Published in final edited form as:

Med Phys. 2012 October ; 39(10): 5814–5824. doi:10.1118/1.4748332.

Second Cancer Incidence Risk Estimates using BEIR VII Models for Standard and Complex External Beam Radiotherapy for Early Breast Cancer

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Abstract

Purpose—To compare organ specific cancer incidence risks for standard and complex external beam radiotherapy including cone beam CT verification following breast conservation surgery for early breast cancer.

Method—Doses from breast radiotherapy and kilovoltage cone beam CT (CBCT) exposures were obtained from thermoluminescent dosimeter (TLD) measurements in an anthropomorphic phantom in which the positions of radiosensitive organs were delineated. Five treatment deliveries were investigated : (i) conventional tangential field whole breast radiotherapy (WBRT), (ii) non-coplanar conformal delivery applicable to accelerated partial breast irradiation (APBI), (iii) two-volume simultaneous integrated boost (SIB) treatment, (iv) forward planned three-volume SIB, (v) inverse-planned three volume SIB. Conformal and intensity modulated radiotherapy (IMRT) methods were used to plan the complex treatments. Techniques spanned the range from simple methods appropriate for patient cohorts with a low local cancer recurrence risk to complex plans relevant to cohorts with high recurrence risk. Delineated organs at risk included brain, salivary glands, thyroid, contra-lateral breast, left and right lung, oesophagus, stomach, liver, colon and bladder. Biological Effects of Ionising Radiation (BEIR) VII cancer incidence models were applied to the measured mean organ doses to determine Lifetime Attributable Risk (LAR) for ages at exposure from 35 to 80 years according to radiotherapy techniques, and included dose from the CBCT imaging.

Results—All LAR decreased with age at exposure and were lowest for brain, thyroid, liver and bladder (< 0.1%). There was little dependence of LAR on radiotherapy technique for these organs and for colon and stomach. LAR values for the lungs for the three SIB techniques were two to three times those from WBRT and APBI. Uncertainties in the LAR models outweigh any differences in lung LAR between the SIB methods. Constraints in the planning of the SIB methods ensured that contra-lateral breast doses and LAR were comparable to WBRT, despite their added complexity. The smaller irradiated volume of the ABPI plan contributed to a halving of LAR for contralateral breast compared with the other plan types. Daily image guided radiotherapy (IGRT)

for a left breast protocol using kilovoltage CBCT contributed <10% to LAR for the majority of organs, and did not exceed 22% of total organ dose.

Conclusion—Phantom measurements and calculations of LAR from the BEIR VII models predict that complex breast radiotherapy techniques do not increase the theoretical risk of second cancer incidence for organs distant from the treated breast, or the contralateral breast where appropriate plan constraints are applied. Complex SIB treatments are predicted to increase the risk of second cancer incidence in the lungs compared to standard whole breast radiotherapy; this is outweighed by the threefold reduction in 5 year local recurrence risk for patients of high risk of recurrence, and young age, from the use of radiotherapy. APBI may have a favourable impact on risk of second cancer in the contra-lateral breast and lung for older patients at low risk of recurrence. Intensive use of IGRT increased the estimated values of LAR but these are dominated by the effect of the dose from the radiotherapy, and any increase in LAR from IGRT is much lower than the models' uncertainties.

Keywords

second cancer incidence; breast radiotherapy; image-guided radiotherapy; partial breast

I Introduction

The increasing use of intensity modulated radiotherapy (IMRT), and the associated increase in whole body exposure to low doses from scattered and leakage radiation, has generated interest on the possible risks of second cancer induction for patients receiving curative radiotherapy.¹⁻³ This issue has become of consequence because of the success of modern techniques, including radiotherapy, in increasing life expectancy for many patients with common cancers. The implications for prostate patients have been examined by a number of groups³⁻⁶, whilst others have assessed the risks to paediatric patients, and patients under 40 years.⁷⁻⁹

Early breast cancer patients have an expectation of good long term survival and contribute a large radiotherapy treatment group.¹⁰ There has been an increasing use of modern methods for the treatment of early breast cancer. Many authors have published IMRT techniques for whole breast treatments¹¹⁻¹⁶ and three clinical trials using IMRT have reported dosimetric, medium and long term follow up.¹⁷⁻²⁰ Baglan *et al*²¹ described a method using non-coplanar conformal planning for accelerated partial breast irradiation (ABPI) and several groups have reported methods for simultaneous integrated boost (SIB) treatments.²²⁻²⁵ The increased complexity of these techniques compared to standard whole breast radiotherapy (WBRT), potentially increases the dose to non-target tissue. In addition, there is often a need to use Image Guided Radiotherapy (IGRT), for example, in partial breast irradiation (PBI), or to achieve specific planning target volume (PTV) margins²⁵.

