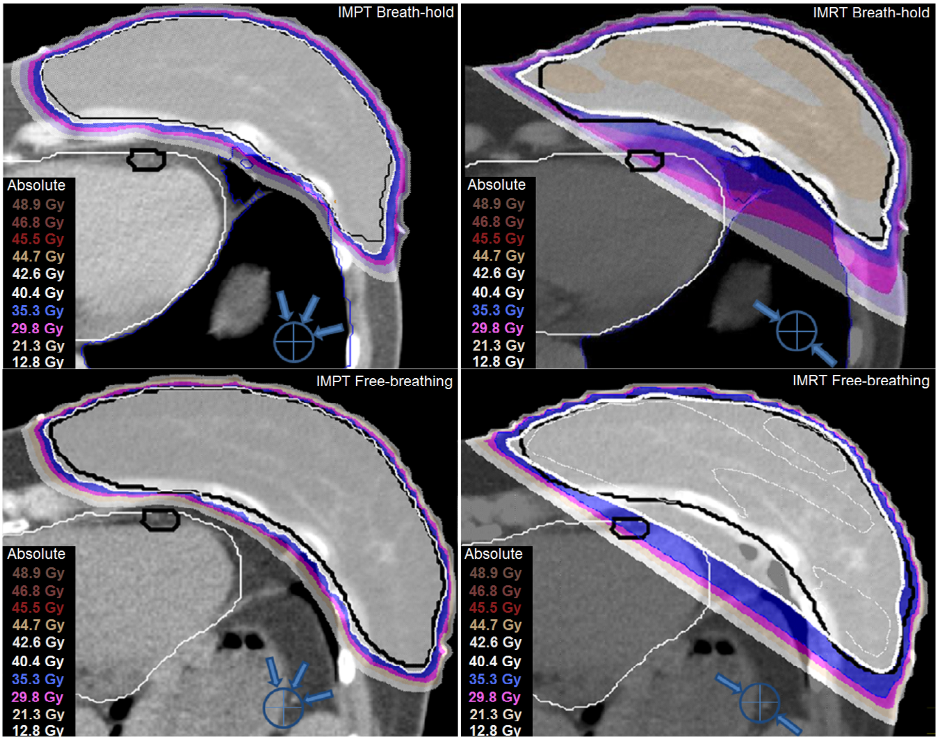

Figure 1 Isodose lines in the caudal part of the patient on the breathhold scan. Delineated organs at risk: white line heart; black line region of the left anterior descending coronary artery. Planning target volume: black line PTV_{trim}; thick white line 95 % isodose line. At the bottom right, the used gantry angles were pointed out, represented by the small arrows.

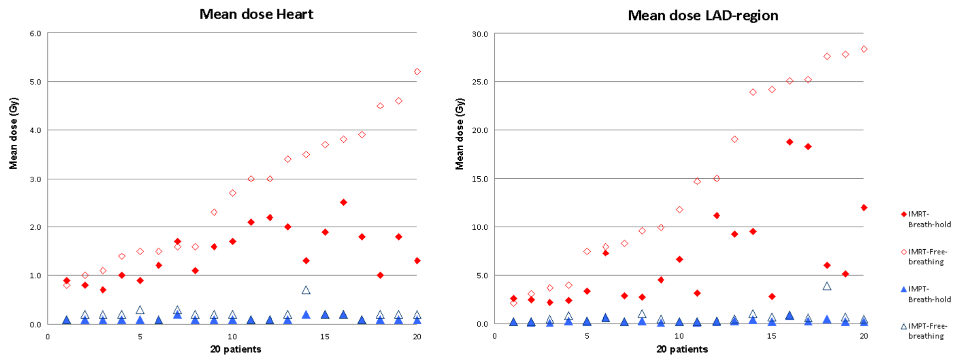

Figure 2 Left: Mean dose administered to the heart. Right: Mean dose administered to the LAD-region; both with intensity modulated radiotherapy (IMRT) and intensity modulated proton therapy (IMPT) in breath-hold (BH) and free-breathing (FB). The cases were rearranged using the increasing (from left to right) IMRT FB technique values.

An additional reduction of the various dose parameters could be obtained with IMPT as well as with breath-hold IMPT. The volume of the heart and LAD-region receiving 20 Gy (V20 Gy) could be reduced to almost zero in all patients (Figure 1 and 2; Table 1).

