Master of Science dissertation:

Evaluation of respiratory gating – dose sparing and set-up

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Lund University, Sweden, 2012

Abstract

Purpose: To evaluate the benefits of using respiratory gating for left-sided breast cancer in the form of dose-sparing and biological effects to the heart and to investigate the set-up deviations for patients treated with respiratory gating in order to find an optimal correction strategy for this group of patients.

Materials and methods: Nineteen patients treated with respiratory gating for left-sided breast cancer using the Real-time Position Management system (RPM, Varian Medical Systems, Inc., Palo Alto, CA) were retrospectively enrolled in this study. All patients had been treated with breast conserving surgery and no nodes were irradiated. Two CT-scans were performed for all patients treated with respiratory gating, one during deep breathing and one during normal free breathing. Since the patients had been treated with respiratory gating, structure delineation and treatment plans had already been made in the gated CT image set. For evaluation of the dose sparing and radiobiological effect, structure delineation was carried out and individually optimized treatment plans were created also for conventional treatment. Comparable target coverage was the main criteria when creating the treatment plans. The relative seriality model was used to calculate the cardiac mortality probability for the two treatment techniques.

For evaluation of the set-up deviations, orthogonal kilovolt set-up images were acquired at every fraction for 18 patients treated with respiratory gating and 17 patients treated conventionally for comparison. In total, 659 images were acquired and manually matched with digitally reconstructed radiographs reconstructed from the CT image sets. Calculations of the set-up deviations were made both with no correction strategy applied and with the currently used correction strategy. The effect of the set-up deviation on the absorbed dose distribution was investigated by simulations in the treatment planning system (Eclipse version 10, Varian Medical Systems, Inc., Palo Alto, CA) and measurements with a biplanar diode array.

Results: The mean absorbed dose to the heart was decreased for all patients in this study using respiratory gating. The average mean absorbed dose to the heart was 2.6 Gy for conventional treatment and 1.4 Gy for respiratory gating, a reduction of 46 %. For the left anterior descending (LAD) coronary artery the average mean absorbed dose was 13.9 Gy for conventional treatment and 4.2 Gy for respiratory gating, a reduction of 70 %. These reductions are statistically significant ($p<0.01$). The average mean absorbed dose to the left lung was 5.8 Gy for both conventional treatment and respiratory gating. As a result of the dose sparing for the heart the cardiac mortality probability could be reduced from 0.58 % for conventional treatment to 0.05 % for respiratory gating.

An overall mean systematic deviation ($m_{overall}$), calculated as the mean deviation for all patients and all treatment fractions, of 6.0 mm in the anterior direction and 8.1 mm in the cranial direction was present for the patients treated with respiratory gating if no correction strategy was applied. This set-up deviation results in increased absorbed dose to the organs at risk (OAR) and affects the absorbed dose distribution to the target. If the currently used correction strategy was applied to the deviations, $m_{overall}$ was reduced to 1.1 mm in the anterior direction and 3.3 mm in the cranial direction. $m_{overall}$ can be further reduced if the AML factor is excluded from the current correction

strategy. If this was done, the $m_{overall}$ was 0.5 mm in the posterior direction and 1.0 mm in the cranial direction. No difference in the random set-up error was seen between the patients treated with conventional treatment and respiratory gating.

Conclusions: Significant dose-sparing to the heart and LAD can be achieved using respiratory gating without compromising the target coverage. As a result of this dose sparing, the cardiac mortality probability can be reduced. This was comparable with earlier results [10, 13]. If no correction strategy is used for respiratory gating large systematic set-up deviations will be present which would increase the absorbed dose to the OARs and affect the dose distribution to the PTV. By excluding the AML factor from the currently used NAL correction strategy, the set-up deviations for the patients treated with respiratory gating will be minimized.

A popularized summary in Swedish:

Strålbehandling under inandning minskar bestrålningen av hjärtat – om patienten positioneras rätt

Strålbehandling kan användas för att behandla olika cancerdiagnoser. Man vill då kunna rikta strålningen mot tumören medan så lite frisk vävnad som möjligt bestrålas. Olika studier visar att för patienter som behandlas med strålbehandling för cancer i vänster bröst är förekomsten av och dödligheten i olika hjärtsjukdomar högre än för de som behandlas med strålbehandling för cancer i höger bröst. Detta beror på den ökade stråldosen till hjärtat vid behandling av cancer i vänster bröst till följd av att hjärtat är placerat närmare vänster bröst än höger bröst. Ett sätt att minska stråldosen till hjärtat vid behandling av bröstcancer i vänster bröst är att använda andningsanpassad strålbehandling. Då får patienten andas in djupare än normalt under behandlingen efter en röst som säger ”andas in” och ”andas ut”. Bestrålningen sker bara när patienten andats in. Då är avståndet mellan bröstet och hjärtat som störst och på så sätt kan stråldosen till hjärtat minskas. I denna studie visas att genom att behandla patienter med vänstersidig bröstcancer med andningsanpassad strålbehandling kan stråldosen till hjärtat minskas med 46 %, vilket resulterar i en minskning av sannolikheten att dö i hjärtsjukdomar för dessa kvinnor.

Innan strålbehandlingen får patienten göra en datortomografiundersökning, vilket är en form av röntgenundersökning som ger snittbilder av patienten i tre dimensioner. I dessa bilder planerar man sedan hur strålfälten ska gå för att få så bra fördelning av stråldosen till det område som ska behandlas samtidigt som man minimerar stråldosen till den friska vävnaden. Det är viktigt att patienten ligger likadant vid behandling som under datortomografin. Ligger patienten annorlunda leder det till att stråldosen inte hamnar på det område som det var tänkt vilket kan leda till bestrålning av riskorgan och att delar av behandlingsområdet inte får den stråldos det var tänkt. På grund av uppläggningsproceduren för de patienter som behandlas med andningsanpassad strålbehandling kommer de att ligga lite annorlunda vid varje behandling. Denna avvikelse i positioneringen är systematisk och påverkar samtliga tillfällen patienten behandlas och kan korrigeras med en korrektionsstrategi. Genom att använda en korrektionsstrategi kan man uppskatta den systematiska avvikelsen och korrigera för den. Om man inte använder någon korrektionsstrategi introducerar man stora systematiska positioneringsavvikelser genom att använda andningsanpassad strålbehandling, vilket påverkar dosfördelningen till behandlingsområdet och hjärtat. Det är därför viktigt att korrigera för dessa systematiska avvikelser. Denna studie visar att den allmänt vedertagna korrektionsstrategin inte är den optimala för de patienter som behandlas med andningsanpassad strålbehandling. En justering av denna korrektionsstrategi, som resulterar i en bättre positionering, föreslås istället användas för denna patientgrupp.

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1. Introduction

The aim of radiotherapy is to kill the tumor cells while minimize the absorbed dose to the surrounding healthy tissue. According to the International Commission on Radiation Units (ICRU) Report 50 and 62 [1,47] the gross tumor volume (GTV) contains the visible and/or palpable tumor. The Clinical Target Volume (CTV) contains the GTV and/or the subclinical malignant disease. The CTV is the volume that needs to be eradicated to achieve the aim of radiotherapy. To account for different uncertainties, margins are added to the CTV, creating the Planning Target Volume (PTV). This is done to ensure that the entire CTV receives the prescribed absorbed dose. The margins added to create the PTV accounts for uncertainties such as changes of the size, shape and position of the CTV (from for example breathing motion) and set-up uncertainties. So a common way to account for breathing motion of the target during radiotherapy is to add margins. Another way to account for the breathing motion is to use breathing adapted radiotherapy techniques (BART). Then the target is only irradiated in a specific part of the respiratory cycle, decreasing the margins needed to be added due to breathing motion. BART can also be used to increase the spatial distance between the target and the organ at risk (OAR), and in that way decrease the absorbed dose to the OAR.

Breast cancer is the most common cancer among women in Sweden. In year 2010, 26 295 cancers were diagnosed among Swedish women according to the Swedish National board of health and welfare [2]. 7917 of these were breast cancer, making 30.1 % of the total diagnosed cancers among Swedish women. The relative five year survival of breast cancer is 87.8 % [3]. Most women treated for breast cancer undergo primary surgery, often followed by adjuvant radiotherapy. Surgery can remove any detected macroscopic disease, but some microscopic tumor foci might remain which could lead to locoregional recurrence or distant metastases (or both) if untreated [4]. Several studies show a decrease in recurrence using postoperative radiotherapy for breast cancer [4-5]. A study showed that the 10-year risk of recurrence decreased from 35.0 % when only treated with surgery to 19.3 % when treated with both surgery and radiotherapy [4]. The 15-year risk of breast cancer mortality decreased from 25.2 % to 21.4 % when surgery and radiotherapy was used compared to only surgery [4]. But studies also show an increased cardiac morbidity and mortality in patients treated with radiotherapy for left-sided breast cancer compared to right-sided [6-9], due to the higher cardiac absorbed dose for the left-sided patients, implying that increased absorbed doses to the heart increase cardiac complications. This reduces the net benefit of the radiotherapy treatment for left-sided breast cancer. But if the absorbed dose to the heart could be decreased, the complications will decrease as well [10]. In recent years treatment such as intensity-modulated radiotherapy and BART have been used to decrease the absorbed dose to the heart and lungs for breast cancer radiotherapy [11]. Several studies using different forms of BART show a decrease in the absorbed dose to the heart [12-18] and to the lungs [13,15-16].

Free breathing respiratory gating is a form of BART where the patient breathes freely, although a bit deeper than normal. Using an individual pre-specified gating window around the maximum of the breathing amplitude, the beam will be turned on only when the breast and heart are the furthest apart. Due to this increased spatial distance, the absorbed dose to the heart can be decreased. In the beginning of 2007, the radiotherapy department at SUS Malmö was the first clinic in Sweden to provide respiratory gating. Since then more than 700 women have been treated with this technique for left-sided breast cancer.

There are several uncertainties in radiotherapy that lead to that the absorbed dose is not delivered where it´s intended. One such uncertainty is patient set-up. Interfractional set-up deviations are the difference between a reference image (i.e. a digitally reconstructed radiograph, DRR, reconstructed from the CT image set) and a set-up image acquired before treatment. This deviation consists of a systematic and a random part [19-20], where the systematic set-up deviation affects all treatment fractions equally much while the random set-up deviation varies from day to day. The systematic part of the set-up deviation can be corrected for by an appropriate correction strategy but it doesn´t reduce the random part. Today, a no action level (NAL) correction strategy with an adaptive maximum likelihood (AML) factor is used at Skåne University Hospital (SUS) [21].

All patients that potentially will receive a gated treatment undergo both a conventional and a gated CT examination to evaluate if the patient will gain from respiratory gating or not. In association with the CT-scanning, skin markers are made at the patient during normal free breathing. A treatment plan is made on the respiratory gated CT-set but in the treatment room the patient is positioned during normal free breathing. This leads to a systematic deviation corresponding to the motion extent induced using respiratory gating for each patient respectively. This set-up deviation will then theoretically be present for all patients treated with respiratory gating, inducing an overall mean systematic deviation, $m_{overall}$. This systematic set-up deviation is today thought to be captured and corrected for using the existing set-up correction strategy protocol.

The aim of this master thesis is to 1) evaluate the dose sparing and radiobiological effects of respiratory gating by a retrospective treatment planning study, 2) investigate set-up deviations for the patients treated with respiratory gating and evaluate the effect of them on the absorbed dose distribution to the target and OARs and 3) evaluate if the existing set-up correction strategy is optimal for patients treated with respiratory gating.

2. Theory

2.1 Respiratory gating

Breathing motion can cause the tumor to move out of the field which gives an underdosage to the tumor and unnecessary dose to healthy tissue. One way to avoid underdosage to the tumor is to increase the margins around it, but this will then increase the normal tissue irradiated. Another way is to account for the breathing motion by different forms of BART. Some of these techniques are breath hold methods, respiratory gating, forced shallow breathing and real-time tumor tracking [22-23]. During breath hold methods the patient breathe in deep and hold his/her breath. This can be achieved with active techniques where a valve temporarily blocks the airflow, or with passive techniques, where the patient voluntarily holds his/her breath [23]. During respiratory gating the patient breathe freely but deeper than normal. During both breath hold methods and respiratory gating, the radiation beam is only on during a pre-specified part of the respiratory cycle. During tumor tracking the radiation beam is synchronized with the respiration and “follows” the target during the respiration [24].

At SUS Malmö respiratory gating is used for patients treated for left-sided breast cancer to reduce the absorbed dose to the heart. The patients are requested to breathe deeper in order to increase

the distance between the breast and heart. This is possible due to the fact that respiratory maneuvers pull the diaphragm and heart inferiorly while expanding the anterior chest wall and thereby increasing the distance between the breast tissue and the heart [12]. The lung mass irradiated will also be reduced due to the decreased lung density during deep inspiration [13,23]. Respiratory gating can also be used to reduce the absorbed dose to the left anterior descending (LAD) coronary artery, which is sensitive to radiation [25].

During respiratory gating, radiation is only administrated in a pre-set window called the "gating window" (figure 1). The gating window can be placed in an arbitrary position in the breathing cycle depending on the aim of the respiratory gating. If the aim is to maximize the distance between the breast and the heart, the gating window is placed in the end-inhalation phase. There are two different types of respiratory gating referred to as amplitude gating or phase gating. In amplitude gating the radiation beam is activated whenever a certain amplitude is reached, regardless of the phase in the patient´s respiratory cycle. In phase gating the radiation beam is on in a certain phase of the respiration cycle. At SUS Malmö amplitude gating is used. The ratio of the beam-on to the overall treatment time is referred to as the duty cycle and is a measurement of the efficiency. Some motion may still occur in the gating window and this motion is referred to as "residual motion". Determination of the width of the gating window is a trade of between the efficiency and the residual motion [22]. Using the same margins as for conventional breast treatment, the residual motion must not exceed the normal breathing amplitude.

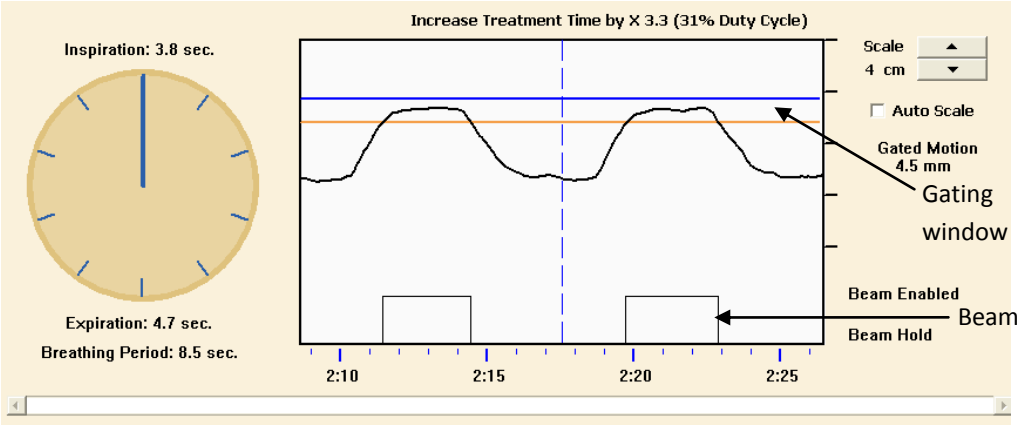


Figure 1 A gating curve acquired by the real-time positioning management system.