There has been discussion over the increased use of imaging, and hence dose from IGRT systems.²⁶⁻³⁰ The contributions of IGRT to non-target organ doses have been put into context by Harrison *et al*²⁸⁻³⁰ who showed that intense IGRT imaging procedures contributed 5 - 30% of the total dose to non-target organs with the remainder dose from the radiotherapy scattered and leakage radiation. Harrison *et al* expressed reluctance to assign risk estimates to their measured organ doses although, other groups have found the risk models useful to compare different treatment methods whilst accepting the large uncertainties in an absolute risk value.³¹⁻³²

Given these developments, it is timely that estimates of second cancer incidence risk with modern methods are made for the early breast cancer group. We present a set of organ doses measured in an anthropomorphic phantom, and estimates of the risk of second cancer

induction in those organs for five techniques to treat the left breast : (i) a conventional tangential field whole breast treatment (WBRT), (ii) a non-coplanar conformal delivery applicable to APBI treatment²¹, (iii) a two volume SIB, (iv) a three volume forward planned SIB (FP SIB) and (v) a three volume inverse planned SIB (IP SIB).²⁵ These techniques span the range from simple tangential fields, applicable to older patients with a low recurrence risk, to complex techniques, which might be appropriate for women with a high recurrence risk (e.g. aged under 50 years). In addition, we present measurements in the phantom for an IGRT protocol suitable for verifying breast radiotherapy which used kilovoltage cone beam CT (CBCT). We used our data to estimate the risk of second cancer induction in specific organs over an age range which reflects the demographic of patients requiring radiotherapy for early breast cancer, and put these into the context of recurrence risk from the disease. The International Commission on Radiological Protection (ICRP) Report 103³³ recommended radiation risk estimates are made for specific organs, thus we have based this work on the Biological Effects of Ionising Radiation (BEIR) VII risk models, which provide age and sex specific parameters for a range of organs.³⁴

II. Methods

II.A Planning for Standard and Complex Techniques

A ^aPhilips Pinnacle³ 9.0 system was used to generate the plans which were prepared on a CT data set of a patient with left breast disease and tumour bed fiducial markers. The simplest technique was a tangential, wedged treatment of the whole breast to 40Gy in 15 fractions (the current UK standard dose prescription). The APBI treatment was planned as described by Baglan *et al*²¹ and prescribed to 38.5Gy in 10 fractions. It consisted of five non-coplanar fields with wedging and conformal shaping to the partial breast PTV using a multileaf collimator (MLC). The method of Hurkmans *et al*²⁴ was used to plan the two volume SIB treatment which was prescribed to 51.5 Gy to whole breast and 74 Gy to the tumour bed in 31 fractions. Two IMRT fields were used to treat the whole breast and three conformal fields used to treat the tumour bed PTV. Beam weight optimisation was applied to these latter beams. The most complex treatment was a three volume SIB IMRT plan designed to deliver 36Gy to whole breast, 40Gy to partial breast and 53Gy to the tumour bed in 15 fractions.²⁵ The plan consisted of tangential fields to cover the whole breast, plus 5 coplanar fields to deliver the dose to the partial breast and the tumour bed PTV. Beam weights, segment weights and MLC shaping were designed using both forward or inverse planning approaches as described by Donovan *et al*.³⁵ Sagittal dose distributions are shown in Figure 1. The 2Gy equivalent dose (EQD₂) for each fractionation regimen is given in Table 1 assuming an α / β ratio of 3 for tumour control³⁶.

