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Original Research Article

Retrospective methods to estimate radiation dose at the site of breast cancer development after Hodgkin lymphoma radiotherapy

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ABSTRACT

Background: An increased risk of breast cancer following radiotherapy for Hodgkin lymphoma (HL) has now been robustly established. In order to estimate the dose–response relationship more accurately, and to aid clinical decision making, a retrospective estimation of the radiation dose delivered to the site of the subsequent breast cancer is required.
Methods: For 174 Dutch and 170 UK female patients with breast cancer following HL treatment, the 3-dimensional position of the breast cancer in the affected breast was determined and transferred onto a CT-based anthropomorphic phantom. Using a radiotherapy treatment planning system the dose distribution on the CT-based phantom was calculated for the 46 different radiation treatment field set-ups used in the study population. The estimated dose at the centre of the breast cancer, and a margin to reflect dose uncertainty were determined on the basis of the location of the tumour and the isodose lines from the treatment planning. We assessed inter-observer variation and for 47 patients we compared the results with a previously applied dosimetry method.
Results: The estimated median point dose at the centre of the breast cancer location was 29.75 Gy (IQR 5.8–37.2), or about 75% of the prescribed radiotherapy dose. The median dose uncertainty range was 5.97 Gy. We observed an excellent inter-observer variation (ICC 0.89 (95% CI: 0.74–0.95)). The absolute agreement intra-class correlation coefficient (ICC) for inter-method variation was 0.59 (95% CI: 0.37–0.75), indicating (nearly) good agreement. There were no systematic differences in the dose estimates between observers or methods.
Conclusion: Estimates of the dose at the point of a subsequent breast cancer show good correlation between methods, but the retrospective nature of the estimates means that there is always some uncertainty to be accounted for.
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Introduction

Several publications have demonstrated a dose-dependent increased risk of breast and other cancers following chest radiation exposure in women, including therapeutic radiation for a first

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primary malignancy [1–10]. In order to obtain accurate estimates of the shape of the dose–response for the risk of radiation-induced primary breast cancer following radiotherapy for Hodgkin Lymphoma (HL), a reliable estimate of the received dose to the site of the breast tumour is required [11]. Although patients currently treated for HL with radiotherapy have computer tomography (CT) planning scans and individual 3-dimensional dosimetry, this is not the case for patients with breast cancer who were treated for HL before 2004. Radiation dose effects can be estimated using nominal data (radiation yes/no), and information on the prescribed dose to the target volume. In our previous study evaluating the dose response effect, we applied a technique to estimate retrospectively the dose at the point of the subsequent breast cancer more specifically [10]. For this method, described in detail by Stovall et al. [12] simulation of the prescribed radiotherapy was performed. Using the original simulation radiographs and the records from the radiation treatment charts, the absorbed dose at the site of the breast cancer was determined using a combination of three techniques: (1) calculation using a three dimensional (3D) mathematical computer model based on measurements made in a water or polystyrene phantom for different beam energies and treatment machines-used for breast tumour sites out of field; (2) direct measurements in an anthropomorphic phantom constructed of tissue equivalent material, and (3) calculation of dose using a treatment planning system (ADAC Pinnacle System, Philips Radiation Oncology Systems, Milpitas, CA). For brevity, in the rest of this report, we will refer to this method as the "radiograph-based" method. However, a limitation of this technique is that the original simulation radiographs are required, and for the majority of patients treated one or more decades ago, these are now no longer available. An alternative method utilizes anthropomorphic phantoms from radiotherapy planning CT scans for retrospective reconstruction of the dose to voxels inside and outside the treated volume, which takes into account leakage and scattered radiation from the machine head and within the patient [13,14]. Here we describe the further development of this method specifically for estimation of the dose at the site of breast cancer development following HL radiotherapy utilizing individual patient and treatment data in three dimensions. In the rest of the manuscript we will refer to this as the "CT phantom-based" method.