2.1.1 Why use respiratory gating for breast cancer radiotherapy?

Studies show an increased late cardiac morbidity and mortality for women treated with radiotherapy for left-sided breast cancer compared to right-sided breast cancer [6-9]. This difference is believed to be caused by the enhanced heart volume irradiated for left-sided breast cancer. McGale et. al. [6] show an increased incident ratio for left-sided breast cancer for acute myocardial infarction, angina, pericarditis and valvular heart disease in a study of 35 000 Swedish and Danish women treated with radiotherapy. The incident ratio for left-sided breast cancer patients compared to right-sided for all heart diseases were 1.08. Heart disease due to radiotherapy is a long-term effect, often not seen until more than 10 years after treatment. Darby et. al. [9] showed an increased cardiac risk with increasing time after diagnosis. The cardiac mortality ratio (left versus right tumor laterality) was 1.20 less than 10 years afterwards, 1.42 10-14 years afterwards and 1.58 after 15 years or more.

According to Taylor et. al. [26], the absorbed dose to the heart has decreased over the years, owing to technical improvements. Due to the long time it takes to see a result on the heart disease incidence due to irradiation the effect from contemporary radiation techniques are not known.

Studies have shown increased perfusion defects for LAD corresponding to the irradiated heart volume for left-sided breast cancer patients treated with radiotherapy [27-29]. According to a study by Evans et. al. [29], set-up deviations may increase the heart perfusion defects due to a larger volume of the heart irradiated when set-up deviations where present. A perfusion defect may result from the blockage of a coronary artery or from microvascular damage to an area of myocardium [25], but it is not yet clear what the long-term effects of these perfusion defects are. Gyenes et. al. [31] showed that cardiac mortality was correlated with the volume of the heart within the radiation field. Nilsson et. al. [46] showed an increase in stenosis in coronary arteries placed close to the breast (there among LAD) for patients irradiated for left-sided breast cancer compared to right-sided, which indicate a direct link between radiation and location of coronary stenosis.

Several studies show an increased incidence of pneumonitis with an increased absorbed dose to the lungs [23,30]. Darby et. al. [9] showed a significantly higher mortality in ipsilateral than contralateral lung cancer for women treated with radiotherapy for breast cancer.

These studies implies that an increased absorbed dose to the heart, LAD and the lungs can increase the incidence of heart and lung diseases which would reduce the beneficial effects of radiotherapy on overall survival.

Studies show that techniques, such as respiratory gating and deep inspiration breath hold, for breast cancer reduce the cardiac volume in the radiation fields for treatment of left-sided breast cancer [12-18]. Korreman et. al. [13] show that the median heart volume receiving more than 50 % of the prescription dose was reduced from 19.2 % with free breathing (FB) to 2.8 % with respiratory gating (RG) and 1.9 % with deep inspiration breath hold (DIBH). The median LAD volume receiving more than 50 % of the prescribed dose was reduced from 88.9 % with FB to 22.4 % with RG and 3.6 % with DIBH [13]. Some studies also show a reduction in the ipsilateral lung volume in the treatment field for breathing adapted treatment for left-sided breast cancer [13,15-16]. Korreman et. al. [13] show that the median ipsilateral relative lung volume irradiated to more than 50 % of the target dose was reduced from 45.6 % with FB to 29.5 % with RG and 27.7 % with DIBH. One study shows an increase in the absolute lung volume in the radiation field but no difference in the relative lung volume in the radiation fields was seen [14]. Some studies show a decrease in cardiac and lung complication probabilities due to this volume decrease [10,16,32]. Korreman et. al. [10] show a pneumonitis probability of 28.1 % with FB, 2.6 % with RG and 4.3 % with DIBH and a cardiac mortality probability of 3.8 % with FB, 0.5 % with RG and 0.1 % with DIBH. This means that the complication probability for pneumonitis and cardiac mortality were reduced with 85 % and 95 %, respectively.

2.1.2 The Real-time Positioning Management system

At SUS Malmö an external motion tracking system called the Real-time Positioning Management system (RPM^{TM}, Varian Medical Systems, Inc., Palo Alto, CA) is used for treatment with respiratory gating. A plastic box containing six reflecting markers is placed on the patient's chest (figure 2). Infrared light from an illuminator is reflected from the markers and detected by a camera. Information of the anterior-posterior movement of the box is projected real-time on a projector

screen, referred to as the “gating curve”. When the gating curve is within the gating window the radiation beam is automatically turned on (figure 1).

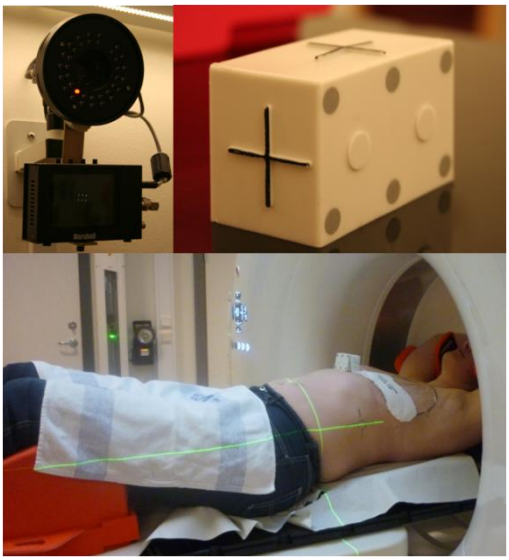


Figure 2 The RPM camera and plastic box with the six reflective markers. The placement of the box on the patient’s chest.

2.1.3 The process of respiratory gating at SUS Malmö

At SUS Malmö there is a respiratory practice room (figure 3), where the patients can practice their breathing, coached by a nurse. The couch and set-up equipment in the practice room are identical to the ones in the CT- and treatment room. To get the desired effect it is important that the patient learn to breathe with her chest and not the stomach. Following a recorded voice saying “breathe in” and “breathe out” at selectable times, the time of inhalation and exhalation is set individually for each patient. These times are decided after practice to suit the patient. The patient should be able to breathe deeper than normal but still stable and reproducible.

The patient is placed in the same way during the CT examination and two CT-scans are acquired, one during respiratory gating and one during normal free breathing. Prospective CT-scanning is used, meaning that the CT-slices are acquired only in a pre-set window of the respiratory cycle. Ones the breathing curve enters the gating window the CT-scanning starts. The gating window is placed so that the residual breathing motion during beam on does not exceed the breathing amplitude during normal free breathing. This is because the intrafraction breathing motion should not become larger for patients treated with respiratory gating compared to patients treated conventionally during normal breathing. Otherwise, the increased “blurring” of the absorbed dose distribution could cause underdosage to the target and overdosage to the normal tissue. A treatment plan is completed using the gated CT-scan.

During treatment, the patient is positioned in the same way as during the CT acquisition and the marker block is placed at the same position on the chest of the patient. The gating window, determined at the CT session, is used and beam-on only occurs when the breathing curve is inside the gating window.

Figure 3 Respiratory practice room at SUS, Malmö

2.2 Set-up deviations and correction strategies

2.2.1 Systematic and random set-up deviations

There are different uncertainties in radiotherapy that potentially can introduce a difference between the volume intended to be irradiated and the volume actually irradiated. To take this difference into account, appropriate margins are added to the CTV, resulting in a planning target volume (PTV) [1]. The PTV includes margins for uncertainties in organ shape and motion, beam geometry and patient set-up [19]. Reducing the uncertainties, the margins can be reduced and healthy tissue can be spared. But too small margins can lead to an underdosage of the target. In radiotherapy, deviations can occur between different treatment fractions (inter-fraction deviations) or during one treatment fraction (intra-fraction deviations). Intra-fraction deviations are caused by random patient movement or organ motion [19]. Organ motion is the variation of organ position and shape relative to the skeletal anatomy [33]. During a single treatment fraction, organ motion can be caused by breathing, heartbeat, swallowing and peristaltic motion. Between treatment fractions it can, for example, be caused by variable filling of the bladder or gastrointestinal tract and weight gain or loss.

A patient set-up deviation is defined as the difference between the actual and intended position of the part of the patient which is to be irradiated [19]. The set-up deviation is measured as the difference between a set-up image and its corresponding reference image and will consist of both a systematic and a random part [19-20]. A systematic deviation affects all treatment fractions equally much while the random deviation varies from day to day. A good immobilization and daily set-up can reduce the random error but a reduction of the systematic error requires a correction [34]. Unless immediate, online correction of daily set up deviation is performed the best way to reduce random set-up deviation is by improving immobilization and set-up reproducibility [35]. In figure 4 an illustration of systematic and random set-up deviations are presented in the lateral and anterior-posterior direction. Each dot in this figure represents a measurement of the patient´s treatment

position compared to the planned position for one treatment fraction. If there is no set-up deviation the dot is placed in the origo. The average position represented by the arrow displays the systematic deviation and the distribution of the dots around this mean value displays the random deviation. The systematic deviation is larger for patient 1 than for patient 2 whereas the random deviation is smaller for patient 1 than for patient 2. Inter-fraction set-up deviations for a whole population are mainly caused by mechanical shortcomings (e.g. laser misalignment), but could also be patient related (e.g. skin mark movement) or fixation related (e.g. patient mobility) [19]. Another major factor influencing the set-up uncertainty is the accuracy with which the radiation technologists are able to position the patient using the set-up marks. The physical and mental state of the patient also influences the set-up accuracy [19].

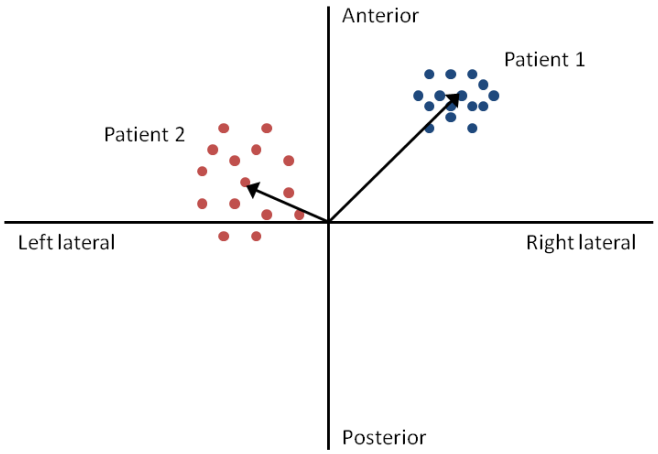


Figure 4 A two dimensional example of systematic and random set-up deviations for two patients in the lateral and anterior-posterior direction. Each dot represents the patient´s position relative the planned. The arrow symbolizes the patient´s systematic deviation and the distribution of the dots the random deviation.

According to van Herk [36], the random deviation has in general a much smaller effect on the dose distribution than the systematic deviations. The random errors give a blurring effect that leads to a small decrease of dose at the edge of the high dose region. The systematic errors on the other hand, lead to a shift that can strongly impact the dose distribution, for example if the target moves outside the high-dose region. Therefore it is important to correct for the systematic deviation.

2.2.2 Calculating the magnitude of systematic and random set-up errors

Only by acquiring multiple images the systematic and random errors can be separated. Greener [20] proposes a way to estimate these components and the accuracy of this approach will depend on the number of patients and images used in the analysis.

The individual systematic set-up deviation for each patient, m_p, is defined as the mean value of the deviations for all images taken for that patient, see Eq. 1. The individual systematic set-up deviation can differ between patients and is due to individual differences between set-up during CT and treatment. The individual random deviation, $\sigma_{rand,p}$, is defined as the standard deviation of the distribution of deviations around the mean value, m_p, for that patient according to Eq. 2. This is due to daily variations in the set-up for the individual patient. The mean of the individual systematic set-up deviations, i.e. the overall mean systematic deviation for all patients, is denoted $m_{overall}$ and takes

into account that different numbers of images has been acquired for different patients, see Eq. 3. If the value of $m_{overall}$ is different from zero, there is a systematic deviation present for an entire patient group in one direction. The systematic set-up error, $\Sigma_{set\text{-}up}$, is the standard deviation of the distribution of m_p around the $m_{overall}$ for a patient population, see Eq. 4. The random set-up error, $\sigma_{set\text{-}up}$, is the standard deviation of the individual random set-up deviations for all the patients in the population, see Eq. 5. Eq. 1-5 can be found in Greener´s "Practical determination of systematic and random set-up errors, $\Sigma_{set\text{-}up}$ and $\sigma_{set\text{-}up}$, using portal imaging" [20]. Explanations of the notations in Eq. 1-5 are found in table 1.

Table 1 Explanation of notations in Eq. 1-5

Symbol	Explanation
i	Image number
p	Patient number
$\mu_{(DRR\text{-}set\text{-}up)}$	Deviation between the set-up image and the reference image
n_p	Number of images taken for patient p
N	Total number of images in the study
P	Total number of patients for which images were acquired
m_p	Mean deviation for patient p for all images taken, i.e. the individual systematic set-up deviation for patient p in a given direction
$m_{overall}$	Overall mean systematic deviation in a given direction, i.e. the average of the m_p for all patients P
$\sigma_{rand,p}$	Individual random set-up deviation, i.e. the standard deviation of the distribution of the deviations μ around m_p for a patient p
$\sigma_{set\text{-}up}$	The random set-up error for all patients P in a given direction, i.e. the standard deviation of the $\sigma_{rand,p}$ distribution
$\Sigma_{set\text{-}up}$	The systematic set-up error for all patients P in a given direction, i.e. the standard deviation of the m_p distribution

Mean deviation of n_p measurements, i.e. the individual systematic set-up deviation for patient p:

$$\mathrm{m_p} = \frac{1}{\mathrm{n_p}} \sum_{\mathrm{i}=1,\mathrm{n_p}} \mu_{(\mathrm{DRR-set-up}),\mathrm{i}} \tag{1}$$

Individual random deviation for patient p:

$$\sigma_{rand,p} = \sqrt{\frac{1}{n_p - 1} \sum_{p=1,n_p} \left(\mu_{(DRR-set-up),i} - m_p\right)^2} \tag{2}$$

Overall mean systematic deviation for all P patients:

$$m_{overall} = \frac{1}{N} \sum_{p=1,P} n_p \cdot m_p \tag{3}$$

Systematic set-up error for the patient population P:

$$\Sigma_{set-up} = \sqrt{\frac{P}{N(P-1)} \sum_{p=1,P} n_p \left(m_p - m_{overall}\right)^2} \tag{4}$$

Random set-up error for the patient population P:

$$\sigma_{set-up} = \sqrt{\frac{1}{N-P}\sum_{p=1,P}\sigma_{rand,p}^2(n_p-1)} \quad (5)$$

If the absolute value of $m_{overall} > t \cdot \frac{\Sigma_{set-up}}{\sqrt{P}}$, where t is the constant of the t-distribution for P-1 degrees of freedom and 95 % confidence limit, it indicates a significant overall systematic deviation at a 95 % confidence limit [20].This deviation arises from errors in data transfer from CT to the linear accelerator and should be minimized [20,34].

2.2.3 The no action level correction strategy and the adaptive maximum likelihood factor

One way of correcting the interfractional set-up deviations is to acquire set-up images and carry out online-corrections at every fraction. Apart from a potentially unnecessary increase in absorbed dose to the patient, this online-strategy is very time consuming and therefore an offline correction strategy is preferred [21]. An optimal correction strategy approximates the systematic deviation and corrects for it as soon as possible from the treatment start. But such an offline correction strategy only corrects for the systematic part of the set-up error and the random part remains unchanged [35].

According to Greener [20], a general example of a correction strategy is to apply a correction of magnitude $k\mu$, where k ≤ 1 and μ is the mean set-up deviation, whenever a measured displacement μ exceeds a given action level. The correction of the patient set-up is then applied at the next fraction and may be based on measured set-up deviations from one or more images. There are different correction strategies clinically implemented. One that is based on the reasoning above is the NAL correction strategy. Then μ of the first n treatment fractions is calculated and a correction of $-\mu$ is made. According to Månsson [21] the optimum value of n to get a good approximation of the systematic component and a low workload is 3, which has been adopted at SUS.