Lung

As compared to IMRT, the mean lung dose, the V5 Gy, and the V20 Gy in both lungs and in the left lung could be reduced significantly. In particular, the mean V20 Gy value for both lungs could be reduced from 5.1 % (SD 2.2) with breath-hold IMRT to 1.3 % (SD 0.8) with breath-hold IMPT (Table 1).

		Mean (SD) (n=20)				p-value	
		BH		FB			
Table 1. Dose distribution parameters		IMPT	IMRT	IMPT	IMRT	BH compared to FB, for both IMPT and IMRT	IMPT compared to IMRT, for both BH and FB
Heart	**Mean (Gy)**	0.1 (0)	1.5 (0.5)	0.2 (0.1)	2.7 (1.3)	p < 0.01	p < 0.01
	Dmax (Gy)	0.3 (0.3)	8.6 (6.2)	1.2 (1.7)	24.7 (14.7)	p < 0.01	p < 0.01
	V5Gy (%)	0.1 (0.2)	2.5 (2.1)	0.5 (0.8)	7.4 (4.7)	p < 0.01	p < 0.01
	V20Gy (%)	0	0.6 (0.8)	0.1 (0.2)	3.5 (3.0)	IMPT: p = 0.02 / IMRT: p < 0.01	p < 0.01
	V30Gy (%)	0	0.3 (0.4)	0	2.4 (2.3)	IMPT: p = 1.80 / IMRT: p < 0.01	p < 0.01
LAD-region	**Mean (Gy)**	0.3 (0.2)	6.7 (5.1)	0.7 (0.8)	14.9 (9.3)	p < 0.01	p < 0.01
	Dmax (Gy)	1.8 (1.9)	18.8 (13.6)	4.5 (3.4)	31.4 (13.0)	p < 0.01	p < 0.01
	V5Gy (%)	0.4 (0.9)	30.3 (25.9)	2.8 (5.8)	54.9 (25.1)	p < 0.01	p < 0.01
	V10Gy (%)	0.1 (0.3)	18.2 (21.5)	0.8 (2.7)	42.9 (26.6)	IMPT: p = 0.04 / IMRT: p < 0.01	p < 0.01
	V20Gy (%)	0	9.7 (15.1)	0.1 (0.6)	32.8 (27.1)	IMPT: p = 0.06 / IMRT: p < 0.01	BH: p = 0.20 / FB: p < 0.01
Bilateral lung	**Mean (Gy)**	0.8 (0.4)	2.6 (0.9)	0.9 (0.3)	2.9 (1.1)	IMPT: p = 0.10 / IMRT: p < 0.02	p < 0.01
	Dmax (Gy)	14.6 (8.0)	33.4 (5.7)	18.0 (6.9)	35.5 (5.0)	p < 0.05	p < 0.01
	V5Gy (%)	3.6 (1.9)	10.1 (3.1)	4.0 (1.2)	10.1 (3.3)	IMPT: p = 0.08 / IMRT: p = 0.90	p < 0.01
	V20Gy (%)	1.3 (0.8)	5.1 (2.2)	1.5 (0.7)	5.7 (2.6)	IMPT: p = 0.06 / IMRT: p = 0.03	p < 0.01
Lung Left	**Mean (Gy)**	1.5 (0.6)	5.4 (1.8)	1.6 (0.6)	6.1 (2.3)	IMPT: p = 0.20 / IMRT: p < 0.01	p < 0.01
	Dmax (Gy)	23.6 (8.2)	37.1 (2.8)	27.0 (7.0)	38.7 (2.3)	p < 0.04	p < 0.01
	V5Gy (%)	7.1 (2.7)	21.4 (6.6)	7.7 (2.7)	21.9 (7.1)	IMPT: p = 0.17 / IMRT: p = 0.59	p < 0.01
	V20Gy (%)	2.5 (1.4)	10.9 (4.7)	2.8 (1.4)	12.4 (5.7)	IMPT: p = 0.04 / IMRT: p = 0.02	p < 0.01
PTV_{trim}	**V95% (%)**	99.6 (0.32)	97.9 (0.15)	99.7 (0.19)	97.9 (0.18)	IMPT: p = 0.09 / IMRT: p = 0.70	p < 0.01
	V107% (%)	0	0.4 (1.0)	0	0.2 (0.4)	IMPT: p = 1.00 / IMRT: p = 0.47	p < 0.02

Table 1. Non-significant data is presented in bold. BH breath-hold, FB free-breathing, IMPT intensity modulated proton therapy, IMRT intensity modulated radiotherapy, V5, V10, V15, V20, V30, and V40 Gy volume receiving 5, 10, 15, 20, 30, and 40 Gy, respectively, Dmax dose encompassing 2 % of the volume. V95 % and V107 % volume receiving 95 and 107 % of the prescribed dose, respectively.