The dosimetry described in this paper was performed as part of a study to estimate the radiation dose–response for breast cancer induction following treatment for HL using *the case-control-matched-location* method, as described by Langholz et al. [15], for case-control studies nested in cohorts of 5-year HL survivors from the Netherlands (updated from [5,10]) and the UK [16]. This method entails determining the location of the breast cancer in the affected breast among cases, and estimating the dose to this point from the radiation treatment given previously for HL. The dose to the same location in the breast is also estimated from the radiotherapy treatment of control patients, who are HL survivors matched for several criteria (age at HL, HL treatment year, treatment centre) but without breast cancer after the same follow-up as the corresponding case with breast cancer. For the radiograph-based method, it is necessary to retrieve the patients' original simulation radiographs. As these are no longer available for all the patients included in the study, we developed a dosimetry method based on a library of generic radiation field types and set-ups. The dose–effect relationship derived from the data described in this report (including the influence of chemotherapy and ovarian hormone exposure), will be reported separately. Here we describe in detail the method developed for the radiation dosimetry.

Methods

The radiation dosimetry was based on a voxel-based anthropomorphic phantom from a radiotherapy planning CT scan obtained from a typical 21 year-old female HL patient, with height 1.70 m and weight 67 kg. (Fig. 1). The scan was acquired in supine position on a flat couch top with the arms abducted alongside the head. We first established a library of the different shapes and combinations of radiation field set-ups based on the treatment charts of patients who had developed breast cancer following HL treatment and also their controls without breast cancer. We drew the individual field types onto a digitally reconstructed radiograph obtained from the CT scan, simulating the original simulation radiographs at the time of the HL treatment. There were variations in the shape and extent of the fields depending on the techniques for individual shielding, year of treatment, and also between radiotherapy centres. In total 46 radiation field types and combinations were used for dosimetry with the planning system. Details of all field types are given in Supplementary material. The three-dimensional (3-D) dose distributions were then simulated for each field set-up on the anthropomorphic CT phantom, using Isogray treatment planning system (TPS) (Dosisoft, Cachan, France). The 3-D dose distributions were computed using the double decomposition Clarkson algorithm with density heterogeneity correction with a voxel size of 5 mm. A radiation energy of 6 MV was assumed for all treatments. The block transmission factor used was 0.04. As the prescribed dose for the same field type varied per patient, the dose scale was set as a percentage of the prescribed dose to the target volume. The dose distribution was reported in 12 transversal planes at 1.5 cm intervals, from the second to the 10th thoracic vertebrae, covering the whole breast tissue in the phantom (Fig. 1). Finally, a pdf file with hyperlinks was produced for each typical field allowing access to the dose distribution on a transversal CT slice by a mouse click and thus provide an interactive and user friendly dosimetry tool.

We first reviewed the HL medical and radiotherapy treatment charts and simulation radiographs or other information to determine which field type was appropriate for each patient. There were 174 Dutch patients assessed among whom one case had breast cancer but no previous radiotherapy. We then determined the breast cancer location for all breast cancer cases. We used all the medical and imaging information available from the medical chart at the time of the diagnosis and treatment of the breast cancer. For each breast cancer, we estimated the position of the centre of the tumour in the breast, usually in relation to the nipple. We then determined which slice level(s) on the anthropomorphic CT phantom corresponded to the cancer location. On the appropriate slice (s), the size and laterality of the cancer was then traced onto a power-point image, scaled to the size of the actual patient, based on the field separation mid-mediastinum (usually 16–18 cm) reported on the chart. Where there seemed to be some discordance, as with a very lateral tumour in a large breast, we adjusted the position so that the tumour was always in the breast issue of the phantom, rather than for example muscle or skin. Polaroid photographs of the treatments set-up helped determine the relative position of the shielding blocks to the nipple, if available (examples in Supplementary material). A second concomitant breast cancer was present in 15 cases, 1 ipsi-lateral in a different quadrant, and 14 contra-lateral. The position and size of these tumours was also established. These data were included in the analysis of the distribution of the cancer locations in the breast, but for the dose–response analyses, only the dose estimation of the largest invasive cancer was included. For the 170 cases from the UK, we had less information on the radiation treatments deliv-