Due to the fact that a deviation contains both a systematic and a random part, a correction of the whole mean value might result in an overcorrection. Therefore the AML factor, k, has been introduced by Gluhchev [37] and Shalev et al. [38]. It is given by:

$$k = \frac{n\Sigma_{set-up}^2}{n\Sigma_{set-up}^2 + \sigma_{set-up}^2} \quad (6)$$

According to Månsson [21] the systematic and random set-up errors are approximately equal and then Eq. 6 can be simplified to:

$$k = \frac{n}{n+1} \quad (7)$$

At SUS a NAL correction strategy with k according to Eq. 7 is used clinically today, which is the optimal correction strategy according to Månsson [21]. Orthogonal kilovoltage set-up images are acquired before the three first treatment fractions. The average displacement, μ, is calculated in the vertical, longitudinal and lateral directions. If the displacement, weighted by k, is larger than an

action level (table 2) a permanent correction of -kμ is made. If the deviation in any direction during the first three treatment fractions is larger than an acute action level (table 2), an online correction of the whole deviation is made for that treatment fraction. But the lines marking the isocenter on the patient are not changed. From treatment fraction 4, set-up images are acquired once every 10th fractions. If the deviation is larger than an acute action level (table 2) an online correction of the whole deviation is made, but the lines on the patient marking the isocenter are not changed. At the following treatment fraction a new set-up image is taken. If the mean deviation for these two treatment fractions, multiplied with k, exceeds the action level for permanent correction (table 2) an offline correction according to the above strategy is performed and applied at the next treatment fraction, but now with n = 2. When an offline correction is made it is always verified with a set-up image.

Table 2 Action levels for breast cancer patients at SUS Malmö

Acute action level online correction fraction 1-3 (mm)	Acute action level online correction fraction 4- (mm)	Action level permanent correction (mm)
4	6	3

3. Materials and methods

3.1 The treatment planning study

In a retrospective study the dosimetric benefit from respiratory gating was investigated. The absorbed dose to the heart, LAD and left lung with respiratory gating and conventional treatment was compared. 19 patients treated with respiratory gating for left-sided breast cancer using the RPM-system at SUS Malmö were enrolled in the study. The patients began their treatment between February and July 2011. They had all been treated with breast conserving surgery, and underwent postoperative tangential radiotherapy to the breast. No nodes were treated. The prescribed dose was 50 Gy and delivered in 25 fractions.

To evaluate whether the patient will benefit from respiratory gating both a conventional and gated CT examination are carried out for comparison. If the patient will undergo a gated treatment, contouring and treatment planning is only made in the gated CT-set. To be able to compare the dose distributions acquired from each treatment technique, contouring and treatment planning had to be done also in the conventional CT-sets.

3.1.1 Contouring

The volumes of interest (VOI) in this study were the heart, LAD, left lung, PTV and CTV and these were only contoured in the gated CT for the patients treated with respiratory gating. To delineate the corresponding structures (except the left lung) in the CT-set acquired during normal free breathing the application Smartadapt (Varian Medical Systems, Inc., Palo Alto, CA) was used. Smartadapt uses deformable registration to deform a structure-set from one CT-set to another. By using this time saving application, possible differences in contouring between physicians could also be avoided. For all patients, however some corrections were made after the suggestion from Smartadapt. The

corrections were performed primarily to meet the structure set in the gated CT rather than have a second opinion about the delineation. Any obvious errors were corrected by the author. Most corrections were made for the heart and LAD and smaller corrections were made for the PTV and CTV. The structure-sets were then reviewed and corrected if necessary by two physicians. The left lung was automatically contoured in both CT-sets using the automatic delineation program "segmentation wizard" in the treatment planning system (TPS) (Eclipse version 10.0, Varian Medical Systems, Inc., Palo Alto, CA). The PTV was the whole breast and the CTV the area were the tumor was placed before surgery (figure 9).

3.1.2 Planning

The treatment plans based on the gated CT consisted of two tangential main fields and one to three additional fields. Multileaf collimators were used to shape the fields and either 6 and 10 MV or 6 and 18 MV photons were used. Wedges were not used since the number of respiratory cycles will increase significantly as a result of the decreased dose rate during treatment. The field edge margins for the two main fields were 5 mm (except out in the air where larger margins were used). Based on the conventional CT-sets, individually optimized treatment plans, similar to the delivered plans, were created by the author. The first priority when constructing the treatment plans in the conventional CT was to have comparable coverage of the PTV as in the gated plan. This allows for direct comparison of OAR absorbed doses. Essential the same margins for the main fields were kept in the conventional plan as in the gated plan. Secondly, the Swedish national guidelines for breast cancer treatment with radiotherapy [39] were followed. The absorbed dose to the heart and left lung were minimized to the extent were the PTV coverage could be kept. Also the absorbed dose to the contralateral breast was minimized. In the conventional treatment plans wedges were used if necessary. The absorbed dose distributions were calculated using the anisotropic analytical algorithm (AAA) version 10.0.28 for both the gated and conventional treatment plans and the absorbed dose was normalized as 100 % as the mean absorbed dose in the PTV.

3.1.3 Evaluation

Dose Volume Histograms (DVHs) were calculated using the TPS. The following quantities were acquired for the heart, LAD and left lung:

- The relative structure volume receiving more than 50 % of the prescribed dose ($V_{50\%}$)
- Mean absorbed dose in Gy

The individual difference in mean absorbed dose between the two treatment techniques for all patients in this study were calculated and presented as histograms. Also the average mean absorbed dose and $V_{50\%}$ were calculated for both treatment techniques. The relative difference (in percent) between the two treatment techniques were calculated and compared. All differences in this study are given in percent and are calculated according to:

$$\frac{X_{convetional} - X_{gating}}{X_{conventional}} \cdot 100 \qquad (8)$$

where X is a given quantity.

Calculations and constructions of diagrams were carried out in Microsoft Excel 2007. A paired Wilcoxon signed rank test was carried out in SPSS version 20 (IBM; IL) to evaluate statistical differences of the average mean absorbed dose and average $V_{50\%}$ between the two treatment techniques. The differences between the two treatment techniques were considered being statistically significant if p<0.01.

3.1.4 Radiobiological effects

To evaluate the radiobiological effect of the differences in absorbed dose to the heart between the two treatment techniques, the probability for cardiac mortality was calculated using the relative seriality model. This has previously been used for this purpose in the literature [10,13]. The normal tissue complication probability (NTCP) was calculated according to the following equations [40]:

$$NTCP = \left\{1 - \prod_{i=1}^{n}[1 - P(D_i)^s]^{\Delta V_i}\right\}^{1/s} \quad (9)$$

$$P(D_i) = 2^{-exp\{e\gamma(1-D_i/D_{50})\}} \quad (10)$$

where n is the number of subvolumes in the dose-calculation volume, $\Delta V_i = V_i/V$ where V_i is the volume of subvolume in the differential histogram and V is the total volume of the organ. D_i is the absorbed dose in each subvolume. s is the seriality factor and describes the tissue architecture and assumes a value between 0 and 1 (parallel and serial organization, respectively). An organ where the substructures are organized in series becomes nonfunctional when one substructure is damaged, while for a parallel organ the probability of complication depends on the fraction of substructures damaged. Eq. 10 describes the dose-response curve for each subvolume in which a homogeneous absorbed dose is assumed, while Eq. 9 describes the tissue response to an arbitrary dose distribution. D_{50} is the dose resulting in 50 % complication probability and γ is the maximum relative slope of the dose-response curve. The NTCP-curve for carciac mortality after radiotherapy for breast cancer according to Gagliardi et.al [41] can be seen in figure 5. Fitting the relative seriality models to this curve results in the following values of the parameters; s = 1, γ=1.28 and D_{50}=52.3 Gy [40].

The calculations in this study are based on differential DVHs of the heart acquired from the TPS for each patient, where the absorbed dose intervals were 0.05 Gy. The center value was used for D_i and V_i is the volume receiving an absorbed dose in that particular interval.

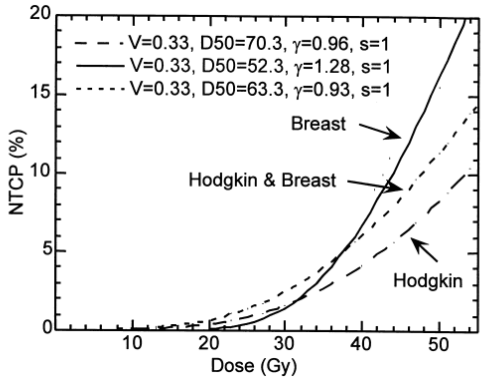


Figure 5 Dose response curves for cardiac mortality for treatment for breast cancer and Hodgin´s disease [41].

3.2 The set-up study

3.2.1 Set-up image acquisition

From the beginning, 39 consecutive patients were enrolled in this study, 19 treated with respiratory gating and 20 treated conventionally. Two patients treated conventionally and two treated with respiratory gating were not considered having representative set-ups and were deleted from the study. Finally, kilovolt (kV) set-up images were acquired at each fraction for 18 patients treated with respiratory gating and for 17 patients treated conventionally using the on-board imager (OBI, Varian Medical Systems, Inc., Palo Alto, CA). While all patients treated with respiratory gating had left-sided breast cancer, both left- and right-sided diagnoses were represented among the patients receiving conventional breast-treatment. It was assumed that there were no differences in set-up uncertainties for patients treated for left-sided and right-sided breast cancer. All patients were positioned in essentially the same way, at a breastboard (Posiboard-2, Civco medical solution, IA) with both arms elevated above the head. The patients were either given 42.5 Gy in 16 fractions or 50 Gy in 25 fractions. So the intention was to acquire either 16 or 25 sets of set-up image pairs for each patient. Due to different reasons, such as technical problems with the OBI system or heavy workload in the clinic at the time, some set-up images were lost or not acquired. All together 659 orthogonal image pairs were acquired and manually matched.

3.2.2 Matching procedure

The kV set-up images were manually matched with DRRs reconstructed from the CT-set. Matching was made by landmarks visible on both the set-up image and the DRR (figure 6). The landmarks were the edge of the lung, sternum, clavicle, vertebras, lung and ribs, and were delineated by an oncology nurse in the DRR. Different landmarks were delineated for different patients, depending on the visibility of these landmarks in the DRR. The deviations, $\mu_{(DRR\text{-}set\text{-}up)}$, were obtained and online or offline corrections were carried out if necessary according to the correction strategy used (see section 2.2.3).

The matching of the set-up images with the DRRs were either performed online by an oncology nurse or offline by the author. If the offline matches gave deviations of 6 mm or more the oncology nurses were notified and an online match was performed at the next fraction. The author and nurses used the same matching criteria.

a,
b,

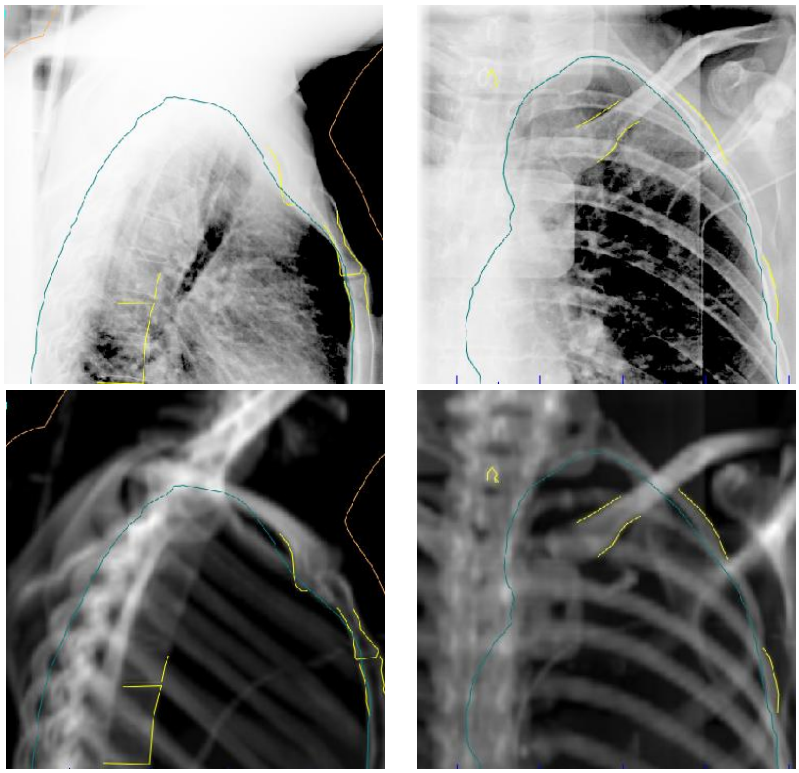


Figure 6 Set-up images aquired with the OBI-system (a) and DRR (b). Bony landmarks are outlined in yellow and the lung edge is outlined in green.

The anterior-posterior direction is in the rest of this thesis called vertical (vert), the superior-inferior direction is called longitudinal (long) and the left-right direction is called lateral (lat). The scale used in this thesis is based on IEC 61217 [42]. This means that the deviation, $\mu_{(DRR\text{-}set\text{-}up)}$ is:

- Positive/negative in the vertical direction if the patient is positioned more posterior/anterior during treatment then during the CT-scanning.
- Positive/negative in the longitudinal direction if the patient is positioned more caudal/cranial during treatment then during the CT-scanning.
- Positive/negative in the lateral direction if the patient is positioned more to the patient´s right/left during treatment then during the CT-scanning.

3.2.3 Calculations

The set-up deviations present if no correction strategy had been applied were calculated. Any correction strategy of interest could then be simulated. A NAL correction strategy combined with an AML factor with n = 3 and k = 0.75 (according to Eq. 7) was applied [21]. m_p and $\sigma_{rand,p}$ were calculated for each patient according to Eq. 1-2, and for both treatment techniques, $m_{overall}$, $\Sigma_{set\text{-}up}$ and $\sigma_{set\text{-}up}$ where calculated using Eq. 3-5, with and without the correction strategy applied.

Calculations and construction of diagrams were made in Excel. A student´s t-test was carried out to evaluate if $m_{overall}$ was statistically significant from zero. The individual mean deviations, m_p, were assumed to follow a t-distribution with the standard deviation $\Sigma_{set\text{-}up}$. The number of patients in the study (P) was 18 (respiratory gating) and 17 (conventional treatment), making the degrees of freedom (P-1) equal to 17 and 16. For a 95 % confidence level (p = 0.05) and 16/17 degrees of

freedom, the tabulated value of t is 2.120/2.110 (43). If the absolute value of $m_{overall} > t \cdot \frac{\Sigma_{set-up}}{\sqrt{P}}$ there is a statistical significant overall mean systematic deviation present.

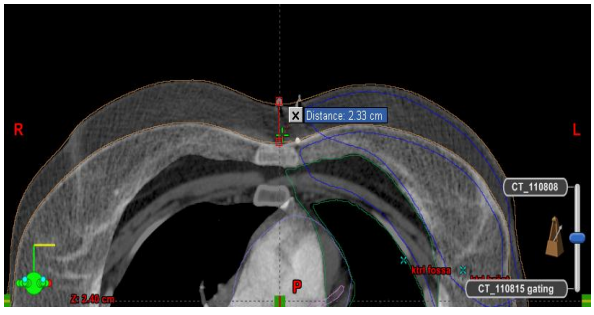
3.2.4 Finding the optimal correction strategy

A way to avoid the systematic deviation introduced by using respiratory gating would be to position the patient during deep inspiration when the respiratory gating has started. But this would be inconvenient for the staff and lead to uncertainties in the set-up. Therefore some other method to correct for the systematic deviation has to be employed. Two possible improvements to the correction strategy are suggested:

- To apply a correction based on the breathing motion extent in the vertical and longitudinal directions before the first treatment fraction.
- To find an optimal value of k to use in the current correction strategy for the patients treated with respiratory gating.