Discussion

The main objective of this study was to investigate if the dose to the heart and LAD-region could be reduced using spot scanning IMPT. The results showed that, with both IMPT techniques (with and without breath-hold), the doses to the heart as well as to the LAD-region could be reduced significantly compared to IMRT with breath-hold. This could be achieved without compromising the doses to the target volumes. It should be stressed that, with IMPT, a further reduction to almost zero to the heart and LADregion could be obtained in the majority of cases. The results show that a breath-hold technique had no added value when using IMPT. However, using breath-hold may improve the robustness of the IMPT technique, since the tissue shift will be less in breath-hold. Protons are more sensitive than photons to the effects of motion due to the range of the Bragg Peak. When using a proton field from a perpendicular direction, a tissue shift could cause thickness changes and thus range changes.

Recently Darby et al. reported a dose–effect relationship between the dose to the heart and the rate of major coronary events [6]. The authors could not identify any threshold dose for the development of coronary events, emphasizing the need to reduce the dose to as low as possible. The average mean heart dose of the left-sided breast cancer patients in their cohort was 6.6 Gy [6]. However, we noted lower mean heart doses with our tangential IMRT (2.7 Gy with free-breathing and 1.5 Gy with breath-hold). With IMPT further reductions could be obtained (0.2 Gy with free-breathing and 0.1 Gy with breath-hold).

Our study compares two techniques using the same fractionation scheme, with a fraction dose of 2.66 Gy and a total dose of 42.65 Gy. However, if the effects on reduction in cardiac dose of this study are being compared to the results of other planning studies, this needs to be taken into account.

It has been shown that decreasing of the mean heart dose is relevant [6]. The lifetime risk of radiation-induced ischemic heart disease for breast cancer patients increases linearly with an increase of the mean dose to the heart of 7.4 % per Gy (95 % confidence interval, 2.9–14.5) [6]. Consequently, the baseline risk should be taken into account. Recently, Duma et al. [24] approximated the increased rate of absolute radiation-induced ischemic heart disease by using the tables of the Darby publication [6]. They reported that, irradiating a 50-year-old breast cancer patient without cardiac risk factors with a mean heart dose of 3 Gy, the risk of having at least one acute coronary event by the age of 80 years rises from 4.5 to 5.4 %. They subsequently noted that in the presence of pre-existent cardiac risk factors, the risk of having at least one acute coronary event by the age of 80 years would rise from 8 to 9.7 %. If the mean heart dose would be 10 Gy and in the presence of cardiac risk factors, this risk would increase from 8 to 13.5 % [24]. Although, with breath-hold IMPT, the mean heart dose could be reduced to almost zero, the question arises whether all left-sided breast cancer patients will have clinically relevant benefit from proton irradiation. Recently, Langendijk et al. described the so-called modelbased approach, to define which patients could be selected for proton therapy. In this model-based approach, the estimated benefit in terms of risk reduction can be obtained by integrating dose differences in prediction models [25]. The excess risk on ischemic heart disease depends on the dose, and the relative increase per Gy is independent of the baseline risk on cardiac events, meaning that the absolute excess risk can be easily estimated by calculating the baseline risk, e.g., the Reynolds score [26], in addition to the mean heart dose.

Apart from the mean heart dose, there are data suggesting that the dose to the LAD coronary artery is most at risk for developing atherosclerosis after left-sided breastconserving radiotherapy due to its anatomical position in relation to the breast [7]. In the current study, the average mean dose to the LAD-region was 6.7 Gy with breath-hold IMRT which could be reduced to 0.3 Gy with breath-hold IMPT. These doses are lower when compared to the mean LAD doses of 20 and 9.4 Gy, without using breath-hold [6, 8]. It should be noted that the methodologies of defining the LAD or LAD-region varied widely among these three studies [6,8,11].