II.B Measurement of Treatment Doses in an Anthropomorphic Phantom

The plans were transferred to a CT scan of a Rando anthropomorphic phantom which had semi-realistic breast attachments added. An experienced clinician (MB) outlined regions representative of radiosensitive organs : brain, salivary glands, thyroid, left and right breast, left and right lung, oesophagus, stomach, liver, colon and bladder. Harshaw TLD-100 (LiF:Ti, Mg) thermoluminescent dosimeters (TLD) were placed uniformly within the positions of the outlined organs from slice 1 (head) to slice 33 (base of pelvis). Table 1 gives the number of TLD in each region. Each TLD was uniquely identified and the dose calculated as given in equation 1.

^aPhilips Medical Systems, Palo Alto, US

$$\text{Dose}_{TLD} = (R_{TLD} - R_{Bkg}) \times CF_{chip} \times CF_{cal} \quad (1)$$

where R_{TLD} = TLD output in nC, R_{Bkg} = unirradiated TLD output in nC, CF_{chip} = individual chip factor, to account for the variability of chip output within the batch, CF_{cal} = calibration factor to convert from nC to Gy. CF_{cal} was derived from a calibration curve produced by irradiating sets of 10 TLD in water equivalent material to doses between 0.02 and 8.5Gy respectively in a 6MV beam. One set was left unirradiated to provide a background signal. The calibration was confirmed with a repeat set of measurements. The difference in calibration factor was 0.6%. The output and linearity of the linear accelerator were confirmed prior to irradiation with an ionisation chamber and electrometer with a calibration traceable to the MV national standard³⁷. The TLD were read out using a ^bHarshaw 5500 reader and annealed using a standard of 400°C for 90 minutes, 80°C for 960 minutes followed by free cooling to air temperature. The time interval between irradiation and readout was 14 hours for calibration and experimental sessions; this minimised any error due to fading. Five fractions were delivered to the phantom for each technique at the measurement session, and the data scaled to give the total dose in Gy for the complete treatment. All plans were delivered with an ^cElekta Synergy linear accelerator at 6MV photon beam energy.

II.C Measurement of Cone Beam CT Doses in an Anthropomorphic Phantom

The CBCT exposures were delivered with an Elekta XVI system, which is integrated on the linac gantry with the kV tube at 90° to the treatment head. 10 exposures were made in the measurement session to ensure sufficient dose to the TLD. The left breast imaging protocol consisted of a scan arc of 185° with a gantry start angle of 260° (kV start angle 350°) and gantry stop angle of 85° (kV stop angle 175°)³⁸. A 100kVp generating potential was set with parameters of 25mA, 40ms and 361 imaging frames. A S20 collimator (= 26 cm reconstruction circle) was used with no beam shaping filter. TLD were calibrated at 100kVp using a Gulmay orthovoltage unit and a dose calibration traceable to the UK kilovoltage primary standard.³⁹

II.D Second Cancer Risk Model

Several risk models have been developed to estimate cancer incidence and mortality: ICRP³³, BEIR³⁴, United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR)⁴⁰. The uncertainties associated with each of the models are close to, or exceed, the variation between the models³². We have chosen to use the BEIR VII model as it provides model parameters for specific organs for each sex and includes a parameter describing incidence with age at exposure and attained age. Our focus was to estimate cancer incidence over an age range of 35 to 80 years (which reflects the typical age distribution of breast cancer incidence in Europe and the US).

We have evaluated Lifetime Attributable Risk (LAR) via the method given in the BEIR VII report, with a slight modification to sum to age 90. This summation gave consistency with the data from ICRP Report 103³³, which is required in the calculation of LAR, but is not stratified above age 90 years. Equation 2 is the BEIR committee recommended model for both Excess Relative Risk (ERR) and Excess Absolute Risk (EAR).

^bThermo Fisher Scientific Inc., Erlangen, Germany

^cElekta Oncology Systems, Crawley, UK

$$ERR \text{ and } EAR = \beta_S D \exp(\gamma e^*) \left(\frac{a}{60} \right)^\eta \quad (2)$$

where D = dose; β_S , γ and η are ERR and EAR specific parameters for various organs for each sex; e is age at exposure; $e^* = (e-30)/10$ for $e < 30$ and 0 for $e > 30$ years; a is attained age.