Correcting with the breathing motion extent is a good strategy if the individual systematic deviation, m_p, is equal to this motion extent. To investigate this, the breathing amplitude in the vertical and longitudinal directions was measured by the placement of the radioopaque marker in the gated and conventional CT-set. The two CT-sets were registered using automatic rigid registration in the TPS. The rigid registration was made on the vertebraes because these were considered being fixed during respiration. A radioopaque marker, used to mark the reference point, was placed on the chest wall to measure the breathing amplitude (figure 7). The movement of the radioopaque marker was measured using the measuring tool in the TPS. The individual systematic set-up deviation, m_p, for each patient was plotted against the measured breathing amplitude in the vertical and longitudinal directions.

To find the optimal value of k, Eq. 6 was used to calculate new values of k for the systematic and random set-up error present for respiratory gating.

a, 

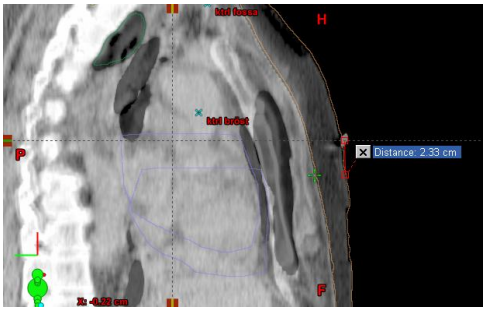
b, 

Figure 7 Measurement of the movement of the radioopaque marker using the rigid registered CT-images in the vertical direction (a) and the longitudinal direction (b)

3.3 The effect of the systematic set-up deviation on the absorbed dose distribution

The effect of the systematic part of the set-up deviation on the absorbed dose distribution to the target and OARs was investigated by simulations in the TPS and measurements with the biplanar diode array Delta[4] (ScandiDos, Inc., Sweden).

3.3.1 Simulations in the TPS

The effect of the systematic set-up deviation on the absorbed dose distribution to the OARs was investigated by shifting the isocenter of the treatment fields in the TPS, corresponding to $m_{overall}$ (table 5). This was made for the 19 patients in the treatment planning study (section 3.1). The mean absorbed dose to the heart, LAD and left lung and the dose received by 99 % and 1% of the PTV ($D_{99\%}$ and $D_{1\%}$) were acquired with 1) no set-up deviations, 2) set-up deviations and no correction strategy, 3) set-up deviations and NAL (k=0.75) and 4) set-up deviations and NAL (k=1). The average values for all the patients were calculated.

3.3.2 Measurements with the Delta^4

Delta^4 is a biplanar diode array containing two orthogonal detector boards (figure 8). The center-to-center distance between the diodes is 5 mm in the central 6x6 cm^2 region and 10 mm in the rest of the array. Six gated breast cancer treatment plans were delivered to the Delta^4 using the Truebeam linear accelerator (Varian Medical Systems, Inc., Palo Alto, CA). Two measurements were carried out for each patient; one without set-up deviations and one where the uncorrected set-up deviations corresponding to $m_{overall}$ (table 5) were introduced.

To compare the two dose distributions, a 3D gamma evaluation was carried out which takes both dosimetric and spatial accuracy into account. The 3D gamma value is calculated in the following way [44]:

$$\gamma(\vec{r}_r) = \min\{\Gamma(\vec{r}_e, \vec{r}_r)\}\ \forall\{\vec{r}_e\} \tag{11}$$

Where $\vec{r}_r$ is the reference point (without set-up deviation introduced in this study) and $\vec{r}_e$ is the evaluated point (with the uncorrected set-up deviations introduced) in three dimensions.

$$\Gamma(\vec{r}_e, \vec{r}_r) = \sqrt{\frac{|\vec{r}_e - \vec{r}_r|^2}{\Delta d^2} + \frac{[D_e(\vec{r}_e) - D_r(\vec{r}_r)]^2}{\Delta D^2}} \tag{12}$$

$D_r(\vec{r}_r)$ and $D_e(\vec{r}_e)$ are the reference and evaluated doses, respectively and Δd and ΔD are the distance to agreement (DTA) and dose difference criteria respectively. In this study the passing criteria Δd=2mm and ΔD=3% was used. The criteria are fulfilled if $\gamma(\vec{r}_r) \leq 1$. A parameter called the γ-agreement index (GAI) is defined as the fraction of the points in a VOI fulfilling the γ criteria [45].

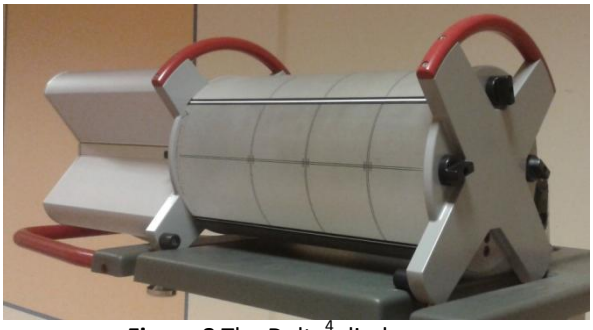


Figure 8 The Delta^4 diode array

Table 3 summarizes the studies in this thesis.

Table 3 Overview of the patient material and purposes within each study

Study	Patients	Purpose
Treatment planning study	19 patients where both conventional and gated CT-scans were available	Investigate difference in absorbed dose to OARs between respiratory gating and conventional treatment
Simulations in the TPS	The 19 patients from the treatment planning study	Investigate the effect of the systematic part of the set-up deviation on the absorbed dose distribution
Measurement with the Delta[4]	Six patients from the treatment planning study	Investigate the effect of the systematic part of the set-up deviation on the absorbed dose distribution
Set-up study	18 patients treated with respiratory gating and 17 patients treated conventional	Investigate set-up deviations and correction strategies

4. Results and discussion

4.1 The treatment planning study

4.1.1 Dose sparing

The breast moves anteriorly and the heart moves caudally during inhalation, increasing the distance between the breast and heart during respiratory gating compared to during normal free breathing. To clarify the results a beam´s eye views for one of the patient in this study is shown (figure 9). The heart is placed almost entirely out of the field during respiratory and LAD is completely outside the treatment field for this patient.

a, 

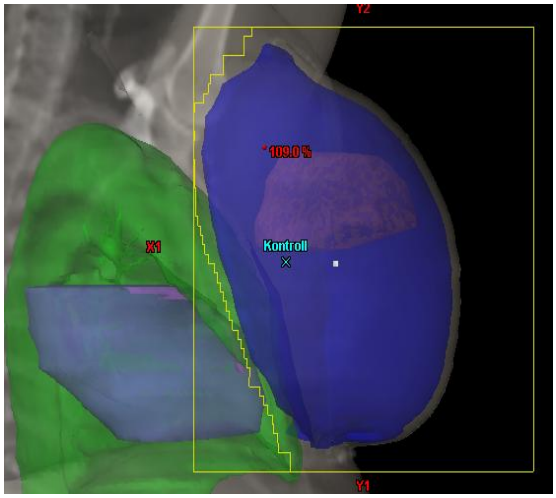
b, 

Figure 9 Beam´s eyes views from the medial tangential field for one of the patients in the study showing the CTV (pink), PTV (blue), heart (purple), LAD (pink) and left lung (green) for conventional treatment (a) and respiratory gating (b).

In figure 10 a comparison cumulative DVH is shown for the same patient, displaying the relative volume of the structures receiving a certain absorbed dose. A dose reduction is seen for this patient for the heart and LAD using respiratory gating. For this patient there is an increase in the absorbed dose to the left lung, but this was not the general case for all patients.

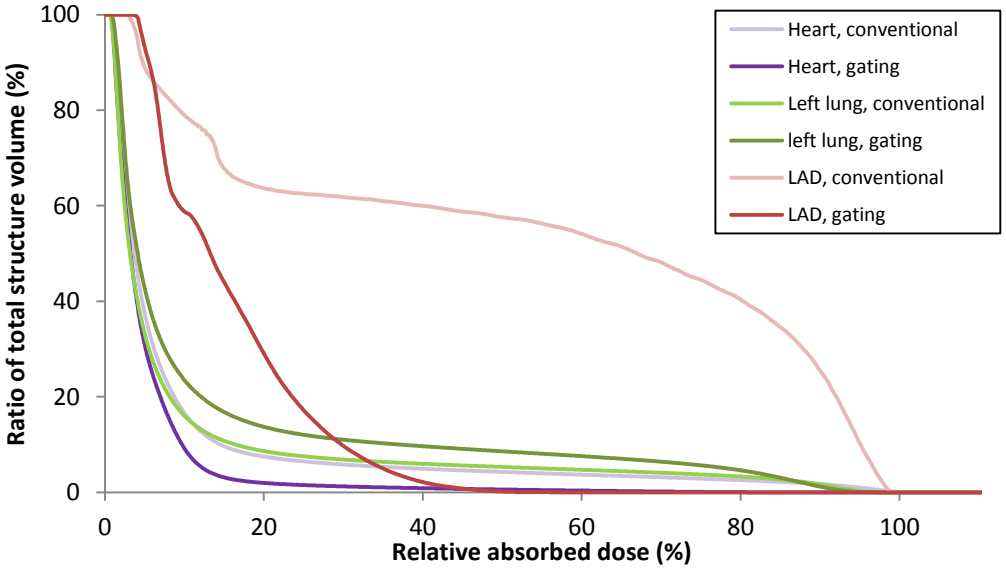
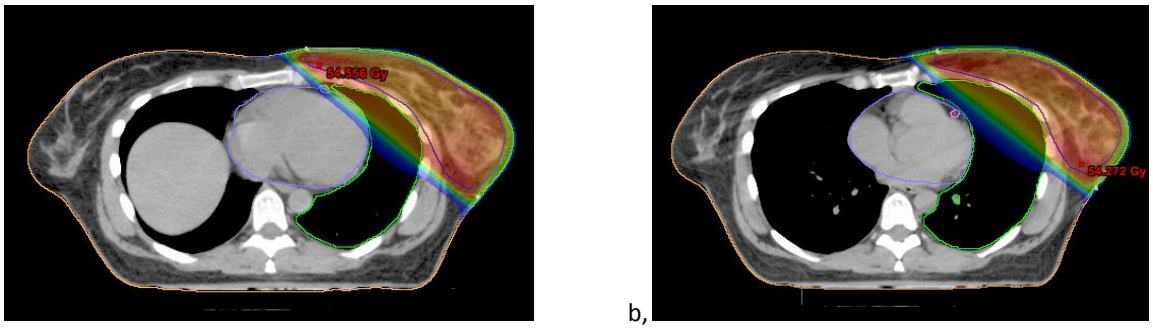


Figure 10 Cumulative DVH for one of the patients in the study comparing the respiratory gating and conventional treatment plans for the heart, LAD and left lung

An example of how the heart and LAD moves out of the high dose area for respiratory gating is shown in figure 11.



a, b,

Figure 11 Dose distributions in the same transversal CT-slice for conventional treatment (a) and respiratory gating (b)

The mean DVH for all patients, i.e. the mean of the volume for each absorbed dose step, is shown in figure 12. A large benefit is seen for the heart and LAD, and at the same time no difference is seen for the left lung. It can also be seen that on average, the target coverage is equal for the two treatment techniques.

The mean absorbed dose to the heart was decreased for all patients in this study (figure 13 a) and for all but one patient for LAD using respiratory gating (figure 13 b). Also $V_{50\%}$ for the heart decreased for all patients using respiratory gating (figure 14 a). For six patients, $V_{50\%}$ for LAD was zero for both conventional and gated treatment (figure 14 b). For seven patients, LAD was entirely out of the area receiving 50 % of the absorbed dose and for five patients $V_{50\%}$ was reduced to very small values using respiratory gating. For one patient a very small increase in the $V_{50\%}$ for LAD was seen using

respiratory gating. No distinct pattern was seen for the mean absorbed dose and $V_{50\%}$ for the left lung (figure 13 c and figure 14 c). For both the heart and LAD, the average mean absorbed dose and average $V_{50\%}$ for all patients in this study were decreased (table 4). These decreases were statistically significant ($p<0.01$). The average mean absorbed dose was decreased by 46 % for the heart and 70 % for LAD and the average $V_{50\%}$ was decreased by 86 % for the heart and 99 % for LAD.

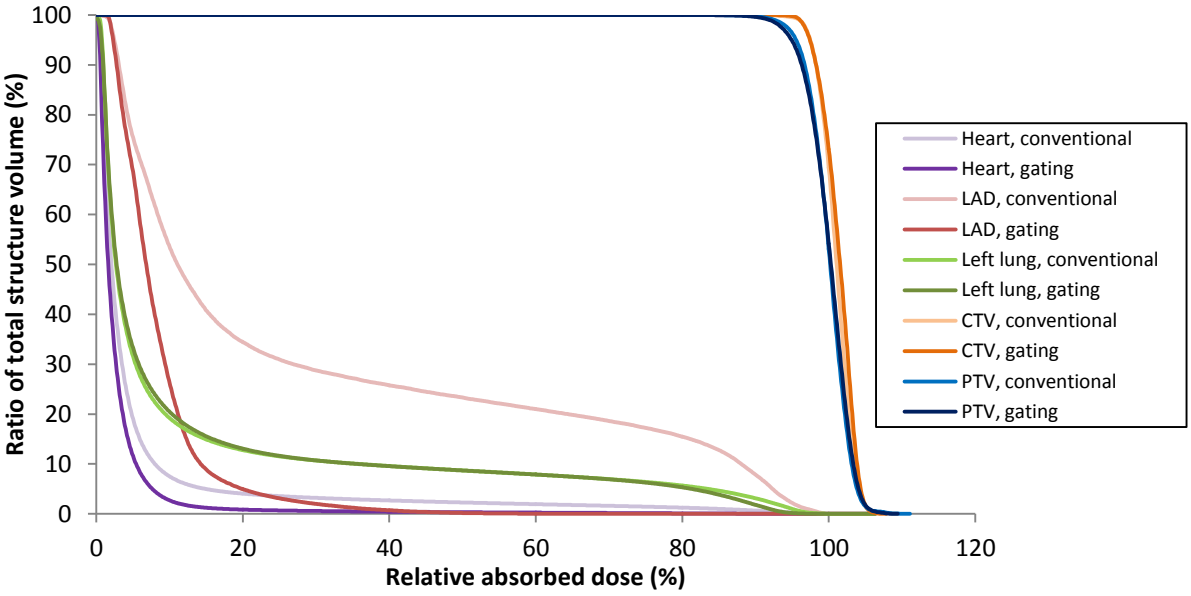
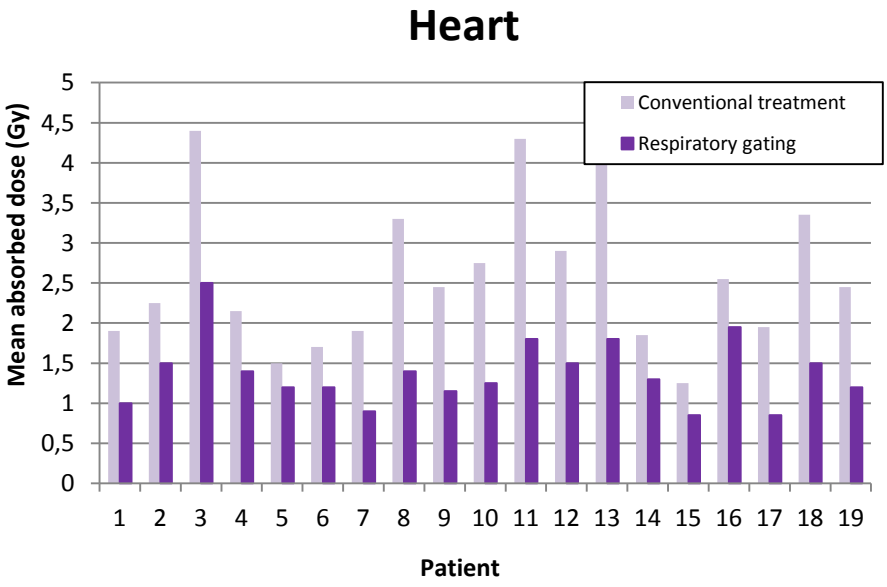


Figure 12 Mean DVH for all 19 patients in this study

If it is assumed that the lung mass is proportional to the relative lung volume through the lung density, the density is uniform over the whole lung and density changes due to respiration are likewise uniform, the relative lung volume is more relevant than the absolute lung volume [13]. The relative $V_{50\%}$ for the left lung is the same for respiratory gating and conventional treatment, implying that the same lung mass is irradiated for the two treatment techniques.