As in most treatment planning comparative studies, some critical notes also apply to this study. First, set-up errors and geometric changes during radiation treatment are more likely to affect the dose distributions when using IMPT. It should be noted that the effect of range uncertainties and patient breathing motion using IMPT were relatively small, as shown by Ares et al. [21] which is in line with the results of Xu et al. [27]. However, Wang et al. compared a passive scattered proton beam with a spot scanning IMPT technique and stated that IMPT is more sensitive for set-up uncertainties and breathing motion [28]. With advanced position verification procedures and adaptive treatment strategies in combination with a breath-hold technique, these uncertainties are expected to be minimized. Furthermore, as pointed out by other authors, set-up errors and range uncertainties need to be accounted for by applying robust IMPT treatment planning techniques rather than by using the traditional CTV-PTV margin concept [29,30].

Second, some authors reported higher skin dose when using protons and, hence, worse cosmetic outcome can be expected. Girodet et al. reported worse cosmetic outcome in accelerated partial breast irradiation (APBI) when using protons. However, they used a single field per treatment and stated that multiple proton beam scanning and advances in patient set-up could result in decreased margins [31]. In our planning comparative study, we were not able to compare the dose to the skin since a treatment planning system is not able to adequately calculate the dose to the skin. Therefore, the clinical experience when using protons in breast cancer treatment is of importance. Several phase-II studies report on the cosmetic results after proton beam therapy [31,32].

Third, for the current study, we decided to use tangential IMRT with 60 % of the dose given with two open tangential fields. Further dose reductions to the heart could be obtained by using IMRT with a larger degree of freedom. However, in most cases this can only be achieved at the expense of dose to other OARS and normal tissue [20, 33]. Ares et al. showed that, using proton irradiation, in leftsided breast cancer the dose to the OARs can significantly be reduced when compared to photons [21]. As yet, no planning study has compared proton and photon irradiation in combination with breath-hold in left-sided breast cancer radiotherapy. In most dep artments, a 3D-CRT photon technique is considered the current standard. However, recently it has been shown that tangential IMRT with breath-hold further reduces the dose to the heart and LAD-region without increasing the dose to other normal tissues [11].

Based on the radiation principles that dose should be “As Low As Reasonably Achievable” (ALARA) there is no doubt that patients will benefit from protons at least to some extent. Due to limited accessibility of proton therapy and higher costs, it will not be feasible to offer protons to all breast cancer patients. A model-based approach will enable the identification of patients who will benefit most from this new technology and thus will ensure a more costeffective use. For all other left-sided breast cancer patients, a tangential IMRT technique with breath-hold can be used to reduce the dose to the heart and LAD-region. In future, it may be possible to make choices based on individual planning comparisons in order to individualize the radiation treatment.

Conclusion

In left-sided breast cancer irradiation, IMPT is the most promising technique to maximally reduce the dose to heart and LAD-region, even without a breath-hold technique. However, as IMPT for breast cancer is currently not widely available, IMPT should be reserved for patients remaining at high risk for major coronary events.

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Conflict of interest

The authors have nothing to disclose and indicate no potential conflict of interest.

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Tangential IMRT versus TomoTherapy with and without breath-hold in left-sided whole breast irradiation

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Abstract

Purpose

Active Breathing Control enables a decrease of cardiac and Left Anterior Descending (LAD) coronary artery dose in left-sided breast cancer radiotherapy. Applying a tangential IMRT technique results in an additional decrease in these organs of risk (OAR). Other studies showed that TomoTherapy decreases the dose in the OARs when compared to tangential IMRT. We investigated whether TomoTherapy enables an additional decrease of cardiac dose in radiotherapy plans with and without breath-hold (BH).

Materials and methods

We compared tangential Intensity Modulated Radiotherapy (IMRT) and TomoTherapy treatment plans based on free-breathing (FB) as well as on BH. Twenty patients referred for whole breast irradiation were included. The glandular breast tissue, heart and LAD-region were contoured. Four treatment plans were generated: FB_IMRT; FB_TomoTherapy; BH_IMRT; BH_TomoTherapy. Several doses were obtained from Dose Volume Histograms and compared.

Results

For the mean dose in the heart and LAD-region a significant reduction of the dose was found when using TomoTherapy instead of tangential IMRT in both breath-hold and free-breathing. For the LAD-region TomoTherapy in breath-hold resulted in a significant lower mean dose of 4.9 Gy, with tangential IMRT in breath-hold a mean dose of 6.7 Gy was found. The doses in the contralateral lung, both lungs and planning target volume (PTV) were comparable for both techniques in breath-hold. However, for the V107% in the PTV significant lower doses were found when using TomoTherapy in breath-hold.