For organs other than breast, lung and thyroid the BEIR VII report recommends calculating Lifetime Attributable Risk (LAR) as given in equation 3.

$$LAR_{(D,e)} = \left(\sum_a^{90} ERR(D, e, a) \cdot \lambda_l^c \cdot S(a) / S(e) da \right)^{0.7} \times \left(\sum_a^{90} EAR(D, e, a) \cdot S(a) / S(e) da \right)^{0.3} \quad (3)$$

$ERR_{(D,e,a)}$ and $EAR_{(D,e,a)}$ are described by equation 2; λ_l^c represents the baseline cancer risk and data were taken from ICRP Report 103; $S(a)/S(e)$ is the probability of surviving to the attained age (a) conditional on survival to exposed age (e) and was derived from the life span tables of the UK Office for National Statistics 2006-2008.⁴¹ The functions are summed from $a=e+L$ to 90 years, with e = age at exposure and L = latency period (5 years for solid cancer). The weights 0.7 and 0.3 are recommended by the BEIR Committee for most organs. They reflect the greater support for relative risk transport between populations rather than absolute risk. The weights of 0.7 and 0.3 are reversed for lung; for breast only the EAR model is recommended (from the work of Preston *et al*⁴²) and for thyroid there is no EAR model and LAR is calculated using the ERR model only. There were no model parameters given for the salivary glands. Hall *et al*², and Pierce *et al*⁴³ show data from the atomic bomb survivors which indicates that risk is linear with dose over the range from 0.1 to 2.5 Gy. The BEIR VII report used the linear no-threshold model. Linear scaling has been used to calculate LAR for the mean organ doses presented in this work. A dose and dose-rate effective factor (DDREF) of 1.5, as recommended in the BEIR VII report, was applied to the calculated LAR.

III Results

III.A Measured Organ Doses

Table 1 shows the mean dose per organ from the radiotherapy deliveries and the total for 15 CBCT imaging exposures. The data are stratified into three dose levels <0.5Gy; 0.5 and < 1.0Gy; 1.0Gy. These data are expressed as a percentage of maximum prescribed dose in Table 2. Table 3 expresses the CBCT organ doses as a percentage of total (radiotherapy plus imaging) doses assuming online verification of each treatment fraction for each schedule. The mean background output of the TLD was $0.1\text{nC} \pm 0.03\text{nC}$; the lowest TLD output from an irradiation session was 1.2nC . The uncertainties in the measured dose from individual TLDs ranged from 2.5% to 6.5%, with a median of 3.4% at 6MV; 2.4% to 6.1% with a median of 2.8% at 100kVp. These quoted uncertainties were based on a standard uncertainty multiplied by a coverage factor $k = 2$, providing a level of confidence of approximately 95%.

The pattern in the dose data was as expected. Distant organs (brain, salivary glands, thyroid, colon, bladder) received mean doses less than 0.2Gy with higher doses close to the treated region. Organs received the lowest doses from the APBI techniques because of the smaller volume irradiated and lower prescribed dose. The three complex SIB techniques delivered higher doses to more organs than the standard whole breast method. The main difference between the SIB techniques was in the mean contra-lateral lung and oesophagus doses.

Whilst doses from the CBCT imaging were low compared to these from the radiotherapy, they contributed 10% to 20% of total organ dose in some cases (Table 3).

III.B Lifetime Attributable Risk

The uncertainties in estimated LAR based on the models presented in the BEIR VII report³⁴ are high. The authors comment, in their analysis of LAR uncertainty, that this is dominated by the uncertainty in the estimated value of the model parameter β in the models of ERR and EAR. The report gives an estimate of LAR for solid cancer incidence in the female breast as 310 cases (95% confidence intervals (CI) 160, 610) per 100,000 of mixed age exposed to 0.1Gy. For lung cancer incidence in females of the same population and dose, LAR is given as 300 (95% CI 120, 780). Other sites have similar levels of uncertainty.

