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Running title: Second Cancer Risk Estimates for Breast Radiotherapy

Keywords: second cancer incidence; breast radiotherapy; image-guided radiotherapy, partial breast
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 contra-lateral 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 contra-lateral 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.
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.\textsuperscript{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 groups\textsuperscript{3-6}, whilst other have assessed the risks to paediatric patients, and patients under 40 years.\textsuperscript{7-9}

Early breast cancer patients have an expectation of good long term survival and contribute a large radiotherapy treatment group.\textsuperscript{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 treatments\textsuperscript{11-16} and three clinical trials using IMRT have reported dosimetric, medium and long term follow up.\textsuperscript{17-20} Baglan \textit{et al}\textsuperscript{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.\textsuperscript{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) margins\textsuperscript{25}.

There has been discussion over the increased use of imaging, and hence dose from IGRT systems.\textsuperscript{26-30} The contributions of IGRT to non-target organ doses have been put into context by Harrison \textit{et al}\textsuperscript{26-30} 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 \textit{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.

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 treatment, (iii) a two volume SIB, (iv) a three volume forward planned SIB (FP SIB) and (v) a three volume inverse planned SIB (IP SIB). 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 103 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.
II. Methods

II.A Planning for Standard and Complex Techniques

A Philips Pinnacle\textsuperscript{3} 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 \textit{et al}\textsuperscript{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 \textit{et al}\textsuperscript{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.\textsuperscript{25} The plan consisted of tangential fields to cover the whole breast, plus 5 co-planar 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 \textit{et al}.\textsuperscript{35} Sagittal dose distributions are shown in Figure 1. The 2Gy equivalent dose (EQD\textsubscript{2}) for each fractionation regimen is given in Table 1 assuming an $\alpha / \beta$ ratio of 3 for tumour control\textsuperscript{36}.

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.

\[ Dose_{TLD} = (R_{TLD} - R_{Bkg}) \times CF_{chip} \times CF_{cal} \]  

(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 un-irradiated 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 standard. The TLD were read out using a Harshaw 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 Elekta Synergy linear accelerator at 6MV photon beam energy.

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

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c Elekta Oncology Systems, Crawley, UK
The CBCT exposures were delivered with an Elekta XVI system, which is integrated on the linac gantry with the kV tube at $90^\circ$ 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 $185^\circ$ with a gantry start angle of $260^\circ$ (kV start angle $350^\circ$) and gantry stop angle of $85^\circ$ (kV stop angle $175^\circ$). 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.

II.D Second Cancer Risk Model

Several risk models have been developed to estimate cancer incidence and mortality: ICRP \textsuperscript{33}, BEIR \textsuperscript{34}, United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) \textsuperscript{40}. The uncertainties associated with each of the models are close to, or exceed, the variation between the models\textsuperscript{32}. 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 103\textsuperscript{33}, 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).
\[ \text{ERR and EAR} = \beta_S D \exp(\gamma e^*) \left(\frac{a}{60}\right)^\eta \]  \hspace{1cm} (2)

where \( D \) = dose; \( \beta_S, \gamma \) and \( \eta \) 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.

\[ \text{LAR}(D, e, a) = \sum_{a=e+L}^{90} \text{ERR}(D, e, a) \cdot \lambda^C I \cdot S(a)/S(e) da \times \left(\sum_{a=e+L}^{90} \text{EAR}(D, e, a) \cdot S(a)/S(e) da\right)^{0.3} \]  \hspace{1cm} (3)

\( \text{ERR}(D, e, a) \) and \( \text{EAR}(D, e, a) \) are described by equation 2; \( \lambda^C I \) 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. 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.\cite{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.\cite{2} and Pierce et al.\cite{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 \(<0.5\,\text{Gy} \leq 0.5 \) and \(< 1.0\,\text{Gy} \leq 1.0\,\text{Gy}\). 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 \(1.2\,\text{nC}\). 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 report\(^3\) 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 \(\beta\) 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 overview. 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 EBCTCG \(^{10}\) 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 considered. The dose burden of IGRT should be weighed against the useful information in the image, e.g. Harris et al 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) trials, the Netherlands boost trial and the UK Intensity Modulated and Partial Organ Radiotherapy (IMPORT) High trial 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 fractions and the US APBI study of 38.5Gy in 10 fractions. 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.
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References