Conclusion

In daily clinical practice tangential IMRT in breath-hold is the preferred technique to maximally reduce the dose to heart and LAD-region in left-sided whole breast irradiation.

Introduction

Whole breast irradiation (WBI), with or without a boost dose, is seen as the standard therapy after breast conserving surgery. But WBI may, amongst others, induce ischaemic heart disease. The incidence of ischaemic heart disease appears to be proportional to the mean dose to the heart and starts within a few years after exposure [1]. It is, therefore, of importance to define the most optimal radiation treatment technique for left-sided WBI. The aims are achieving the lowest dose in the critical structures as well as achieving optimal target coverage.

Using a breath-hold technique during left-sided breast cancer radiotherapy reduces the dose in the heart [2]. Tangential beam intensity modulated radiotherapy (IMRT) in combination with a breath-hold technique, when compared to 3D-CRT with breath-hold, resulted in a significantly larger decrease of the dose in the heart and left anterior descending coronary (LAD) artery [3]. However, others reported that TomoTherapy resulted in less dose in the critical structures when compared to tangential IMRT [4, 5]. The question is, does this finding still hold when tangential IMRT is used with a breath-hold technique?

The aim of this comparative planning study, therefore, was to determine whether a further dose reduction to the heart and the LAD-region could be obtained with TomoTherapy compared to tangential IMRT, with (and without) breath-hold.

Materials and methods

The study population consisted of 20 consecutive female breast cancer patients (pT1-2; N0-1; M0). All patients underwent breast-conserving surgery. Axillary staging was carried out by performing a sentinel node biopsy. We used the same methods as described in our former treatment planning comparison studies 3D-CRT and tangential IMRT (with and without breath-hold), and comparing tangential IMRT to proton therapy (with and without breath-hold) in the Pinnacle3 planning system (Philips Medical Systems, Cleveland, OH, United States). The delineated volumes were described in these studies as well [3, 6].

The PTV was retracted 5 mm from the patient surface (PTV_{trim}) [3, 6], in order to be able to compare the same volumes; we applied the same margins to the TomoTherapy plans. For all tangential IMRT and TomoTherapy plans, 97% of the PTV_{trim} had to be covered by at least 95% of the prescribed dose with a maximum of 2% receiving more than 107% of the prescribed dose [7]. No compromises on the PTV coverage with either of the techniques were made to ensure a fair comparison. The prescribed dose was 42.56 Gy in 16 fractions in all cases.

Tangential IMRT-planning

With the applied tangential IMRT technique, approximately 60% of the dose was given with two tangential open fields, and 40% with four inversely planned tangential IMRT fields, using the same gantry angles, with a 'step-and-shoot' technique [8]. The nominal energy used was 6 MV in most of the cases, and occasionally 10 MV.

For the PTV_{trim} the following constraints were used: uniform dose (42.56 Gy), maximum dose (45.5 Gy, point dose) and minimum dose (40.6 Gy). The maximum dose (D_{max}) was defined as the maximal dose to a volume of at least 2% of that specific volume; according to ICRU 83.

For tangential IMRT and TomoTherapy treatment plans, based on the breath-hold as well as on the free-breathing scans, were compared in all patients. Furthermore, various

dose volume parameters of PTV_{trim}, heart, LAD-region and lung (both lungs as well as the left lung separately) were generated and evaluated, and were the same as in the earlier study [3].
For treatment optimisation, the Direct Machine Parameter Optimization (DMPO) [7] was used with the following criteria: the maximum number of segments was restricted to 12 (to achieve a better sparing of the critical structures; and to keep the same time slot as for conventional treatment, in order to make a breath-hold treatment feasible); the minimum segment area was set to 9 cm2. For the heart we started defining a maximum dose (point dose) of 20 Gy; after which the weights for the heart and LAD-region were set individually per patient to make a maximum sparing of these structures possible. All plans were calculated with a Collapsed Cone algorithm.