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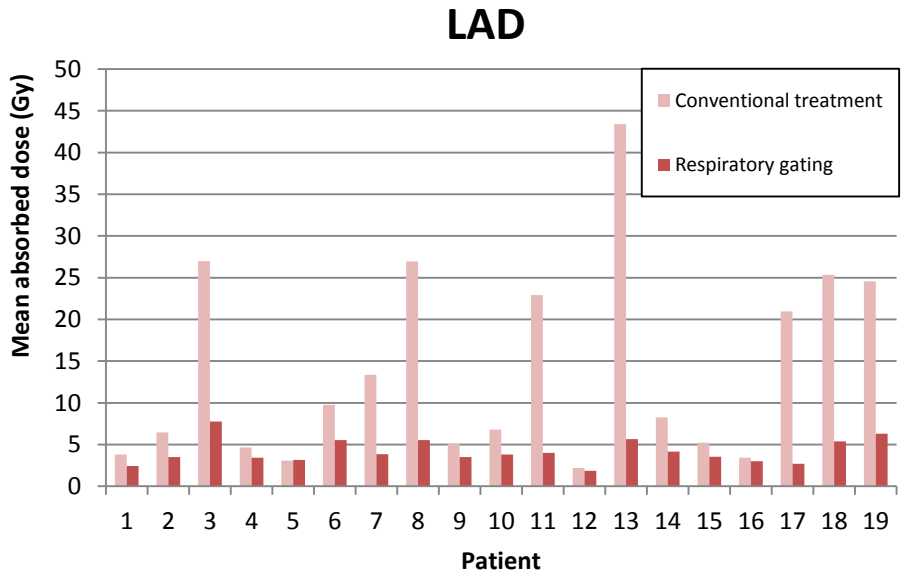

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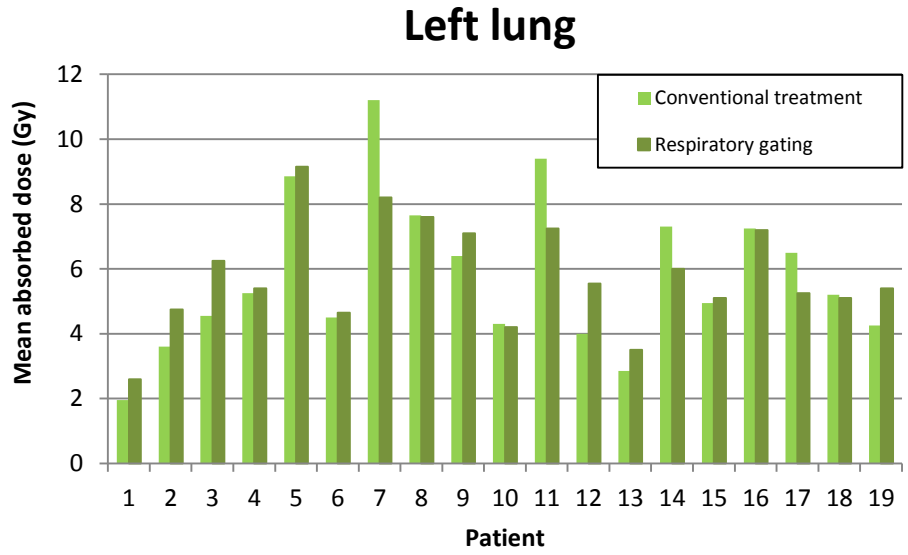
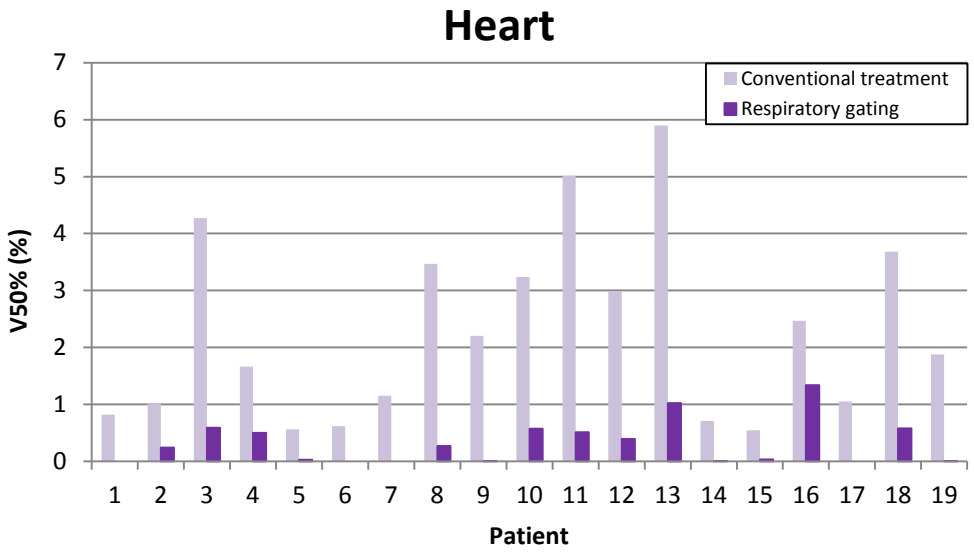


c,

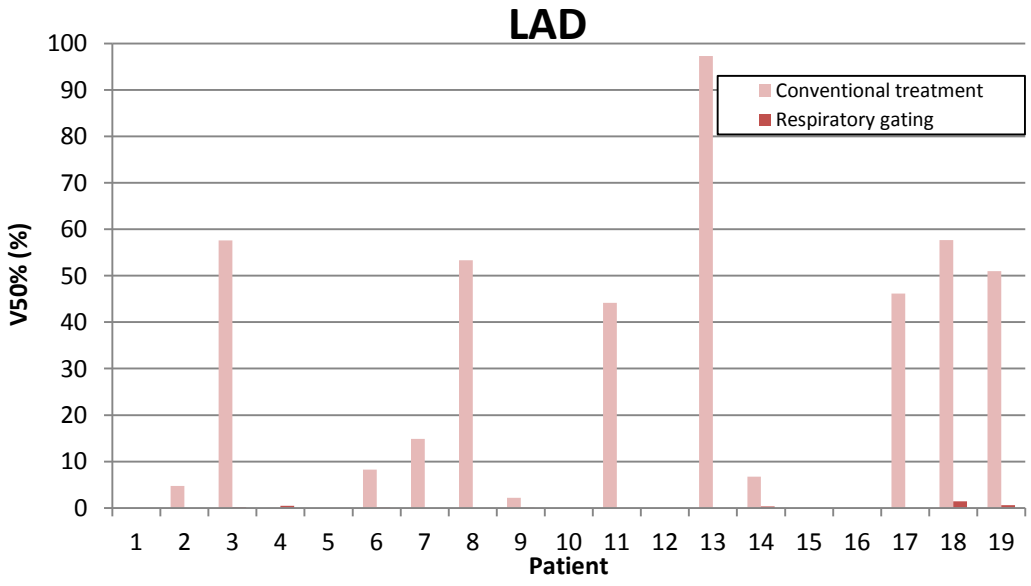
Figure 13 The mean absorbed dose for conventional treatment and respiratory gating for the heart (a), LAD (b) and left lung (c)

Performing a treatment planning study in two different respiratory phases it is important that the dose calculation algorithm performs equally well for both phases. Fogliata et. al. [45] have compared the ability of different dose calculation algorithms to compute the absorbed dose to the lung for different respiratory phases (FB and DIBH). The pencil beam (PB), anisotropic analytical algorithm (AAA) and collapsed cone (CC) were compared, and Monte Carlo (MC) was used as benchmark. Large differences in the absorbed dose distributions computed for FB and DIBH were observed for the PB algorithm, but only small differences were observed for the AAA and CC algorithms. The reason for this is that lateral electron transport is taken insufficient into account for the PB algorithm, resulting in inaccurate calculations in heterogeneous areas, such as the thorax. A 3D gamma evaluation showed that the fraction of lung voxels with $\gamma > 1$ for the PB algorithm were 25 % in DIBH and 15 % in FB. For the AAA and CC algorithms the fractions of voxels with a value of $\gamma>1$ were 2 % in FB and 4-5 % (AAA) and 6-8 % (CC) respectively in DIBH. This implies that the accuracy of the dose calculation algorithms decreases as the lung density decreases, though much less for the CC and AAA algorithm.

In this study the AAA algorithm was used and hence only small differences in the computed absorbed dose distribution should be expected between the different respiratory phases due to the dose calculation algorithm used. In addition, in the study by Fogliata et. al., the mean lung volume were increased by 75 % during DIBH compared to 58 % during respiratory gating observed in this study. This implies that the difference in lung density is smaller between the respiratory phases in this study and hence the difference in the absorbed dose distribution due to the dose calculation algorithm should be smaller too. According to Korreman et. al. [13] differences in the computed absorbed dose distributions for different respiratory phases are present using the PB algorithm. Hence more complex algorithms, such as the CC and AAA algorithms, should be used when performing a treatment planning study in different respiratory phases.



a,



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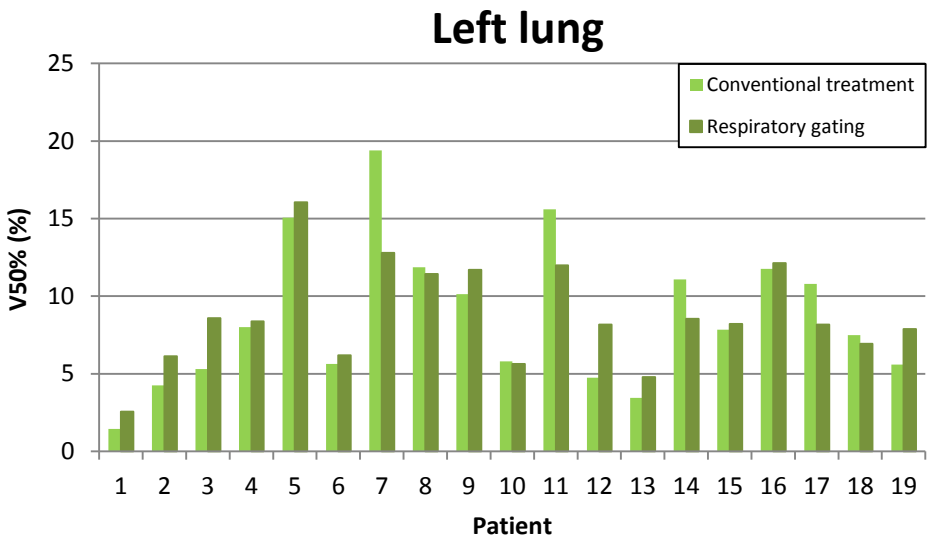


c,

Figure 14 $V_{50\%}$ for conventional treatment and respiratory gating for the heart (a), LAD (b) and left lung (c)

The reduction of $V_{50\%}$ in percent for the heart and LAD were larger in this study then earlier published data [13]. However, in the study by Korreman et. al. [13] the $V_{50\%}$ was larger for both respiratory gating and conventional treatment. This difference is believed to depend on that in the study by Korreman et. al. [13], the target included the breast, internal mammary nodes and periclavicular nodes but in this study the target consisted only of the breast. This implies that the patients in this study, where the target only consists of the breast, may not have been the patients that benefit most from treatment with respiratory gating. There may be other patients in our clinic, were the nodes are treated, that benefit even more from gated treatment. The study by Korreman et. al. showed a decrease in $V_{50\%}$ for the left lung, which was not seen in this study.

Table 4 The average mean absorbed dose and $V_{50\%}$ (range) for the 19 patients in the study. Values of p for the Wilcoxon signed rank test.

OAR	Average mean absorbed dose (Gy)			Average $V_{50\%}$ (%)		
	Conventional treatment	Respiratory gating	p	Conventional treatment	Respiratory gating	p
Heart	2.6 (1.25-4.4)	1.4 (0.85-2.5)	<0.001	2.3 (0.5-5.9)	0.3 (0-1.0)	<0.001
LAD	13.9 (2.2-43.4)	4.2 (1.85-7.75)	<0.001	23.4 (0-97.3)	0.2 (0-0.6)	0.002
Left lung	5.8 (1.95-11.2)	5.8 (2.6-9.15)	0.444	8.7 (1.4-19.4)	8.7 (2.6-12.8)	0.520

The changes in mean absorbed dose for each individual patient are presented as differential histograms (figure 15). It is shown that all patients have a decrease in mean absorbed dose larger than 20 % for the heart. The majority of the patients have a decrease between 50-60 %. For LAD the mean absorbed dose is decreased for all but one patient, and for that patient there is a very small increase in the mean absorbed dose. For almost half of the patients there is a reduction of 70-90 % for respiratory gating and for the rest of the patients there is a reduction of 10-50 %. For the left lung there is an increase of the mean absorbed dose between 0 – 40 % for 11 patients and a decrease of the mean absorbed dose between 0 – 30 % for the remaining 8 patients. The average values of the difference in mean absorbed dose for all patients in the study are 44 % for the heart, 52 % for LAD and -6 % for the left lung, where positive values imply a decrease in mean absorbed dose using respiratory gating.

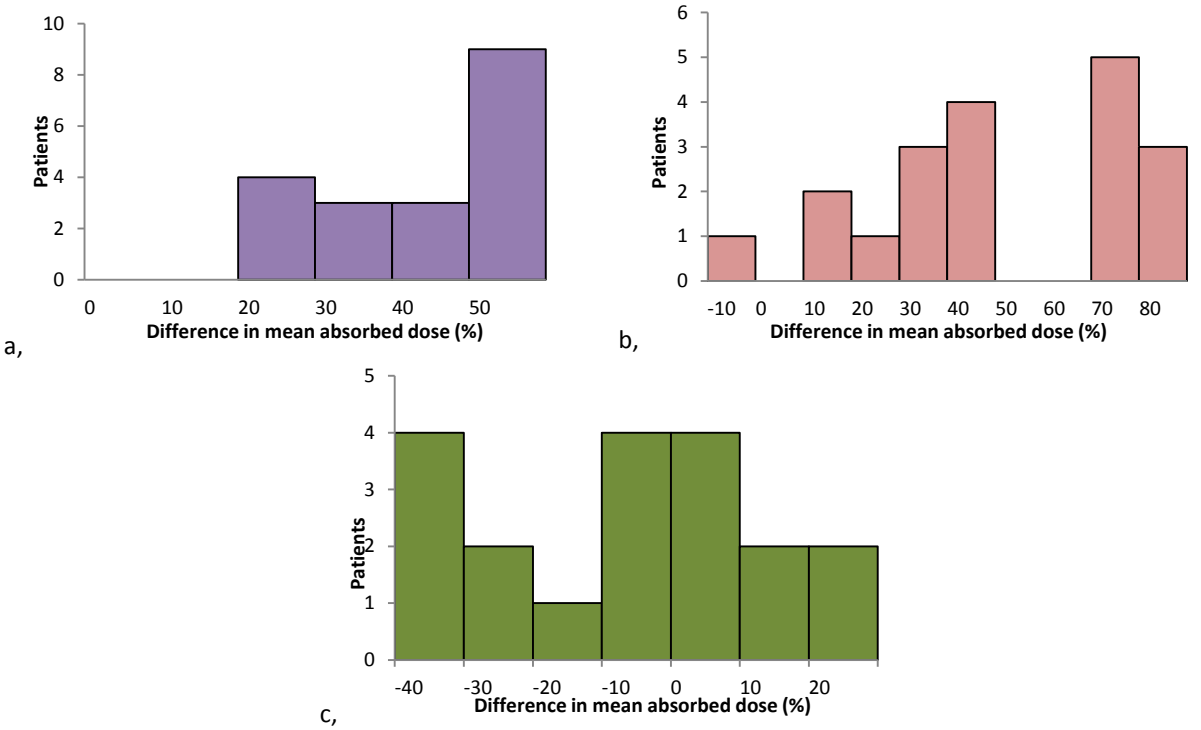


Figure 15 Histograms of the difference in mean absorbed dose for each individual patients for the heart (a) LAD (b) and left lung (c). Positive values means that the mean absorbed dose is less for respiratory gating then for conventional treatment.