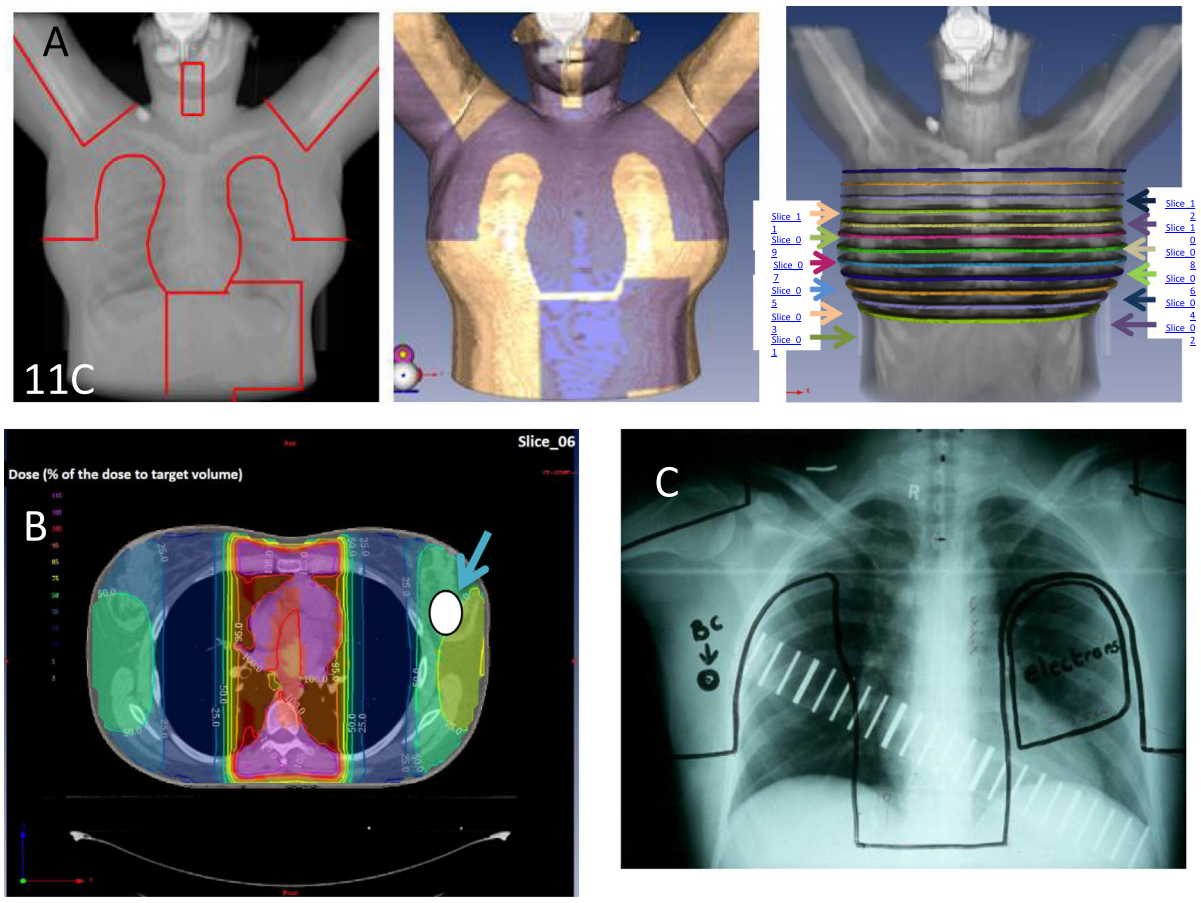

Fig. 1. Voxel-based anthropomorphic phantom from a radiotherapy planning CT scan obtained from a 21 year-old female adult. A: Example of field set-up type 11C, B: location and size of the breast cancer in the left breast drawn on the appropriate position in the CT-based phantom with colour-wash of dose distribution. C: determination of the position of subsequent breast cancer (BC) drawn onto the simulation radiograph of the individual patient (for use with the radiograph-based method).

ered for HL, only a general description of the type of field or target areas, the dose and the year of treatment, and no simulation radiographs. One of the field types allocated to the Dutch patients was then chosen based on the information available and the clinical experience of NR who has clinical experience of treating HL patients both in the UK and the Netherlands from the 1980's, and who also discussed earlier treatment fields with older colleagues. The UK cohort provided for all breast cancer cases detailed information derived from the mammograms [16] with coordination points for quadrant, distance of the cancer from the nipple and breast edge in Medial-Lateral-Oblique (MLO) and cranio-caudal (CC) views, size of the breast and size of the cancer. For the UK patients we had no other clinical sources of information such as surgical or pathology reports, which we did have available for the Dutch patients. All patient data was coded, removing individual identification.