TomoTherapy planning
The TomoTherapy Hi-ART treatment planning system used a different set of factors than Pinnacle to control the dose administration. For treatment, only 'tight' pitch factors were applied between 0.25 and 0.30. The primary collimation jaws were set to a field width of 2.45 cm at isocentre to determine the fan beam width. A modulation factor of 2.0 was used for all plans. Using TomoTherapy for breast cancer cases demands the addition of a constraint to the contralateral breast. Since TomoTherapy is a rotational technique, the contralateral breast needs to be avoided. This technique was also used in another planning comparison study. We used these dose constraints which were described by Reynders et al. [9].

Statistics
A Wilcoxon Signed Rank Test was carried out to compare dose and volume differences, since the number of eligible cases was less than 30. For the convenience of comparison the values in Table 1 were averaged over twenty patients. For this analysis, we used SPSS Statistics version 20.0 (IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.). The level of statistical significance was defined by a p-value of ≤0.05 (two-sided) for all tests.

Results

For the mean dose in the heart a significant reduction of the dose was found when using TomoTherapy instead of IMRT in both breath-hold and free-breathing. The mean dose for TomoTherapy in breath-hold was reduced to 1.1 Gy compared to 1.5 Gy when using IMRT. For the LAD-region TomoTherapy in breath-hold, when compared to IMRT in breath-hold, resulted in a significant lower mean dose of 4.9 Gy versus 6.7 Gy, respectively. See the Table 1 and Figure 1.

For the other dose-volume values (V5Gy, V10Gy, V20Gy, V30Gy) no significant differences were noted between the two techniques for the heart and LAD-region, when using breath-hold. With breath-hold in both IMRT and TomoTherapy, a significant lower dose could be achieved in all dose-volume values, see Table 1.

The doses in the contralateral lung and both lungs were comparable for both techniques in breath-hold; a mean dose of 5.2 Gy and 5.4 Gy was found for the left lung for TomoTherapy and IMRT, respectively. For PTV_{trim} comparable dose values were found for both techniques as well; however, for the V107% significant lower doses were found when using TomoTherapy in breath-hold. See Table 1.

		Mean (SD) (n=20)				p-value	
		BH		FB			
Dose distribution parameters		Tomo	IMRT	Tomo	IMRT	BH compared to FB, for both IMRT and Tomo	IMRT compared to Tomo, for both BH and FB
Heart	**Mean (Gy)**	1.1 (0.4)	1.5 (0.5)	2.1 (1.0)	2.7 (1.3)	p **< 0.01**	p **< 0.01**
	Dmax (Gy)	6.5 (5.4)	8.6 (6.2)	17.0 (9.7)	24.7 (14.7)	p **< 0.01**	p **< 0.01**
	V5Gy (%)	2.1 (1.8)	2.5 (2.1)	6.9 (4.2)	7.4 (4.7)	p **< 0.01**	BH: p = 0.06 / FB: p = 0.55
	V20Gy (%)	0.4 (0.6)	0.6 (0.8)	1.9 (1.9)	3.5 (3.0)	p **< 0.01**	p **< 0.03**
	V30Gy (%)	0.1 (0.2)	0.3 (0.4)	0.6 (1.0)	2.4 (2.3)	p **< 0.01**	BH: p = 0.06 / FB: p **< 0.01**
LAD-region	**Mean (Gy)**	4.9 (3.8)	6.7 (5.1)	11.3 (6.7)	14.9 (9.3)	p < **0.01**	p < **0.01**
	Dmax (Gy)	15.0 (11.2)	18.8 (13.6)	27.1 (11.2)	31.4 (13.0)	p **< 0.01**	p **< 0.04**
	V5Gy (%)	26.3 (23.9)	30.3 (25.9)	55.2 (23.4)	54.9 (25.1)	p **< 0.01**	BH: p = 0.05 / FB: p = 1.0
	V10Gy (%)	15.3 (18.2)	18.2 (21.5)	40.8 (24.9)	42.9 (26.6)	p **< 0.01**	p > 0.10
	V20Gy (%)	5.4 (9.7)	9.7 (15.1)	22.4 (22.2)	32.8 (27.1)	p **< 0.01**	BH: p = 0.05 / FB: p **< 0.01**
Bilateral lung	**Mean (Gy)**	2.7 (0.8)	2.6 (0.9)	2.8 (0.9)	2.9 (1.1)	IMRT: p = **0.02** / Tomo: p = 0.79	p > 0.10
	Dmax (Gy)	37.5 (3.4)	33.4 (5.7)	29.7 (8.0)	35.5 (5.0)	p **< 0.01**	p **< 0.01**
	V5Gy (%)	10 (2.4)	10.1 (3.1)	11 (2.3)	10.1 (3.3)	IMRT: p > 0.10 / Tomo: p **< 0.02**	BH: p > 0.10 / FB: p **< 0.02**
	V20Gy (%)	4.9 (1.9)	5.1 (2.2)	4.4 (2.5)	5.7 (2.6)	IMRT: p **< 0.03**/ Tomo: p > 0.10	BH: p > 0.10 / FB: p < 0.04
Lung Left	**Mean (Gy)**	5.2 (1.5)	5.4 (1.8)	5.3 (1.8)	6.1 (2.3)	IMRT: p **< 0.01** / Tomo: p > 0.10	p > 0.10
	Dmax (Gy)	37.5 (3.4)	37.1 (2.8)	34.1 (6.1)	38.7 (2.3)	IMRT: p > 0.10 / Tomo: p **< 0.02**	p **< 0.03**
	V5Gy (%)	20.5 (5)	21.4 (6.6)	23.0 (5)	21.9 (7.1)	IMRT: p > 0.10 / Tomo: p **< 0.01**	p > 0.10
	V20Gy (%)	9.8 (3.9)	10.9 (4.7)	8.8 (5.2)	12.4 (5.7)	IMRT: p **< 0.02** / Tomo: p > 0.10	BH: p > 0.10 / FB: p **< 0.02**
PTVtrim	**V95% (%)**	98.2 (1.0)	97.9 (0.15)	97.8 (1.4)	97.9 (0.18)	p > 0.10	p > 0.10
	V107% (%)	0	0.4 (1.0)	0 (0.1)	0.2 (0.4)	p > 0.10	BH: p = **0.03** / FB: p = 0.06