4.1.2 Radiobiological effect

To evaluate the radiobiological effects of the dose sparing to the heart seen in section 4.1.1 the cardiac mortality probability for the patients in this study have been calculated using Eq. 9-10. The cardiac mortality probability is reduced for all patients using respiratory gating (figure 16). The average cardiac mortality probability is 0.58 % (range 0.05-1.69) for conventional treatment and 0.05 % (range 0.00-0.29) for respiratory gating. That means, according to the model used, that the patients dying in heart disease as a late side effect of their radiotherapy would decrease from 58 out of 10 000 to 5 out of 10 000 using respiratory gating, a reduction of 91 %. The NTCP values for cardiac mortality is already low for the conventional treatment but can be reduced even further using respiratory gating.

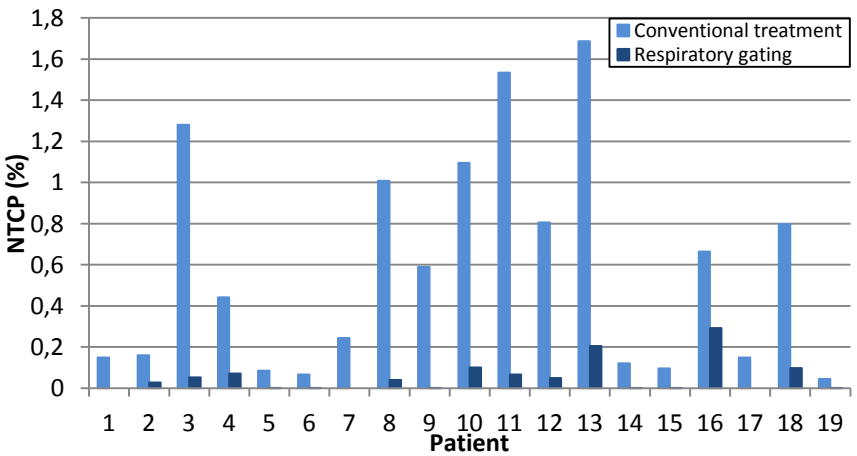


Figure 16 Cardiac mortality probability

In a study by Korreman et. al. [10] the reduction in average long-term cardiac mortality was 83 %, comparable with the results in this study. But in that study the average cardiac mortality probability was 5.4 % for conventional treatment and 0.9 % for respiratory gating, hence much larger than in this study. This is a consequence of that the absorbed doses to the heart were larger in that study compared to this one.

The relative seriality model, used in this study, assumes homogeneous radiation sensitivity, which for an organ such as the heart could be a crude approximation [41]. In figure 5 it can be seen that the NTCP curve for the heart varies for radiation therapy for breast cancer or Hodgin´s disease. This is believed to depend on which part of the heart that is irradiated [41]. Therefore irradiation to specific parts of the heart, such as LAD, may have a large effect on the risk. No NTCP calculations were carried out for the left lung because the similarity in absorbed dose between respiratory gating and conventional treatment.

This study shows a decrease in absorbed dose to the heart and LAD using respiratory gating. Due to the decreased absorbed dose to the heart a decrease in cardiac mortality probability was seen. But the direct effects of using respiratory gating still need to be investigated. No study, to our knowledge, has compared cardiovascular side effects in women treated with respiratory gating to women treated conventionally. But studies show that cardiovascular complications increase with increased absorbed dose to the heart [6-9] and coronary arteries [46] and therefore the absorbed dose to these structures should be minimized.

4.2 The set-up study

4.2.1 The uncorrected set-up deviations

Evaluating the motion of the radioopaque marker in the CT-sets acquired during normal free breathing and respiratory gating (see section 3.2.5) it can be seen that the motion during deep breathing is primarily in the vertical and longitudinal directions. The motion extent induced by a deep inhale was defined as the measured shift of the radioopaque marker between the two CT-sets. In this study the shifts in the slices were the marker is seen is approximated to be the shift for the whole CT-acquisitions. The shift was 4-16 mm in the anterior direction and 4-29 mm in the cranial direction for 17 of the 18 patients treated with respiratory gating. For one patient no conventional CT-scanning was performed. In the lateral direction motion is seen in both directions but the extent is much smaller than in the vertical and longitudinal directions. The mean motion extent in the lateral direction is +0.2 mm (see section 3.2.2). Therefore the main effort of this study has been to investigate the systematic set-up deviation in the vertical and longitudinal directions for the patients treated with respiratory gating.

For each patient and each fraction the displacement $\mu_{(DRR\text{-}set\text{-}up)}$ was measured. The displacements that would have been present if no correction strategy had been applied were then calculated. These displacements are shown as scatter diagrams in the vertical and longitudinal directions in figure 17 and for the lateral and longitudinal directions in figure 18. These distributions imply that the patients treated with respiratory gating are positioned more anterior and cranial during treatment compared to CT-scanning (negative shift in both the vertical and longitudinal directions). No such shift of the distribution is seen for the breast cancer patients treated conventionally or in the lateral direction for

those patients treated with respiratory gating. However, some divergent displacements are presented (figure 17 and 18), which are all associated with two patients.

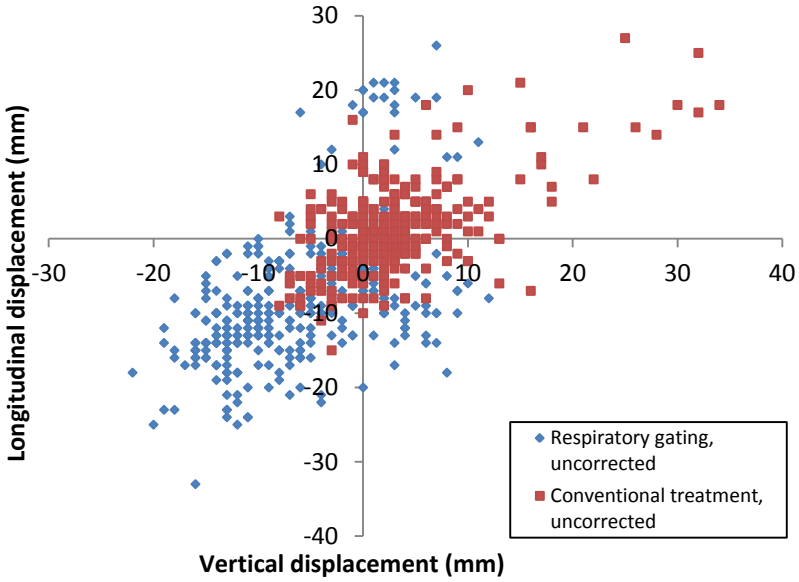


Figure 17 The uncorrected displacements for each patient and each fraction in the vertical and longitudinal directions

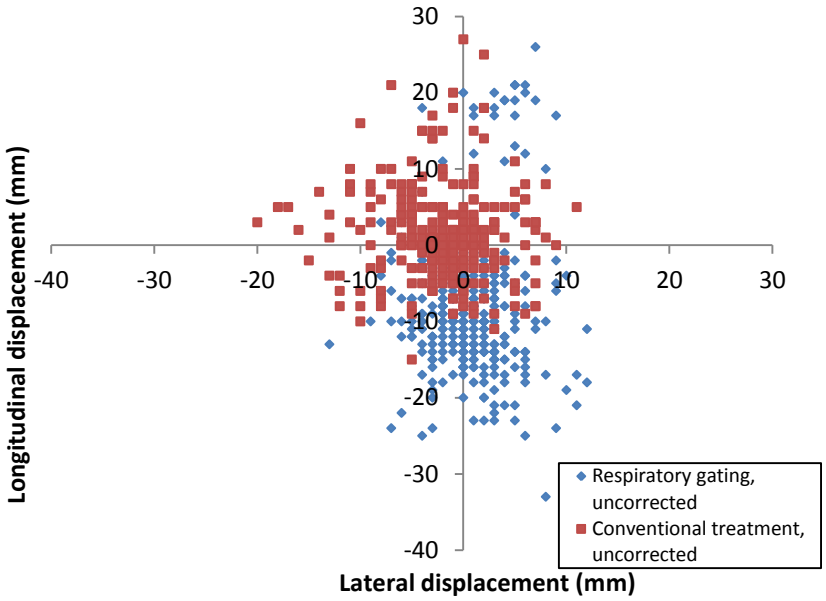


Figure 18 The uncorrected displacements for each patient and each fraction in the lateral and longitudinal directions

The overall mean systematic deviation, $m_{overall}$, was calculated for the uncorrected values according to Eq. 3, and the systematic set-up error, $\Sigma_{set\text{-}up}$, according to Eq. 4 and the random set-up error, $\sigma_{set\text{-}up}$, according to Eq.5. These results are shown in table 5 for both respiratory gating and conventional treatment.

Table 5 The result of the set-up study for both respiratory gating and conventional treatment, with and without correction strategies applied

Direction	Respiratory gating			Conventional treatment		
	Vert (mm)	Long (mm)	Lat (mm)	Vert (mm)	Long (mm)	Lat (mm)
			Uncorrected results			
$m_{overall}$	-6.0	-8.1	0.7	3.1	1.4	-1.9
$\Sigma_{set\text{-}up}$	6.3	8.6	2.4	5.5	4.7	3.7
$\sigma_{set\text{-}up}$	3.6	3.5	2.9	3.6	4.1	3.1
			Corrected results, NAL k = 0.75			
$m_{overall}$	-1.1	-3.3	1.3	1.2	0.7	-0.8
$\Sigma_{set\text{-}up}$	2.8	3.7	2.8	3.7	3.2	2.4
			Corrected results, NAL k = 1			
$m_{overall}$	0.5	-1.0	1.2	-	-	-
$\Sigma_{set\text{-}up}$	3.0	2.5	2.2	-	-	-

Without any correction strategy applied, the $m_{overall}$ is -6.0 mm in the vertical direction and -8.1 mm in the longitudinal direction (table 5), which implies that the patient group treated with respiratory gating is positioned more anterior and cranial during treatment then during CT-scanning, which is in consistency with what we expected when we started this study. This was not seen for the conventional treatment, where $m_{overall}$ is 3.1 mm in the vertical direction and 1.4 mm in the longitudinal direction. The systematic set-up error, $\Sigma_{set\text{-}up}$, is larger in the vertical and longitudinal directions for respiratory gating compared to conventional treatment, implying a larger spread of the individual systematic set-up deviation around the $m_{overall}$. The random set-up errors are in the same magnitude for both treatment techniques, so no additional random component is induced in the set-up using respiratory gating.

T-tests were carried out to evaluate if $m_{overall}$ differed statistically significant from zero (table 6). Not surprisingly, for respiratory gating $m_{overall}$ in the vertical and longitudinal directions are statistical significant. It is known that the reason for this is the motion extent induced by respiratory gating after set-up of the patient. But that $m_{overall}$ for conventional treatments were statistically significant in the vertical and lateral directions were not expected. For the vertical direction, it could be explained by one patient that have very large deviation in the vertical direction, see figure 17. If this patient is excluded from the study, $m_{overall}$ in the vertical direction is no longer statistically significant. The statistical significant $m_{overall}$ in the lateral direction needs further investigation.

Table 6 Results of the t-tests carried out to investigate if $m_{overall}$ differ statistically significant from zero

Treatment technique	Direction	Statistical significant (p<0.05)
Respiratory gating	Vert	Yes
	Long	Yes
	Lat	No
Conventional treatment	Vert	Yes
	Long	No
	Lat	Yes

From the results above it is clear that a correction strategy for patients treated with respiratory gating is needed, otherwise large systematic deviations will be present in the vertical and longitudinal directions.

4.2.2 Evaluation of the NAL correction strategy with k=0.75

A NAL correction strategy with k=0.75 was applied to the uncorrected displacements and the results are presented in figure 19 and 20 for the patients treated with respiratory gating. There is still a clear systematic set-up deviation in the cranial direction (negative shift), implying that this correction strategy is not the optimal one for the patients treated with respiratory gating.

In both the vertical and longitudinal directions and for both treatment techniques, $\Sigma_{set\text{-}up}$ and $m_{overall}$ are reduced when this correction strategy is applied (table 5). $\Sigma_{set\text{-}up}$ is reduced to comparable magnitude for the two treatment techniques. For respiratory gating there still is a systematic deviation in the vertical and longitudinal directions after this correction strategy has been applied. The random set-up error, $\sigma_{set\text{-}up}$, is not affected by the correction strategy and is not shown for the corrected results.

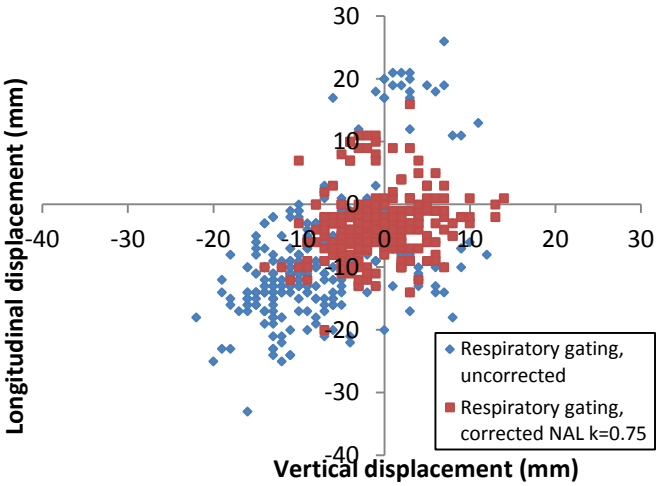


Figure 19 The displacements for each patient and each fraction in the vertical and longitudinal directions for the patients treated with respiratory gating, both uncorrected and corrected with NAL k = 0.75

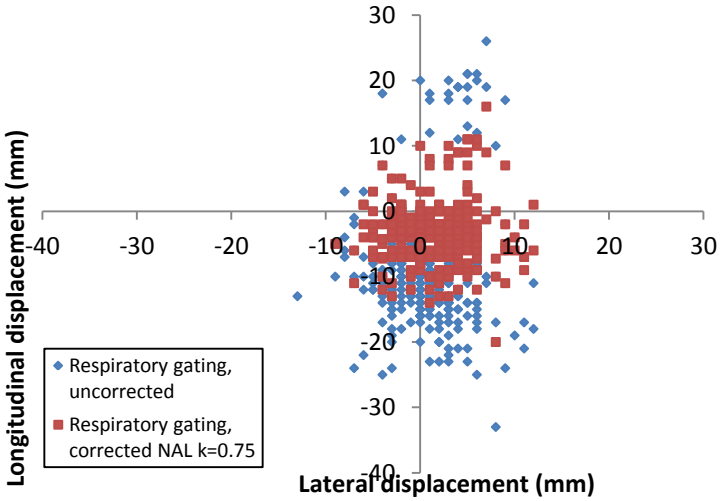


Figure 20 The displacements for each patient and each fraction in the lateral and longitudinal directions for the patients treated with respiratory gating, both uncorrected and corrected with NAL k = 0.75

Looking at the individual patients treated with respiratory gating, the individual systematic deviations, m_p, can be seen in figure 22-24. There is an undercorrection present for all patients in the

longitudinal direction with this correction strategy (figure 23). In the vertical direction there is an undercorrection present for the majority of the patients (figure 22). This is what gives rise to the negative values of $m_{overall}$ that can be seen in table 5. Due to the undercorrection seen for the majority of the patients, the currently used correction strategy is not the optimal one.