To take into account uncertainties in the estimate of the breast cancer position we then added an uncertainty margin around the tumour delineation. In some cases where we had full clinical, pathological and imaging information, this margin was 0 cm. In other cases where we only had information such as "lateral upper quadrant", we added up to 2 cm in three dimensions.

We registered the estimated dose at the centre of the cancer from the isodose curves in the central slice covered by the cancer position, and documented this as the point dose. We also registered the range of dose between the maximum and minimum possible dose at the breast cancer site taking into account the cancer size, location and an uncertainty margin in 3 dimensions and called this the dose uncertainty range. As a measure of inter-observer variation, a random sub-set of 22 cases were assessed again independently by a second radiation oncologist (BA).

The breast cancer location according to ICD-10 definition [17] was recorded for the UK and Dutch patients groups and according to laterality.

For 47 cases included in an earlier study we had data available to compare the inter-method variation in dose estimation with the CT phantom-based method to that obtained with the radiograph-based method [10].

Statistical methods

Descriptive statistics were used to define the data from the two cohorts. For comparison of the dose estimates a Mann-Whitney test was applied. We evaluated variation between methods and observers by estimating absolute-agreement Intra-class Correlation Coefficients (ICC) using two-way random-effects models and Bland–Altman [18,19] plots. We considered an ICC of >0.60 as good, and >0.75 as excellent according to standard criteria [20]. The Chi-square statistic was applied to the decile data of the dose uncertainty range.

Results

The breast cancer position and dosimetry for 344 patients (174 Dutch and 170 UK patients) and a total of 359 individual cancers was determined, showing that this approach was feasible, albeit

time consuming. Per patient an average of 20 min was spent on determining the field type and breast cancer location.

Dosimetry

Table 1 and Supplementary Table 3 give the descriptive statistics of the dose estimates at the central point of the breast cancer (the point dose) for Dutch and UK patients, both combined and separately. On average, the point dose was about 75% of the prescribed dose. The distribution of point doses for the two groups is illustrated in histograms in Fig. 2A and B. We observed a biphasic distribution with a peak at the lower dose end and one at the higher dose end, reflecting the fact that breast tissue was partially under the shielding and partially in the full beams. There was a higher median point dose estimate in the Dutch patients (31.7 Gy) compared to the UK patients (28.5 Gy), $p = 0.016$, reflecting a slightly higher average prescribed dose in the Dutch patients.

Inter-method variation

The ICC for inter-method variation was 0.59 (95% CI: 0.37–0.75), indicating a (nearly) good agreement (scatter plot in Fig. 2C). The Bland–Altman Plot (Fig. 2D), showed no systematic differences in dose estimates. The mean difference in dose estimate was −3.7 Gy, standard deviation 14.7 Gy, levels of agreement −33.1 to 25.7 Gy. We examined in detail the "outlier" cases from the scatter plots. The reason for the apparent discrepancy in most cases was the estimation of the tumour position relative to a shielding block edge. This could be due to assessment of the position of the tumour in the breast, or the position of the block relative to the breast tissue. As the same researcher (NR) determined the tumour position for both methods, this also reflects some intra-observer variation.

Inter-observer variation

We observed an excellent agreement between observers regarding estimated radiation dose (ICC 0.89 (95% CI: 0.74–0.95)) as illustrated in Fig. 2E. Bland–Altman plots (Fig. 2F) showed that there was no systematically higher or lower dose estimation between observers. The mean difference in dose estimate was 0.9 Gy, standard deviation = 7.5 Gy, levels of agreement −6.6 to 8.4 Gy. The estimated position of the breast cancer could vary between the observers by up to 2 cm and this could lead to variation in point dose estimate, especially if the position was near the edge of shielding blocks. However, with one exception (case with a multi-centric tumour) the cancer locations were all within the uncertainty margin. There was a non-significant difference between the two observers if this outlier was excluded from the analysis.

We also quantified uncertainties in the dose estimates. The UK patients had a significantly smaller dose uncertainty range, with a median of 5.2 Gy (SD = 8.5 Gy) compared to 9.8 Gy (SD = 12.3 Gy) for the Dutch patients, $p < 0.001$ (Fig. 2G and H), which we attribute to the availability of solely mammographic information in the UK patients, but more extensive and varied clinical sources of information for the Dutch patients.