Table 1. Non-significant data is presented in bold. BH breath-hold; FB free-breathing; IMRT intensity modulated radiotherapy; Tomo TmoTherapy; V5, V10, V15, V20, V30, and V40 Gy volume receiving 5, 10, 15, 20, 30, and 40 Gy, respectively; Dmax dose encompassing 2 % of the volume; V95 % and V107 % volume receiving 95 and 107 % of the prescribed dose, respectively.

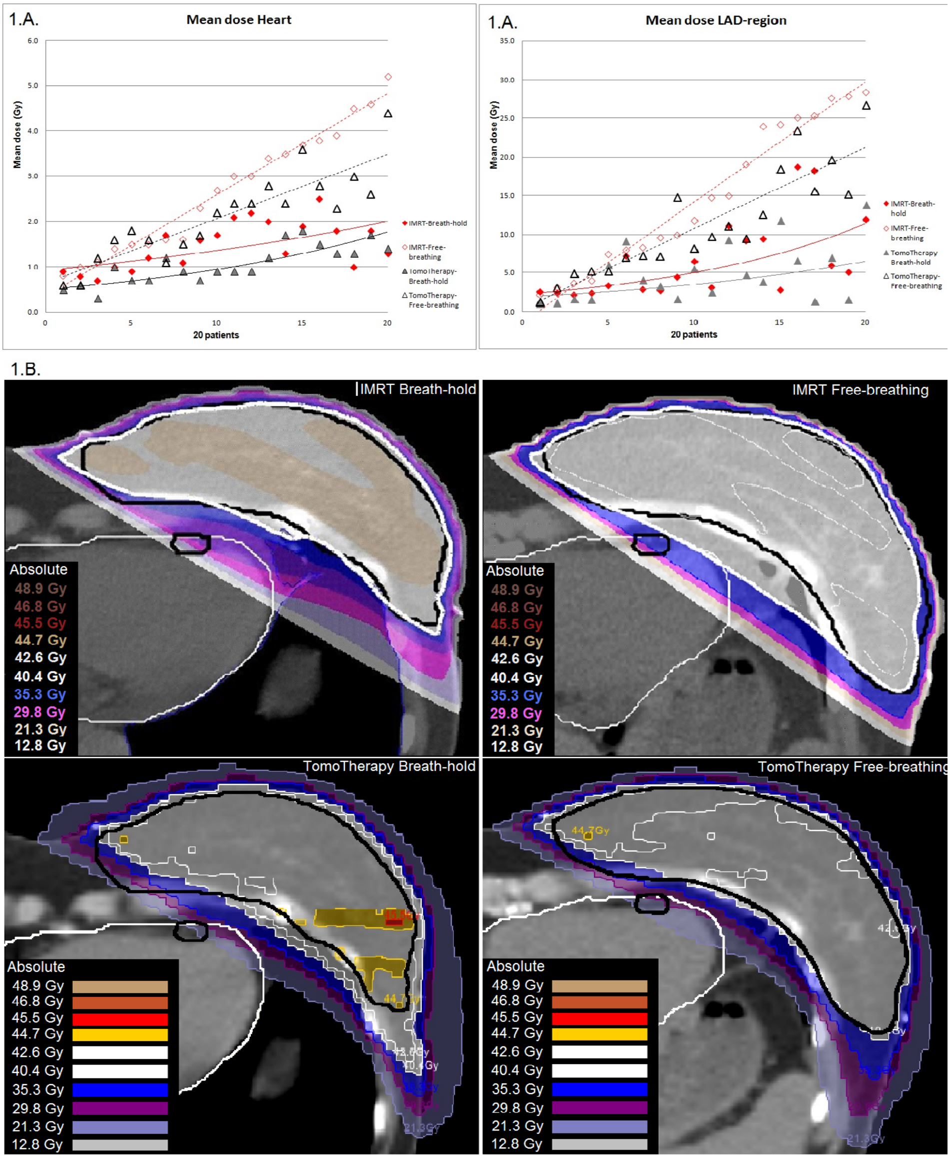

Figure 1A: Left: Mean dose administered to the heart in breath-hold and free-breathing for Intensity Modulated Radiotherapy (IMRT) and TomoTherapy (Tomo). Right: Mean dose administered to the LAD-region in breath-hold and free-breathing for Intensity Modulated Radiotherapy (IMRT) and TomoTherapy (Tomo). The cases were rearranged using the increasing (from left to right) IMRT FB technique values. For the convenience of comparison regression lines were added in the graphs.

Figure 1B: Isodose lines in the caudal part of the patient on the breath-hold scan. Delineated Organs at Risk: white line = heart; thick black line = region of the Left Anterior Descending coronary artery; Planning Target Volume: black line = PTV_{trim}; 95% isodose = thick white line. Left: IMRT and TomoTherapy in breath-hold. Right: IMRT and TomoTherapy in free-breathing.

Discussion

The results show that, with TomoTherapy in breath-hold, when compared to tangential IMRT in breath-hold, the mean doses to the heart as well as to the LAD-region could be reduced significantly. This was achieved without compromising the doses to the target volumes. For the other dose values both techniques in breath-hold were comparable. The difference between the mean heart dose when using a tangential IMRT technique in breath-hold compared to TomoTherapy in breath-hold, was limited 1.5Gy (SD 0.5Gy) and 1.1Gy (SD 0.4Gy), respectively. However, it should be emphasised that the combination of a breath-hold technique