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Figure 1 Sagittal dose distributions

(a) Whole breast (WBRT)  (b) APBI

(c) Two volume SIB  (d) Three volume SIB FP IMRT

(e) Three volume SIB IP IMRT

Purple represents the whole breast planning target volume (PTV); green represents the partial breast PTV; blue represents the tumour bed PTV. 95% isodoses at each dose level are represented in yellow, 100% isodoses in red and 107% isodoses in bright green.
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.

**Lifetime Attributable Risk (LAR) (%) age at exposure = 40 years**

- Organ at risk: Brain
- LAR (%): 0.00%

- Organ at risk: Thyroid
- LAR (%): 0.50%

- Organ at risk: Ipsilateral Lung
- LAR (%): 1.00%

- Organ at risk: Contralateral Lung
- LAR (%): 1.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 2.00%

- Organ at risk: Contralateral Breast
- LAR (%): 2.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 3.00%

- Organ at risk: Ipsilateral Lung
- LAR (%): 3.50%

- Organ at risk: Ipsilateral Lung
- LAR (%): 4.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 4.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 5.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 5.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 6.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 6.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 7.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 7.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 8.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 8.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 9.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 9.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 10.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 10.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 11.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 11.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 12.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 12.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 13.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 13.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 14.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 14.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 15.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 15.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 16.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 16.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 17.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 17.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 18.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 18.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 19.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 19.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 20.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 20.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 21.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 21.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 22.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 22.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 23.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 23.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 24.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 24.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 25.00%

**Lifetime Attributable Risk (LAR) (%) age at exposure = 60 years**

- Organ at risk: Brain
- LAR (%): 0.00%

- Organ at risk: Thyroid
- LAR (%): 0.50%

- Organ at risk: Ipsilateral Lung
- LAR (%): 1.00%

- Organ at risk: Contralateral Lung
- LAR (%): 1.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 2.00%

- Organ at risk: Contralateral Breast
- LAR (%): 2.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 3.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 3.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 4.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 4.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 5.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 5.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 6.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 6.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 7.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 7.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 8.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 8.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 9.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 9.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 10.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 10.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 11.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 11.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 12.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 12.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 13.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 13.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 14.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 14.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 15.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 15.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 16.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 16.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 17.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 17.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 18.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 18.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 19.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 19.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 20.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 20.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 21.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 21.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 22.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 22.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 23.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 23.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 24.00%