LAR data for all radiotherapy techniques from age at exposure of 35 to 90 years for each measured organ are given in Tables 4 and 5 and assumed to have uncertainty levels as discussed. The data were separated by class of plan. Whole breast and ABPI were considered as applicable to patients with low recurrence risk (Table 4); the SIB methods appropriate for cohorts with high recurrence risk (Table 5). The LAR data show the strong age dependency of the cancer incidence risk in the BEIR VII model. This is pronounced in the breast data where there is a 60 fold decrease in LAR from age at exposure of 35 years to that at 80 years; the decrease is 5 to 10 fold for other organs. The variation in the magnitude of the LAR data follows the pattern of the measured doses.

Data for all techniques, plus that from daily IGRT, for age at exposure of 40 and 60 years are taken from Tables 4 and 5 and presented graphically in Figure 2 (a) and (b). These ages represent younger women, who would be at a higher risk of recurrence at the time of diagnosis, and older women with a lower risk. The LAR values are dominated by the radiotherapy contribution to total dose. The LAR values are lowest for brain, thyroid, liver and bladder and there is little impact from radiotherapy technique observed in the data for these organs, or the colon and stomach. The uncertainties in the LAR model outweigh any differences in the risk to the lungs from the three SIB methods. However the LAR for the three SIB techniques is 2 -3 times that from the whole breast RT and APBI deliveries. Constraints in the planning of the SIB methods meant that contra-lateral breast doses, were of a similar order to a whole breast plan despite the complexity of the SIB plans. This is reflected in the LAR values. The consequence of the smaller irradiated volume of the ABPI plan is seen in the lower magnitude of LAR for contra-lateral breast compared with the other four plan types.

Figure 3 places the calculated LAR for the techniques in the context of the local recurrence risk estimates (with and without radiotherapy) from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2005 overview¹⁰. EBCTCG data show an increase in lung and contra-lateral breast second cancers following radiotherapy; LAR for these at risk organs is plotted in Figure 3. The data and techniques are separated as for Tables 4 and 5. For the specific plans and equipment used in this work, LAR are predicted to be low for all techniques compared to the gain from radiotherapy which reduces 5 year recurrence from 33% to 11% for a cohort of 40 year old women, and from 11% to 4% for a population of 60 year old women.

IV Discussion

We have described measured out-of-field doses, and presented estimated LAR for cancer incidence, for standard whole breast and four complex breast treatments over a range of organs delineated in an anthropomorphic phantom. The data have been used to assess the

change in risk of second cancer incidence for complex deliveries compared to standard whole breast radiotherapy.

The analysis of the EBCTCG¹⁰ shows both lung and contra-lateral breast second cancer incidence increased with the use of radiotherapy. Figure 3 shows our estimates of LAR for these organs, with an example of a risk from the disease (the 5 year local recurrence rate), in order to give the risks from treatment (which includes the CBCT imaging) a relevant context. More complex techniques are likely to be used either where there is complex anatomy making standard planning difficult, or in patients at higher risk of disease recurrence. As younger age is a risk factor for recurrence we have compared the SIB treatments to recurrence risk for a 40 year old woman in Figure 3 (a). Technical solutions for older patients may be simpler, or irradiate only part of the breast, and deliver lower dose to non-target regions. The whole breast and APBI treatments have been compared with recurrence risk for a 60 year old woman in Figure 3(b). The balance between disease risk and treatment risk will change if recurrence rates fall and/or complex deliveries increase doses such that LAR values approach the recurrence rates. Mannino and Yarnold *et al* present data which indicates recurrence rates have reduced.⁴⁴ Only cancer induction has been considered as a treatment risk in this work; it is noted that other damage from radiotherapy is relevant e.g. the risk of cardiac morbidity, lung fibrosis and damage to the oesophagus.

The effect of measured dose from the intensive use of IGRT with CBCT on the total LAR for cancer incidence was shown to be small relative to the impact of the radiotherapy. The values of LAR from the radiotherapy and the uncertainty associated with the estimates indicate that a large change in the magnitude of the CBCT dose may be made (e.g. doubling or halving the dose) without affecting the estimated risk. It is a requirement, and good practice, to have a protocol appropriate for the task to limit unnecessary organ exposure. The one used in this work used a 180° scan to minimise contra-lateral organ dose. Whilst this work indicates that daily online imaging for breast cancer patients does not significantly increase the predicted cancer incidence risk, correction strategies which limit the concomitant dose but still reduce the systematic and random set up errors should be considered⁴⁵. The dose burden of IGRT should be weighed against the useful information in the image, e.g. Harris *et al*⁴⁶ have tracked the distortion of tumour beds over a treatment course. This may require a higher imaging dose but is justified by the increase in understanding and improvement to treatment accuracy.