Tumour location

A schematic diagram representation of all 359 breast cancers from both countries is given in Fig. 3 and the Supplementary material. The majority of tumours were located in the upper and outer quadrants.

Table 1
Radiation dose prescription and dose estimates for the breast tumour for the Dutch and UK patients combined and separately.

	All patients		UK patients				Dutch patients			
	Prescribed dose	Point dose estimate	Prescribed dose	Point dose estimate	Minimum dose estimate	Maximum dose estimate	Prescribed dose	Point dose estimate	Minimum dose estimate	Maximum dose estimate
N	344	344	170	170	170	170	174	174	174	174
mean	37.10	23.02	36.19	21.67	17.40	25.02	38.01	24.34	16.21	30.42
Std Deviation	5.61	15.19	6.29	15.03	13.74	15.46	4.70	15.28	13.66	14.56
Minimum	0.00	0.00	6.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Maximum	56.80	53.96	56.80	53.96	48.28	56.80	50.29	49.01	44.35	51.53
Percentiles 25	35.00	5.80	35.00	5.25	5.06	6.00	36.00	7.77	5.25	23.64
(median) 50	39.33	29.75	36.00	28.50	14.00	33.25	39.60	31.68	10.00	37.55
75	40	37.19	40.00	34.30	30.00	38.00	40.13	38.20	30.55	41.07