- Organ at risk: Ipsilateral Breast
- LAR (%): 24.50%

- Organ at risk: Ipsilateral Breast
- LAR (%): 25.00%
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 Group. The figure illustrates the recurrence risks and estimated treatment risks for both 40 and 60-year-old populations, showing the impact of radiotherapy on recurrence rates and contralateral breast, ipsilateral lung, and contralateral lung cancer incidence. The figure includes bar graphs and incidence percentages for different treatment regimens, highlighting the benefits of treatment in reducing recurrence risks.
<table>
<thead>
<tr>
<th>Organ</th>
<th>Number of TLD</th>
<th>WBRT</th>
<th>APBI</th>
<th>SIB 2 volumes</th>
<th>SIB 3 volumes</th>
<th>SIB 3 volumes</th>
<th>Cone beam CT Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>40 Gy whole breast</td>
<td>38.5 Gy partial breast</td>
<td>51.5 Gy whole breast</td>
<td>74 Gy tumour bed</td>
<td>31 fractions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 fractions</td>
<td>10 fractions</td>
<td>31 fractions</td>
<td>74 Gy tumour bed</td>
<td>31 fractions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>25</td>
<td>0.05</td>
<td>0.04</td>
<td>0.07</td>
<td>0.06</td>
<td>0.07</td>
<td>0.001</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>2</td>
<td>0.08</td>
<td>0.06</td>
<td>0.12</td>
<td>0.10</td>
<td>0.08</td>
<td>0.003</td>
</tr>
<tr>
<td>Thyroid</td>
<td>2</td>
<td>0.10</td>
<td>0.09</td>
<td>0.16</td>
<td>0.13</td>
<td>0.12</td>
<td>0.01</td>
</tr>
<tr>
<td>Contra-lateral breast</td>
<td>20</td>
<td>0.59</td>
<td>0.19</td>
<td>0.72</td>
<td>0.63</td>
<td>1.14</td>
<td>0.03</td>
</tr>
<tr>
<td>Ipsi-lateral Lung</td>
<td>39</td>
<td>0.69</td>
<td>0.70</td>
<td>1.92</td>
<td>1.34</td>
<td>1.79</td>
<td>0.06</td>
</tr>
<tr>
<td>Contra-lateral lung</td>
<td>39</td>
<td>0.11</td>
<td>0.07</td>
<td>1.05</td>
<td>0.28</td>
<td>0.64</td>
<td>0.02</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>8</td>
<td>0.13</td>
<td>0.10</td>
<td>2.05</td>
<td>0.39</td>
<td>0.61</td>
<td>0.03</td>
</tr>
<tr>
<td>Liver</td>
<td>41</td>
<td>0.15</td>
<td>0.19</td>
<td>0.26</td>
<td>0.16</td>
<td>0.25</td>
<td>0.03</td>
</tr>
<tr>
<td>Stomach</td>
<td>13</td>
<td>0.70</td>
<td>0.25</td>
<td>0.68</td>
<td>0.61</td>
<td>0.62</td>
<td>0.08</td>
</tr>
<tr>
<td>Colon</td>
<td>20</td>
<td>0.09</td>
<td>0.07</td>
<td>0.12</td>
<td>0.19</td>
<td>0.09</td>
<td>0.01</td>
</tr>
<tr>
<td>Bladder</td>
<td>5</td>
<td>0.02</td>
<td>0.02</td>
<td>0.03</td>
<td>0.03</td>
<td>0.02</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Data highlighted in dark grey ≥ 1 Gy; data highlighted in grey ≥ 0.5 Gy and <1.0 Gy; other data < 0.5 Gy. *EDQ₂ is Equivalent dose in 2Gy fraction size. Calculations assume \( \alpha / \beta = 3^{36} \). *Incomplete repair with t₁/₂ = 4.4 hours.
**Table 2 Mean organ dose as a percentage of maximum prescribed dose (%)**

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

<table>
<thead>
<tr>
<th>Organ</th>
<th>WBRT</th>
<th>APBI</th>
<th>SIB 2 volumes</th>
<th>SIB 3 volumes FP IMRT</th>
<th>SIB 3 volumes IP IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 imaging exposures</td>
<td>10 imaging exposures</td>
<td>31 imaging exposures</td>
<td>15 imaging exposures</td>
<td>15 imaging exposures</td>
</tr>
<tr>
<td>Brain</td>
<td>2.1</td>
<td>1.6</td>
<td>2.8</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>3.6</td>
<td>3.2</td>
<td>4.9</td>
<td>2.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Thyroid</td>
<td>9.1</td>
<td>6.7</td>
<td>11.5</td>
<td>7.1</td>
<td>7.7</td>
</tr>
<tr>
<td>Contra-lateral breast</td>
<td>4.8</td>
<td>9.1</td>
<td>7.9</td>
<td>4.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Ipsi-lateral Lung</td>
<td>8.0</td>
<td>5.3</td>
<td>6.1</td>
<td>4.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Contra-lateral lung</td>
<td>15.4</td>
<td>14.8</td>
<td>3.8</td>
<td>6.7</td>
<td>3.0</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>18.8</td>
<td>15.4</td>
<td>2.9</td>
<td>7.1</td>
<td>4.7</td>
</tr>
<tr>
<td>Liver</td>
<td>16.7</td>
<td>9.1</td>
<td>19.3</td>
<td>15.8</td>
<td>10.7</td>
</tr>
<tr>
<td>Stomach</td>
<td>10.3</td>
<td>16.2</td>
<td>19.6</td>
<td>11.6</td>
<td>11.4</td>
</tr>
<tr>
<td>Colon</td>
<td>10.0</td>
<td>8.3</td>
<td>14.7</td>
<td>5.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Bladder</td>
<td>16.7</td>
<td>11.1</td>
<td>21.6</td>
<td>11.8</td>
<td>16.7</td>
</tr>
</tbody>
</table>
### Table 4