Trials of advanced methods, for example, the US Accelerated Partial Breast Irradiation (APBI) trials⁴⁷, the Netherlands boost trial⁴⁸ and the UK Intensity Modulated and Partial Organ Radiotherapy (IMPORT) High trial²⁵ have detailed specifications for target and organ at risk doses. The strong age dependency in the data which forms the basis of the BEIR VII model, indicate that it may be appropriate to stratify the trial constraints further based on age, for example, for the contra-lateral breast. The risk of recurrence in the younger age group is higher than that for older women (Figure 3), and control of primary disease may be of greater importance than a theoretical increase in cancer induction risk when assessing the merits of different types of treatment deliveries.

There is much interest in hypofractionated and accelerated schedules for early breast cancer. These result in lower total physical doses, for example, the UK Faster Radiotherapy for Breast Cancer patients (FAST) trial of 30Gy in 5 fractions⁴⁹ and the US APBI study of 38.5Gy in 10 fractions.³³³ The BEIR VII models do not include a term for dose per fraction per organ, only total dose, hence the use of the models predicts a decrease in second cancer risk for some organs even if sophisticated techniques are needed for radiotherapy delivery.

Data to improve the risk estimates will only be obtained by good mapping of both recurrences and new primaries against RT dose distributions and the out-of-field doses. We suggest clinical trials testing new RT techniques could, as part of the pre-trial QA, incorporate the measurement of anthropomorphic phantom whole body doses or use MC simulation of out-of-field doses if available. Whilst this would not inform on a per patient basis, it would give useful information about relative changes in dose in the regions outside of the RT CT planning scan. The nature of these doses is that they do not need to be known to the level of accuracy of those within the region covered by the CT scan, hence the inevitably larger measurement errors would not outweigh the usefulness. Our data in Tables 1 and 2 shows differences in technique are observed by doing this. This information and the detailed dosimetry of the treatment region could be used in combination with the epidemiological studies to help improve the risk models. The era of good quality and widely available imaging should allow this mapping.

V Conclusions

The dose measurements and calculations of LAR presented indicate that more sophisticated methods for breast radiotherapy do not increase the theoretical risk of second cancer incidence for organs distant from the treated breast. Complex SIB treatments are predicted to increase the risk of second cancer in the lungs compared to standard whole breast radiotherapy, however, this is outweighed by the threefold reduction in 5 year local recurrence risk for patients of high risk of recurrence and young age. If dose constraints for the contra-lateral breast are set so that they do not exceed those of standard tangents, then complex methods do not increase LAR, although age specific contra-lateral breast dose constraints could be considered in clinical trials of breast radiotherapy. APBI may have a favourable impact on risk of second cancer in the contra-lateral breast for older patients at low risk of recurrence. Intensive use of IGRT theoretically increases the estimated values of LAR but these are dominated by the effect of the dose from the radiotherapy, and any increase in LAR from IGRT is much lower than the uncertainty in the models. Whilst appropriate imaging protocols should be used, daily imaging using CBCT of patients at high risk of recurrence receiving complex radiotherapy is unlikely on its own to result in an unacceptable increase in the risk of second cancer.

Acknowledgments

Dr Ellen Donovan : This report is independent research arising from a Healthcare Scientist Post Doctoral award supported by the National Institute for Health Research (NIHR) and the Chief Scientific Officer (CSO). The views expressed in this publication are those of the author(s) and not necessarily those of the National Health Service (NHS), the National Institute for Health Research or the Department of Health.

We acknowledge NHS funding of the NIHR Biomedical Research Centre at Institute of Cancer Research/Royal Marsden Hospital and Cancer Research UK.

We would like to thank Dr. Charlotte Coles for helpful comments.