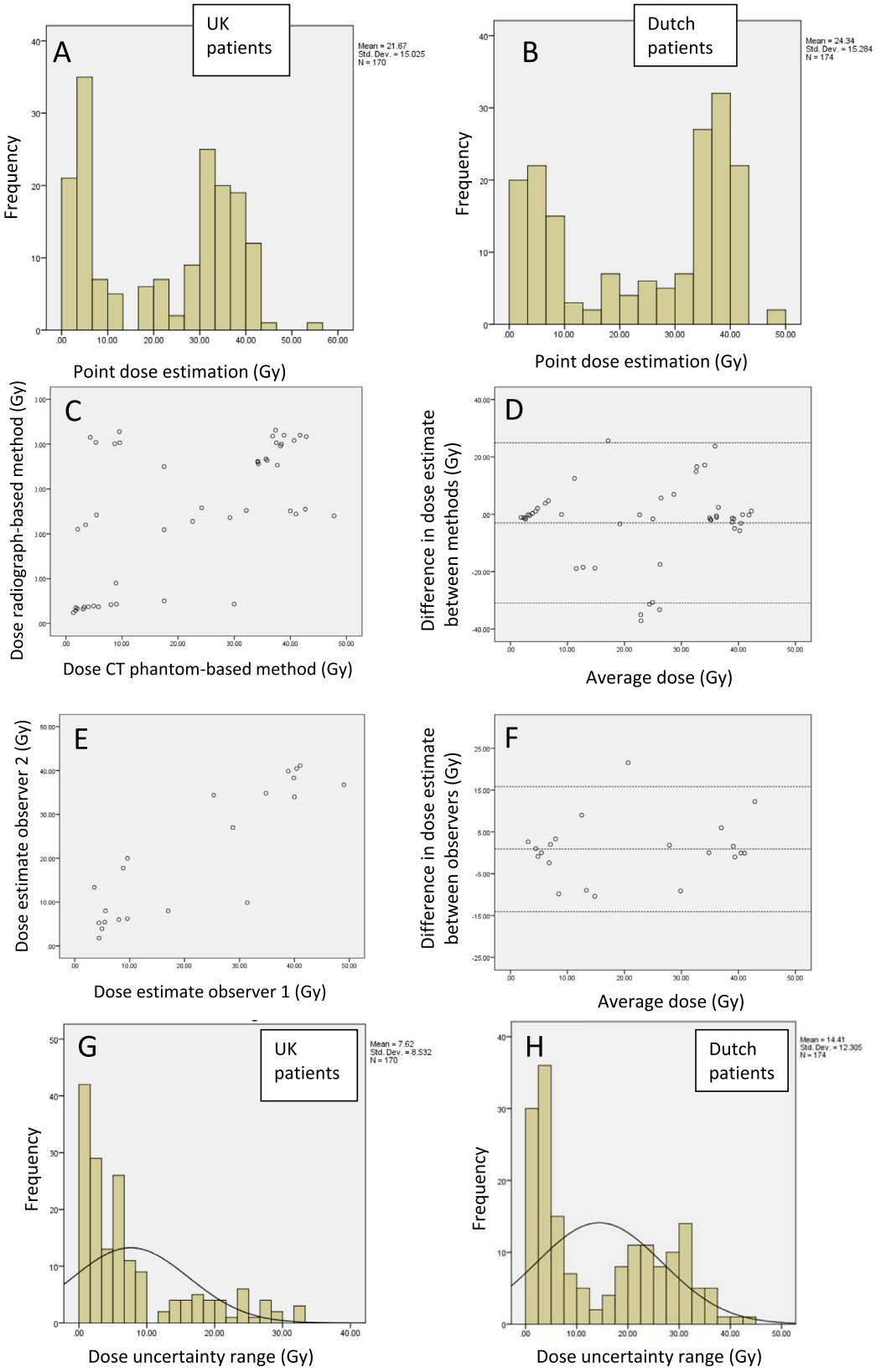

Fig. 2. A: histogram of the distribution of the estimated point dose for UK patients. B: histogram of distribution of the estimated point dose for Dutch patients. C: Scatter plot of inter-method variation between the radiograph-based versus the CT phantom-based method. D: Bland–Altman plot of inter-method variation. E: scatter plot of inter-observer variation in dose estimate. F: Bland–Altman plot of variation between observers. G: histogram of dose uncertainty range for UK patients. H: histogram of dose uncertainty range for Dutch patients.

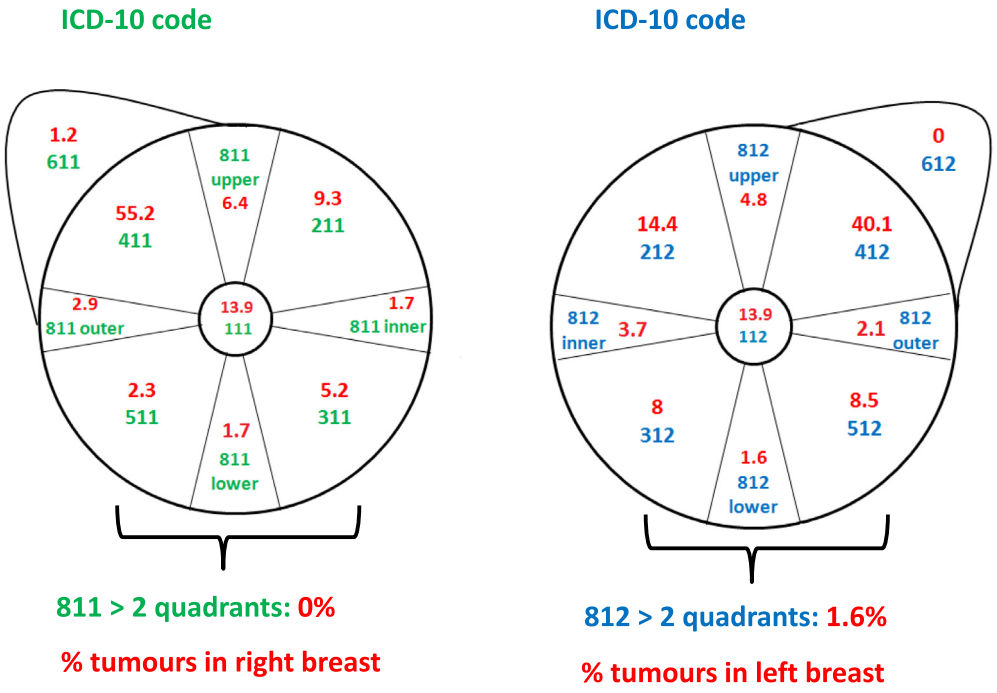

Fig. 3. Distribution of breast cancer locations in the breast according to ICD-10 codes, right and left breast separately, for UK and Dutch patients combined. Green: ICD-10 code for tumour locations in the right breast; blue: ICD-10 code for tumour locations in the left breast; red: percentage of tumours in specified location. Details of the ICD-10 coding system is given in supplementary material. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Discussion