with TomoTherapy cannot be performed in daily clinical practice, due to the longer beam-on time (a TomoTherapy treatment session in free-breathing fraction lasts about 20 minutes) and rotating technique [9]. Therefore, TomoTherapy can only be applied without breath-hold. We also showed, that less dose to the heart and LAD-region will be administered when using tangential IMRT in breath-hold compared to TomoTherapy in free-breathing, see Figure 1. Theoretically, the tangential IMRT technique could be optimised. A higher dose reduction to the heart could be achieved by using a multiple field IMRT technique. However, Borges et al., reported that this could only be achieved at the expense of a higher dose in OARs and normal tissue [10]. Furthermore, we did not evaluate the dose in the contralateral breast as this item was analysed in other studies. Shiau et al. found no significant difference in mean doses in the contralateral breast between TomoTherapy and tangential IMRT. However, as the low dose (V5Gy) in the contralateral breast was higher for TomoTherapy compared to tangential IMRT, this should be taken into account when using a TomoTherapy technique [5]. Recently, TomoDirect was introduced, allowing the administration of radiation using fixed gantry angles. As Qi et al. described in their study, the TomoDirect technique leads to less dose in the contralateral breast compared to helical TomoTherapy [11]. Finally, we underline the statement of Qi et al., that individualised radiation treatment is of importance and that the appropriate radiation technique needs to be selected according to the patients risk factor [11].

Conclusion

In daily clinical practice tangential IMRT in breath-hold is the preferred technique to maximally reduce the dose to heart and LAD-region in left-sided whole breast irradiation.

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