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Figure 1.
Sagittal dose distributions

Figure 2. LAR for age at exposure of (a) 40 and (b) 60 years for all measured organs, all treatment deliveries and assuming daily CBCT imaging.

Figure 3. (a) and (b) Recurrence risks and estimated treatment risks (radiotherapy and intensive CBCT imaging) at for population of 40 and 60 years
Data on recurrence from Early Breast Trialists' Collaborative Group¹⁰.

Table 1

Measured Mean Organ Doses in Phantom (Gy)

Organ	Number of TLD	WBRT	APBI	SIB 2 volumes	SIB 3 volumes FP IMTR	SIB 3 volumes IP IMRT	Cone beam CT Imaging
		40 Gy whole breast 15 fractions	38.5 Gy partial breast 10 fractions	51.5 Gy whole breast 74 Gy tumour bed 31 fractions	36 Gy whole breast 40 Gy partial breast 53 Gy tumour bed 15 fractions		15 imaging exposures
		[*] $EQD_2 = 46 \text{ Gy}$	⁺ $EQD_2 = 65 \text{ Gy}$	$EQD_2 = 48\text{Gy} \text{ \& } 79\text{Gy}$	$EQD_2 = 40\text{Gy} \text{ \& } 46\text{Gy} \text{ \& } 69\text{Gy}$		
Brain	25	0.05	0.04	0.07	0.06	0.07	0.001
Salivary glands	2	0.08	0.06	0.12	0.10	0.08	0.003
Thyroid	2	0.10	0.09	0.16	0.13	0.12	0.01
Contra-lateral breast	20	0.59	0.19	0.72	0.63	1.14	0.03
Ipsi-lateral Lung	39	0.69	0.70	1.92	1.34	1.79	0.06
Contra-lateral lung	39	0.11	0.07	1.05	0.28	0.64	0.02
Oesophagus	8	0.13	0.10	2.05	0.39	0.61	0.03
Liver	41	0.15	0.19	0.26	0.16	0.25	0.03
Stomach	13	0.70	0.25	0.68	0.61	0.62	0.08
Colon	20	0.09	0.07	0.12	0.19	0.09	0.01
Bladder	5	0.02	0.02	0.03	0.03	0.02	0.004

Data highlighted in dark grey $\geq 1 \text{ Gy}$; data highlighted in grey $\geq 0.5 \text{ Gy}$ and $< 1.0 \text{ Gy}$; other data $< 0.5 \text{ Gy}$.^{*} EQD_2 is Equivalent dose in 2Gy fraction size. Calculations assume $\alpha / \beta = 3^{36}$.⁺ Incomplete repair with $t_{1/2} = 4.4 \text{ hours}$.

Table 2

Mean organ dose as a percentage of maximum prescribed dose (%)

Organ	WBRT	APBI	SIB 2 volumes	SIB 3 volumes FP IMRT	SIB 3 volumes IP IMRT
Brain	0.1	0.1	0.1	0.1	0.1
Salivary glands	0.2	0.2	0.2	0.2	0.2
Thyroid	0.3	0.2	0.2	0.2	0.2
Contra-lateral breast	1.5	0.5	1.0	1.2	2.2
Ipsi-lateral Lung	1.7	1.8	2.6	2.5	3.4
Contra-lateral lung	0.3	0.2	1.4	0.5	1.2
Oesophagus	0.3	0.3	2.8	0.7	1.2
Liver	0.4	0.5	0.4	0.3	0.5
Stomach	1.8	0.6	0.9	1.2	1.2
Colon	0.2	0.2	0.2	0.4	0.2
Bladder	0.1	0.1	0.1	0.1	0.1

Table 3
Cone beam CT organ dose as a percentage of total organ dose from radiotherapy and imaging (%). Left breast treatment and imaging

Data assumes online verification of all treatment fractions for each technique and prescription.