This study provides important information on the reliability and validity of the methods applied, showing good–excellent agreement between methods and observers. One of the strengths of our study is that we compared the dose estimates obtained with the CT phantom-based method with a previously applied method based on simulation radiographs (one frequently applied previously by our group and others to determine the dose effect relationship) [7,10,21]. In addition, we estimated the inter-observer variation, which to our knowledge is unique to this study. However, both the radiograph- and the CT phantom-based methods have several limitations. Table 2 addresses the main issues and considerations related to uncertainty, and whether these factors generate a systematic effect on the dose estimate. In other words, do they cause consistent under-, or over-estimation of the dose at the site of the breast tumour? We concluded that generally this was not the case, except for the fact that the CT-phantom estimations were performed with a CT in deep inspiration breath hold (DIBH). Aznar et al. [22] have demonstrated a reduction in breast dose when using DIBH for involved nodal irradiation for HL compared to free breathing techniques.

The approach of applying various historical field types and set-ups for dosimetry based on a CT-phantom obtained from a patient of typical build was previously used by Taylor et al. [23,24] in determining the dose received by heart structures from breast cancer radiotherapy. These data were then utilized to determine a dose response relationship for ischemic heart disease by Darby et al. [25]. It can be argued that this is a valid approach to generate dosimetry data for establishing dose–response relationships, as errors in estimation are unlikely to be systematic (this manuscript). On the other hand, to estimate the individual risk of a secondary event more detailed individual dose parameters should be determined [26].

All methods used generate retrospective estimates, which means that certain assumptions must be made. Ng and colleagues have demonstrated a good correlation between dose estimates from 2-D treatment planning information and actual CT-based 3-D plans [27], suggesting that CT phantom-based method, which is a hybrid of the two techniques, is probably a reasonable approximation.

Uncertainty quantification

Applying an uncertainty range makes the data as complete as possible, but could affect the estimated dose–response relationship because of the large variations of dose across some volumes either due to large cancers or large uncertainty margins. We do not know whether the cancers originate at one point in the centre of mass, or indeed whether there is a *field cancerization* effect across a larger portion of the breast tissue in general [28], or mediation through bystander effects of breast stromal elements as suggested from experimental data of Barcellos-Hoff et al. [29]. If this were the case, then possibly a mean breast dose would be sufficient to estimate risk, in analogy to the mean heart dose used for analysis of radiation-induced cardiac disease [30]. Further, although some tumours were screen-detected and quite small (5 mm), others were large T3 tumours growing in almost the whole of the breast over multiple quadrants, resulting in a large dose-gradient across the tumour position from the HL radiotherapy. In the WECARE study of asynchronous contra-lateral breast cancer [15] most second breast cancers were detected early as the patients were under regular screening following their first breast cancer diagnosis. However, 99/708 were excluded from the analysis due to multiple tumours in different locations, or single tumours that spanned multiple locations, or lack of information on location. In our study we included these tumour types by choosing the first largest tumour as the index tumour, and utilizing clinical and pathology

Table 2
Comparison of uncertainties between CT-phantom and radiograph-based methods of retrospective dosimetry.