The larger systematic deviation for respiratory gating also shows in the number of corrections made after three treatment fractions (table 7). Due to the fact that corrections are made in 78 and 72 % in the vertical and longitudinal directions respectively, it is very important that the correction strategy is the optimal one. This also implies a higher workload for the patients treated with respiratory gating.

Table 7 Fraction of patients where a permanent correction were made after three treatment fractions

Direction	Respiratory gating (%)	Conventional treatment (%)
Vert	78	53
Long	72	24
Lat	11	35

Set-up images are acquired also later in the treatment, according to section 2.2.3. If systematic deviations larger than a certain action level are seen, permanent corrections are made. This means that deviations not captured during the first three treatment fractions or induced later in the treatment can be corrected for. This is not taken into account in this study. There are strong reasons, however, to improve the correction strategy used for the first three treatment fractions instead:

- Optimal correction earlier in the treatment.
- Less workload for the staff.
- A small systematic set-up deviation may not be captured later in the treatment if it is lower than the action level (table 2).

It can be seen for some patients that deviations are present also after permanent correction, see for example patient 9 in the vertical direction (figure 22). Possible reasons for this deviation can be a different set-up when new lines are drawn compared to when the set-up images were acquired or that three treatment fractions were not enough to estimate the systematic part of the set-up deviation. To be able to detect and correct for this is another good reason to acquire set-up images later in the treatment.

Due to the undercorrection seen with the currently used correction strategy for the patients treated with respiratory gating, it is of interest to find a better correction strategy for this group of patients.

4.2.3 The optimal correction strategy

Two possible correction strategies were suggested, to correct by the motion extent induced by respiratory gating before the first fraction and to change the value of the AML factor in the NAL correction strategy.

Correction with the motion extent

The motion extent induced by respiratory gating was measured (see section 3.2.5) and plotted against m_p (figure 21). The solid line shows where the motion extent and m_p are equal. The dashed lines show an interval of ±3 mm, the action level for permanent correction. The values of the motion

extent were used to correct all deviations and then the individual mean deviation was recalculated. This correction strategy gives inconsistent results, however (figure 22-23). For some patients it was a good approach, but for others it resulted in large deviations. Due to the inconsistency it was concluded that the approach using the measured breathing motion extent to correct the patient set-up before the first treatment is not an optimal correction strategy.

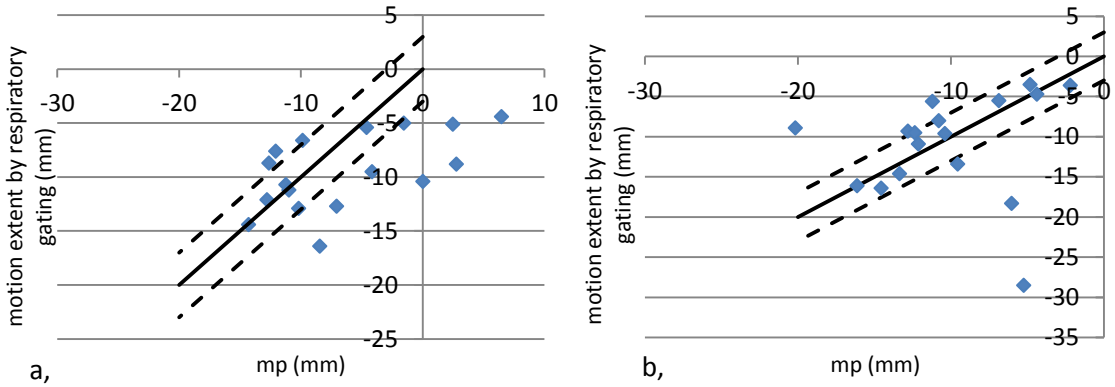


Figure 21 The motion extent induced by respiratory gating plotted against the individual systematic set-up deviation, m_p, in the vertical direction (a) and the longitudinal direction (b).

Calculation of optimal AML factor

In figure 22-23 it is shown that the current correction strategy leads to an undercorrection in both vertical and longitudinal directions. For respiratory gating $\Sigma_{set\text{-}up}=1.75\sigma_{set\text{-}up}$ in the vertical direction and $\Sigma_{set\text{-}up}=2.46\sigma_{set\text{-}up}$ in the longitudinal direction, compared to conventional treatment were $\Sigma_{set\text{-}up}=1.51\sigma_{set\text{-}up}$ in the vertical direction and $\Sigma_{set\text{-}up}=1.12\sigma_{set\text{-}up}$ in the longitudinal direction. Thus basing the value of k on Eq. 7 assuming that $\Sigma_{set\text{-}up}= \sigma_{set\text{-}up}$ is not correct for respiratory gating, where the systematic and random errors are far from equal. Calculating the AML factor using Eq. 6 gives values of k=0.90 in the vertical direction and k=0.95 in the longitudinal direction for respiratory gating. In figure 22-23 the individual mean systematic deviations corrected with these values of the AML factor is presented. The $m_{overall}$ is -0.1 mm in the vertical direction and -1.8 mm in the longitudinal direction. Thus, it is still not an optimal value of k in the longitudinal direction. This is due to the statistically significant $m_{overall}$ present for this group of patient, making the systematic part of the set-up deviation much larger than the random part.

Excluding the AML factor

To further optimize in the longitudinal direction and to get an uncomplicated correction strategy usable in the clinic, the AML factor was excluded, i.e. k=1, was evaluated (figure 22-23). Using k=1, $m_{overall}$ is 0.5 mm in the vertical direction and -1.0 mm in the longitudinal direction (table 5), compared to $m_{overall}$ equal to -1.1 and -3.3 mm respectively for k=0.75. As a compromise for both the vertical and longitudinal directions, and to get a correction strategy that is easy to implement in the clinic, the best correction strategy for the patients treated with respiratory gating is to exclude the AML factor.

The systematic set-up error, $\Sigma_{set\text{-}up}$, is 3.0 and 2.5 mm respectively for k=1 compared to 2.8 and 3.7 mm for k=0.75 in the vertical and longitudinal directions. It can also be seen that the $m_{overall}$ and $\Sigma_{set\text{-}up}$ are decreased also in the lateral direction when excluding the AML factor (table 5).

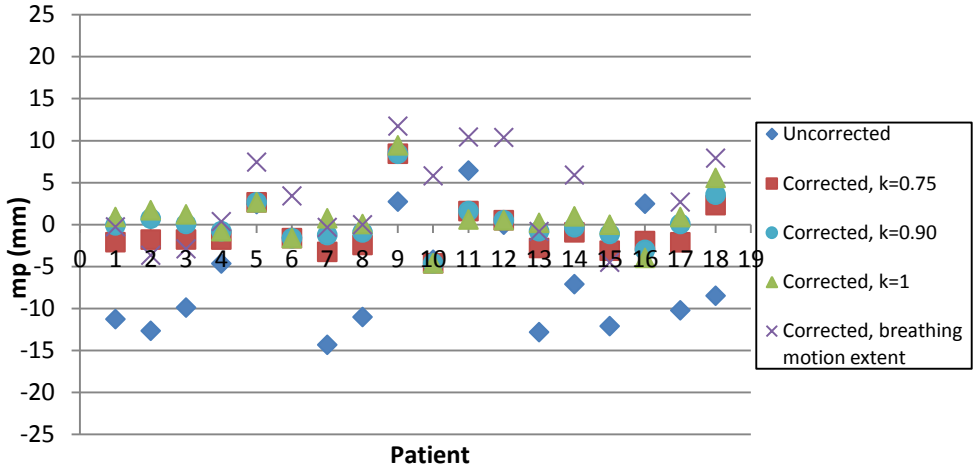


Figure 22 The individual systematic set-up deviation in the vertical direction for all 18 patients treated with respiratory gating. Both the uncorrected values and corrected with different correction strategies.

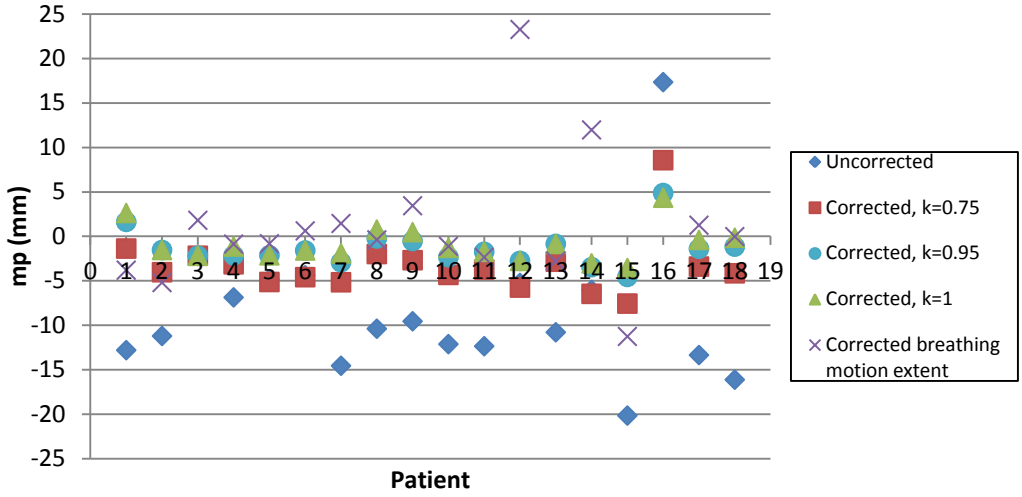


Figure 23 The individual systematic set-up deviation in the longitudinal direction for all 18 patients treated with respiratory gating. Both the uncorrected values and corrected with different correction strategies.

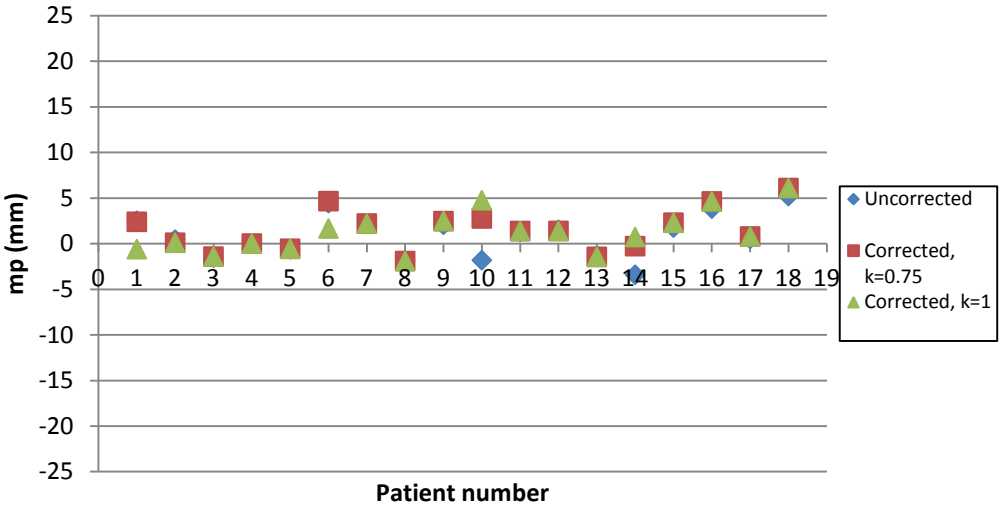


Figure 24 The individual systematic set-up deviation in the lateral direction for all 18 patients treated with respiratory gating. Both the uncorrected values and corrected with different correction strategies.

In figure 25 cumulative histograms for no correction strategy applied, the currently used correction strategy and the proposed new correction strategy are presented. The cumulative histograms show the fraction of the patients having more or equal to a certain absolute value of the individual systematic set-up deviation. The narrower the distribution is, the more effective the correction strategy is. The narrowest distributions are seen for the NAL correction strategy with k = 1. So this correction strategy is more effective than the currently used one and is therefore proposed as a new correction strategy for the patients treated with respiratory gating, in all three directions.

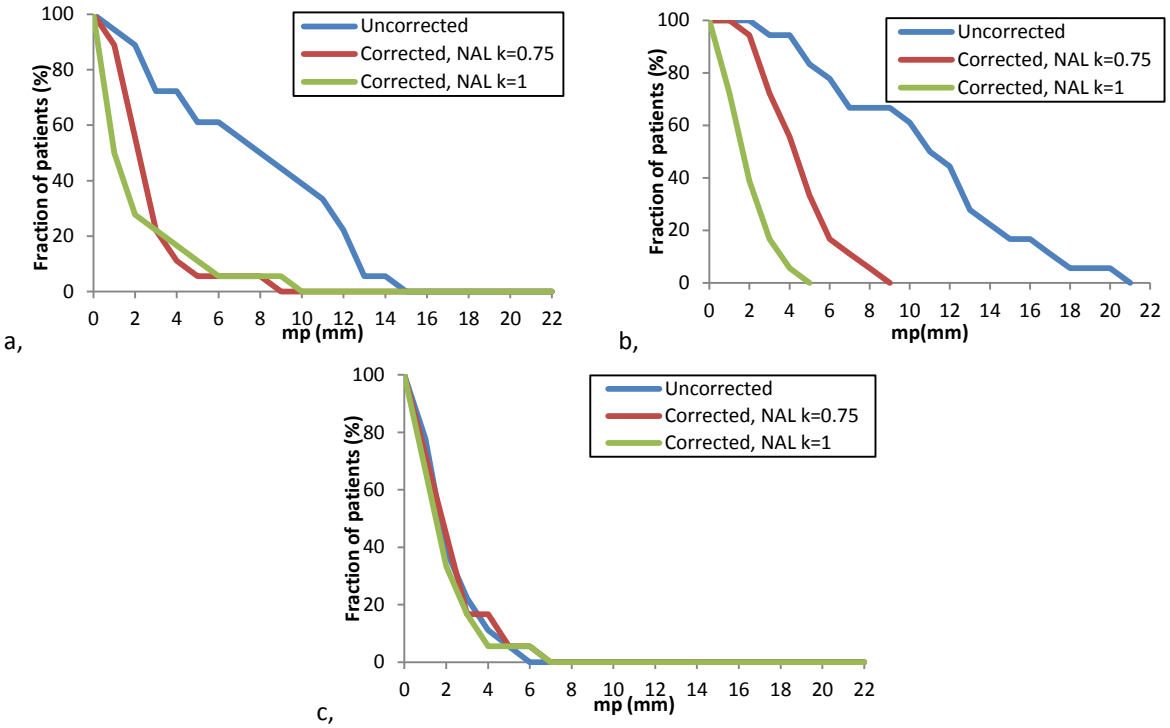
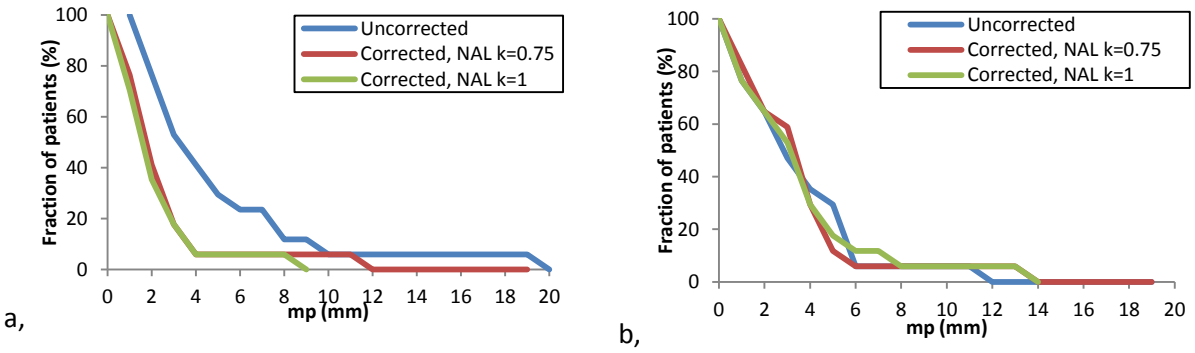
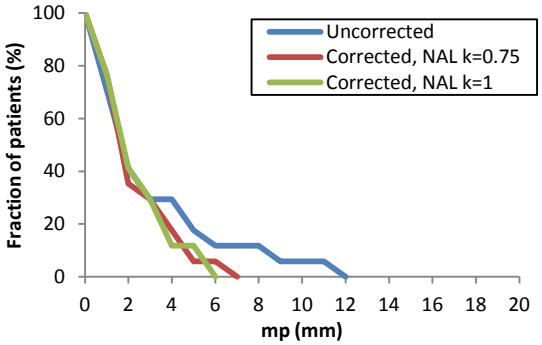


Figure 25 Cumulative histograms of the individual systematic set-up deviation for different correction strategies for the patients treated with respiratory gating in the vertical (a) longitudinal (b) and lateral (c) directions.