LAR data for all organs and ages at exposure summed to 90 years:

**WBRT and APBI techniques (no boost)**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Technique</th>
<th>35</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>WBRT</td>
<td>17</td>
<td>15</td>
<td>12</td>
<td>9</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>APBI</td>
<td>13</td>
<td>12</td>
<td>9</td>
<td>7</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Thyroid</td>
<td>WBRT</td>
<td>28</td>
<td>23</td>
<td>21</td>
<td>18</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>APBI</td>
<td>25</td>
<td>21</td>
<td>19</td>
<td>16</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Contra-lateral lung</td>
<td>WBRT</td>
<td>116</td>
<td>114</td>
<td>108</td>
<td>93</td>
<td>63</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>APBI</td>
<td>74</td>
<td>73</td>
<td>69</td>
<td>59</td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>Contra-lateral breast</td>
<td>WBRT</td>
<td>566</td>
<td>425</td>
<td>218</td>
<td>97</td>
<td>35</td>
<td>9</td>
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<td>APBI</td>
<td>182</td>
<td>137</td>
<td>70</td>
<td>31</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>WBRT</td>
<td>27</td>
<td>26</td>
<td>23</td>
<td>18</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
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<td>20</td>
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<td>14</td>
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<td>3</td>
</tr>
<tr>
<td>Liver</td>
<td>WBRT</td>
<td>17</td>
<td>15</td>
<td>15</td>
<td>12</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>APBI</td>
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<td>19</td>
<td>19</td>
<td>15</td>
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<td>2</td>
</tr>
<tr>
<td>Stomach</td>
<td>WBRT</td>
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<td>63</td>
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<tr>
<td></td>
<td>APBI</td>
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<td>80</td>
<td>58</td>
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<tr>
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<tr>
<td></td>
<td>APBI</td>
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</tr>
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<td>8</td>
<td>8</td>
<td>6</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
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<td>APBI</td>
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<td>8</td>
<td>8</td>
<td>6</td>
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</tr>
</tbody>
</table>
Table 5
LAR data for all organs and ages at exposure summed to 90 years:
Simultaneous Integrated Boost techniques

<table>
<thead>
<tr>
<th>Organ</th>
<th>Technique</th>
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<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
</tr>
</thead>
<tbody>
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<td>20</td>
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<td>12</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>SIB 3 volume FP IMRT</td>
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<td>10</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>SIB 3 volume IP IMRT</td>
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<td>16</td>
<td>12</td>
<td>7</td>
<td>3</td>
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<td>SIB 2 volume</td>
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<td>28</td>
<td>25</td>
<td>22</td>
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<td>6</td>
</tr>
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<td>1034</td>
<td>887</td>
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<td>365</td>
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<td>422</td>
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<td>369</td>
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<tr>
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<td>18</td>
</tr>
<tr>
<td>Liver</td>
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<td>26</td>
<td>26</td>
<td>21</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>SIB 3 volume FP IMRT</td>
<td>18</td>
<td>16</td>
<td>16</td>
<td>13</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>SIB 3 volume IP IMRT</td>
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<td>25</td>
<td>25</td>
<td>20</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Stomach</td>
<td>SIB 2 volume</td>
<td>286</td>
<td>279</td>
<td>258</td>
<td>218</td>
<td>156</td>
<td>61</td>
</tr>
<tr>
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<td>250</td>
<td>232</td>
<td>195</td>
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<td>55</td>
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<td>SIB 3 volume IP IMRT</td>
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<td>46</td>
<td>38</td>
<td>25</td>
<td>9</td>
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<tr>
<td></td>
<td>SIB 3 volume FP IMRT</td>
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<td>133</td>
<td>124</td>
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