Uncertainty	Issue with CT phantom-based method?	Systematic effect on dose estimate? YES/NO	Issue with radiograph-based method?	Systematic effect on dose estimate? YES/NO	Details
Patient anatomy factors					
Patient/phantom matching: volume and shape of the breast	Yes	No	Yes	No	Maraldo et al. [26] have demonstrated a inter-patient variation with a standard deviation of around 13% of the prescribed dose for the dose to breast tissue from a simulated mantle field in 21 female patients. With the radiograph method as the size and shape of the breasts is often visible on the radiograph, anthropomorphic phantom can be modified for various breast sizes [12]
Size/shape of breast changes with aging	Yes	No	Yes	No	Cannot be evaluated
Daily set-up uncertainty	Yes	No	Yes	No	Daily set-up was on the basis of skin marks, portal films and off-line corrections. In earlier time periods loose shielding was positioned daily on Perspex blocks in the beam. Later custom-made shielding was used, but there still could be daily shifts in positioning
Position/shape of breast in prone position	Yes	No	Yes	No	Same as patient/phantom matching (shape of the breast), but with specific change in breast shape. For the radiograph method, the tumour position was drawn onto the AP radiograph in supine position, no correction was made for changes in the prone position
Size of patient					AP diameter of patient in cm taken from radiotherapy charts. Tumour size and position scaled to patient PA diameter with CT-based method. For radiograph method actual radiograph used and standard adult anthropomorphic phantom
Location, size, shape of tumour in the breast	Yes	No	Yes	No	All available clinical and radiological data used for both methods. Size given in histology report used, otherwise size on mammography or other imaging. Size of tumour scaled to patient diameter recorded on the RT chart. Radiograph-based method: only 2D information on position available for dosimetry. Dose uncertainty range takes into account uncertainty in size/position/shape/quality of data available for localization. Estimated centre of tumour used to determine point dose, but in large tumours this point may not be the point of origin of the tumour
Use of CT scan with arms next to head, actual treatments with conventional simulation and arms abducted 45–90°	Yes	No	No	No	Could influence estimate especially in locations in lateral quadrants. Not an issue with radiograph-based method. Actual quantification of this effect would require CT phantoms obtained from patients scanned with the arms abducted in an extra wide bore scanner
Use of CT phantom with deep inspiration Breath hold (DIBH)	Yes	Yes	No	No	Deep inspiration causes diaphragm to move caudally, so the cranial border of the splenic field is more caudal relative to the left breast, giving an underestimation of the dose to the lower quadrants. Aznar et al. [22] have demonstrated a reduction in mean breast dose using DIBH free breathing for involved node radiotherapy following chemotherapy. For the radiograph method, this factor not an issue, as the tumour position was drawn onto the simulator radiograph
Dose calculation factors					
In some patients dose defined for separate parts of the field e.g. mediastinum, axilla, neck	Yes, accounted for	No	No	No	For CT-based method, the dose reconstruction was based on one dose prescription for whole mantle field, on beam central axis. Assessment of the dose to the tumour according to the prescription used for the part of the field closest to the tumour (axillary, mediastinum, neck). Not an issue with the radiograph method, as the whole treatment was simulated
Treatments with Cobalt/6 MV/ 8 MV/10 MV photons. Model dose estimate with 6 MV for all patients	Yes	No	No	No	As tumour originates in breast tissue and not in skin, variations in build-up dose have little effect on dose estimation. In the radiograph-based method, the dose distribution data took into account the radiation quality and output from the therapy machine type that the patient was actually treated with.
Contribution of dose from boost field to points outside boost field	No, accounted for	No	No, accounted for	No	For the CT-based method, the contribution of dose from boost fields where no breast tissue was directly in the field was taken account of by performing out of field dose calculation [13,14]. For the radiograph-based method out of field measurements were performed [12]
Individual variation in head leakage and scatter from different machines	Yes	No	No, accounted for	No	CT-based method: Individual variation in head leakage and scatter from different machines could not be taken account of. It was considered that if the breast was relatively close to the field border (<30 cm), the in-patient scattering was predominant. In the radiograph-based method, the dose distribution data took into account the radiation quality and output from the therapy machine type that the patient was actually treated with
Observer variation					
Determining position of tumour in the breast relative to the field	Yes, quantified	No	Yes	No	CT-based method: Inter-observer variation assessed by tumour localization determined by 2nd observer in sample of patients was excellent. Observer 1 for the CT based method also determined the tumour positions for the radiograph-based method

reports if no mammography was available. This makes our dataset more complete as we did not exclude the larger tumours.

Implications and future research

As a general discussion point, for the purposes of defining the dose–response relationship, it is probably not very critical that an exact reproduction is obtained per individual treatment, as long as there is no systematic error. The dose–response estimate will however be attenuated by known or unknown uncertainty in the dose estimation. (Quantification of this attenuation has been reported by our group in Krul et al. [31]). The situation is of course different when one wants to estimate the breast cancer risk for an individual patient based on her previously given treatment. Therefore other methods will be more applicable. In ongoing research we are currently applying the *case-control-all-location* method [15] to this data-set. The comparison is between the cases' breast cancer dose and each of the cases' non-cancer locations and the doses at all the control subject locations. This method has the advantage that data is incorporated on dose throughout the breast volume. Also, the volume of the tumour in the breast can be incorporated into the analysis, thus avoiding the issue of whether the point dose at the centre of the tumour is the most relevant point in breast carcinogenesis, as discussed above. Also corrections factors for the uncertainty margin can be included. This research will aid clinical decision making regarding screening strategy and counselling for previously treated HL patients, and the treatment (modality) strategy for future patients.

Conflict of interest statement

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ctro.2017.09.004.

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