Cumulative histograms for the patients treated with conventional treatment are shown in figure 26. No difference in the set-up is seen between k = 0.75 and k = 1 for this patient group. A narrowing of the distribution can be seen using a correction strategy compared to the uncorrected result, especially in the vertical and lateral directions. Therefore no change of the correction strategy is proposed for the patients treated conventionally.





c,

Figure 26 Cumulative histograms of the individual systematic set-up deviation for different correction strategies for the patients treated with conventional treatment. In the vertical (a) longitudinal (b) and lateral (c) directions.

4.3 The effect of the systematic set-up deviation on the absorbed dose distribution

4.3.1 Simulations in the TPS

The systematic component of the set-up deviation was simulated in the TPS for the 19 patients in the treatment planning study (section 3.1). The average mean absorbed dose was increased from 1.38 to 2.21 Gy for the heart, from 4.17 to 8.86 Gy for LAD and from 5.80 to 7.64 for the left lung when the uncorrected set-up deviations were simulated (table 8). When the two correction strategies were simulated the differences in the mean absorbed dose were much smaller.

Table 8 Average mean absorbed dose to the OARs. The difference in percent compared to no set-up deviation simulated in parentheses.

	Heart (Gy)	LAD (Gy)	Left lung (Gy)
No set-up deviations simulated	1.38	4.17	5.80
No correction strategy	2.21 (60.2)	8.86 (112.7)	7.64 (31.7)
NAL k = 0.75	1.48 (6.9)	4.53 (8.8)	6.00 (3.4)
NAL k=1	1.31 (-5.3)	3.86 (-7.5)	5.51 (-5.1)

Cumulative histograms of the mean absorbed dose are shown in figure 27. An increased absorbed dose to the OARs is shown if no correction strategy is applied to correct for the systematic set-up deviation. In figure 28 it is shown that this increase in mean absorbed dose to the OARs is a result of both the anterior and cranial set-up deviations and that the effect on the absorbed dose to the PTV is mainly caused by the set-up deviation in the cranial direction.

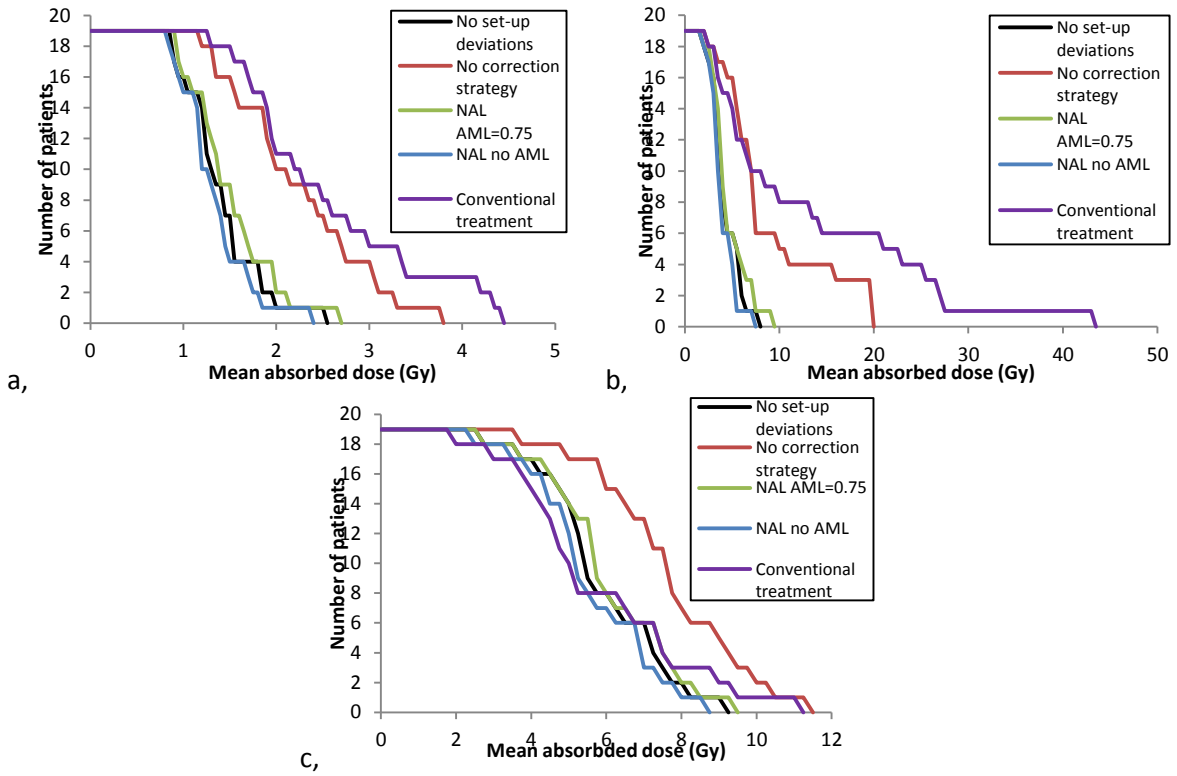


Figure 27 Cumulative histograms for the mean absorbed dose for the heart (a), LAD (b) and left lung (c)

To avoid the impact of superficial low absorbed doses the $D_{99\%}$ and $D_{1\%}$ were used as metrics of the minimal and maximal absorbed doses to the PTV. The average value of the $D_{99\%}$ is decreased and $D_{1\%}$ increased if the uncorrected set-up deviations are simulated and unchanged if the correction strategies are applied (table 9). The quite small impact of the set-up deviations on the absorbed dose distribution to the PTV is due to the large field edge margin in the anterior direction (figure 28).

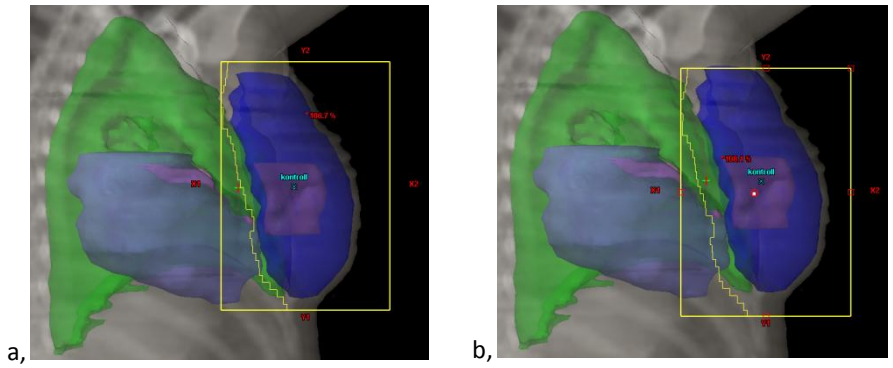


Figure 28 Beam´s eyes views for one patient in the study for no simulated set-up deviations (a) and with the uncorrected set-up deviations applied (b).

The systematic set-up deviation will lead to an increased absorbed dose to the OARs and affect the absorbed dose distribution to the PTV if not corrected for. So implementing respiratory gating in the clinic without a set-up correction strategy, might cancel out some of the dose sparing seen in section 4.1.1 using respiratory gating.

Table 9 The average value of the dose received by 99 % and 1% of the PTV ($D_{99\%}$ and $D_{1\%}$) for all patients in this study

	$D_{99\%}$ (Gy)	$D_{1\%}$ (Gy)
No set-up deviations simulated	45.9	52,6
No correction strategy	44.5	53.4
NAL AML = 0.75	45.9	52.7
NAL no AML	45.9	52.7

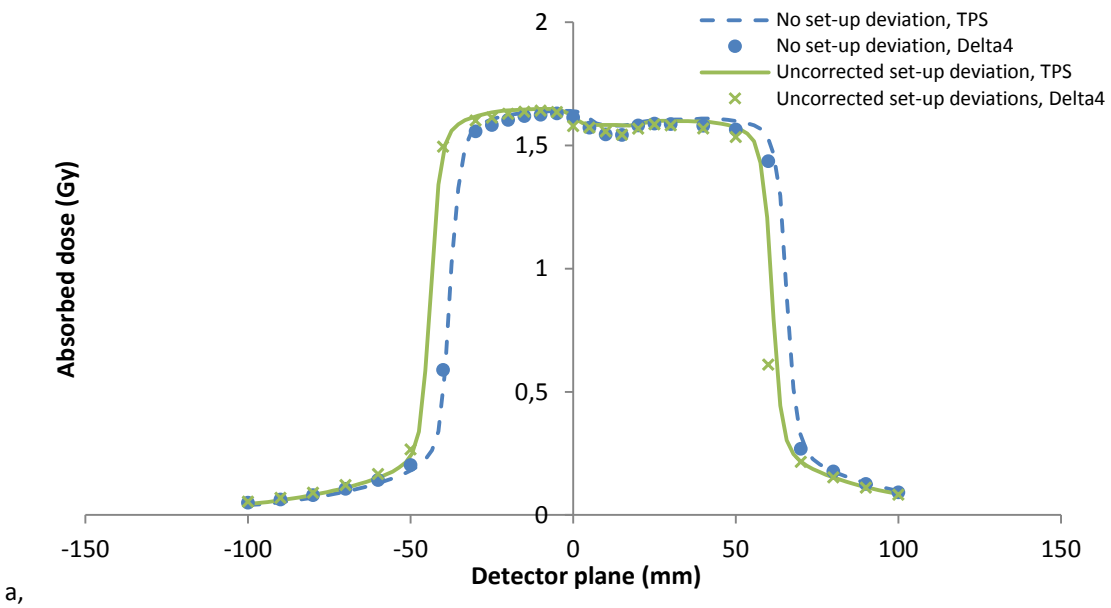
4.3.2 Measurements with Delta[4]

For the measurement with Delta[4], a dose deviation and DTA criteria of 3 %/2 mm were used in the gamma evaluation. The average GAI were 64.2 % when the uncorrected set-up deviations were induced compared to 97.3 % in the original treatment plan (table 10).

Table 10 The γ-agreement index (GAI) for the measurement with delta[4] using the criteria 3 %/2 mm

Patient number	GAI	
	Uncorrected set-up deviation	No set-up deviation
1	60.9	99.7
2	68.2	96.9
3	53.6	96.6
4	66.3	95.0
5	66.5	99.2
6	69.5	96.6
Average	**64.2**	**97.3**

This difference in GAI implies that the systematic set-up deviations result in a large difference between the two dose distributions. The measuring points using the Delta[4] were compared to dose profiles acquired from the TPS, both with and without the uncorrected set-up deviations induced (figure 29)**.** A shift in the dose profile is introduced with the set-up deviation. Good agreement between the measurement and the simulation in the TPS were observed.



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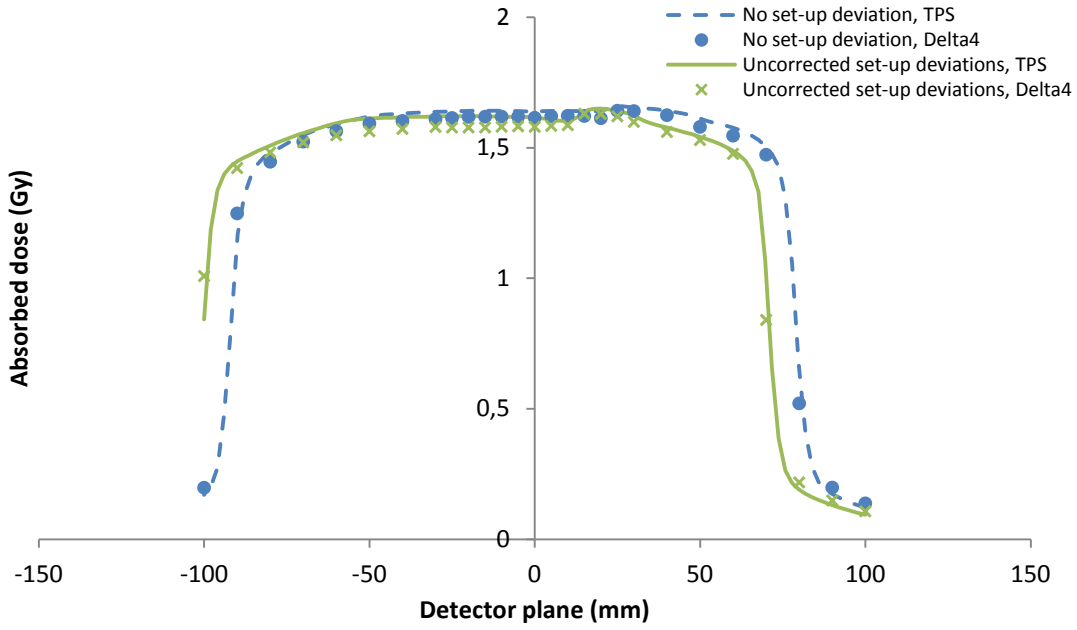

b,

Figure 29 Absorbed dose profile for the detector boards showing the shift in the absorbed dose distribution induced by the systematic set-up deviation in the vertical direction (a) and the longitudinal direction (b) for one patient in this study.

5. Conclusions

There is a significant dose sparing for the heart and LAD using respiratory gating compared to conventional treatment due to increased spatial distance between the breast and heart, while there is no difference for the left lung. The average mean absorbed dose is reduced by 46 % for the heart and 70 % for LAD using respiratory gating, without compromising the coverage of the target. The dose sparing to the heart results in reduced cardiac mortality probability.

A systematic set-up deviation is induced using the set-up procedure used at our clinic for patients treated with respiratory gating. The dosimetric consequences if this is not corrected for would be an increased absorbed dose to the OARs and the absorbed dose distribution to the PTV would be affected. Therefore it is important with a solid correction strategy using respiratory gating.

The currently used and generally accepted NAL correction strategy with an AML factor of 0.75 leads to an undercorrection for most of the patients treated with respiratory gating, and is thus not the optimal correction strategy for this patient group. The reason for this is the systematic part of the set-up deviation is much larger than the random part. To exclude the AML factor, i.e. to use k = 1, result in an improved set-up for the patients treated with respiratory gating.

6. Acknowledgments

There are many people that have helped me with this master thesis, and I would like to thank them all. Special thanks to:

- My supervisor Sofie Ceberg, for all her help and support and for her enthusiasm and engagement in this thesis.
- The staff at the linear accelerators L1 and L22 at the radiotherapy clinic at SUS Malmö for acquiring all the set-up images, although it increased their workload.
- The physicians Lars Ekberg and Sousana Amptoulach for reviewing the delineations.
- Marie Tärnhuvud for helping me with the treatment planning.
- Fredrik Nordström for his help and valuable comments on this thesis.

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