Organ	WBRT	APBI	SIB 2 volumes	SIB 3 volumes FP IMRT	SIB 3 volumes IP IMRT
	<i>15 imaging exposures</i>	<i>10 imaging exposures</i>	<i>31 imaging exposures</i>	<i>15 imaging exposures</i>	<i>15 imaging exposures</i>
Brain	2.1	1.6	2.8	1.6	1.4
Salivary glands	3.6	3.2	4.9	2.9	3.6
Thyroid	9.1	6.7	11.5	7.1	7.7
Contra-lateral breast	4.8	9.1	7.9	4.5	2.6
Ipsi-lateral Lung	8.0	5.3	6.1	4.3	3.2
Contra-lateral lung	15.4	14.8	3.8	6.7	3.0
Oesophagus	18.8	15.4	2.9	7.1	4.7
Liver	16.7	9.1	19.3	15.8	10.7
Stomach	10.3	16.2	19.6	11.6	11.4
Colon	10.0	8.3	14.7	5.0	10.0
Bladder	16.7	11.1	21.6	11.8	16.7

Table 4

LAR data for all organs and ages at exposure summed to 90 years : WBRT and APBI techniques (no boost)

LAR (cancer incidence per 100 000 population)							
Organ	Technique	Age at Exposure					
		35	40	50	60	70	80
Brain	WBRT	17	15	12	9	5	2
	APBI	13	12	9	7	4	2
Thyroid	WBRT	28	23	21	18	13	5
	APBI	25	21	19	16	12	5
Contra-lateral lung	WBRT	116	114	108	93	63	24
	APBI	74	73	69	59	40	15
Contra-lateral breast	WBRT	566	425	218	97	35	9
	APBI	182	137	70	31	11	3
Oesophagus	WBRT	27	26	23	18	12	4
	APBI	21	20	18	14	9	3
Liver	WBRT	17	15	15	12	8	2
	APBI	21	19	19	15	10	2
Stomach	WBRT	294	287	266	224	161	63
	APBI	105	103	95	80	58	23
Colon	WBRT	65	63	59	49	32	12
	APBI	50	49	46	38	25	9
Bladder	WBRT	8	8	8	6	5	2
	APBI	8	8	8	6	5	2

Table 5

LAR data for all organs and ages at exposure summed to 90 years : Simultaneous Integrated Boost techniques

LAR (cancer incidence per 100 000 population)							
Age at Exposure							
Organ	Technique	35	40	50	60	70	80
Brain	SIB 2 volume	23	20	16	12	7	3
	SIB 3 volume <i>FP IMRT</i>	20	17	14	10	6	2
	SIB 3 volume <i>IP IMRT</i>	23	20	16	12	7	3
Thyroid	SIB 2 volume	45	37	34	29	21	8
	SIB 3 volume <i>FP IMRT</i>	36	30	27	23	17	7
	SIB 3 volume <i>IP IMRT</i>	34	28	25	22	16	6
Contra-lateral lung	SIB 2 volume	1108	1092	1034	887	599	226
	SIB 3 volume <i>FP IMRT</i>	295	291	276	237	160	60
	SIB 3 volume <i>IP IMRT</i>	675	666	630	541	365	138
Contra-lateral breast	SIB 2 volume	691	518	266	119	43	11
	SIB 3 volume <i>FP IMRT</i>	605	454	233	104	38	9
	SIB 3 volume <i>IP IMRT</i>	1094	821	422	188	68	17
Oesophagus	SIB 2 volume	431	410	369	287	185	62
	SIB 3 volume <i>FP IMRT</i>	82	78	70	55	35	12
	SIB 3 volume <i>IP IMRT</i>	128	122	110	85	55	18
Liver	SIB 2 volume	29	26	26	21	13	3
	SIB 3 volume <i>FP IMRT</i>	18	16	16	13	8	2
	SIB 3 volume <i>IP IMRT</i>	28	25	25	20	13	3
Stomach	SIB 2 volume	286	279	258	218	156	61
	SIB 3 volume <i>FP IMRT</i>	256	250	232	195	140	55
	SIB 3 volume <i>IP IMRT</i>	260	254	236	198	143	56
Colon	SIB 2 volume	86	49	46	38	25	9
	SIB 3 volume <i>FP IMRT</i>	137	133	124	103	68	25
	SIB 3 volume <i>IP IMRT</i>	65	63	59	49	32	12
Bladder	SIB 2 volume	13	12	11	10	7	3
	SIB 3 volume <i>FP IMRT</i>	13	12	11	10	7	3