Identifying Surrogates for Heart and Ipsilateral Lung Dose to Guide Field Placement and Treatment Modality Selection during Virtual Simulation of Breast Radiotherapy

Authors:
Sairanne Wickers; Caroline Thould; Jo Keeble; Rachel Bodey; Csilla Harsanyi; Gary Royle; Mark N. Gaze

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Introduction: Virtual simulation (VSim) of tangential photon fields is a common method of field localisation for breast radiotherapy (RT). Heart and ipsilateral lung (IL) dose is unknown until the dosimetric plan is produced. If heart and IL tolerance doses are exceeded, this can prolong the pre-treatment pathway, particularly if a change of technique is required. The aim of this study was to identify predictive surrogates for heart and IL dose during VSim to aid optimum field placement and treatment modality selection.

Materials & Methods: CT data from 50 patients referred for left breast/chest wall RT were retrospectively analysed (model-building cohort). The prescribed dose was 40.05 Gy in 15# using a tangential photon technique. The heart and IL contours were duplicated, cropped to within the field borders and labelled heart-in-field (HIF) and IL-in-field (ILF). The percentage of HIF (%HIF) and ILF (%ILF) was calculated and correlated with mean heart dose (MHD) and IL $V18_{Gy}$. Linear regression models were calculated. A validation cohort of 10 left and 10 right-sided cases with an anterior supraclavicular fossa (SCF) field; and 10 left and 10 right-sided cases including the internal mammary nodes (IMN) using a wide tangential technique and anterior SCF field, tested the predictive model. Threshold values for %HIF and %ILF were calculated for clinically relevant MHD and IL $V18_{Gy}$ tolerance doses.

Results: For the model-building cohort, median %HIF and MHD were 2.6 (0.4 – 16.7) and 2.3 (1.2 - 8) Gy. Median %ILF and IL $V18_{Gy}$ were 12.1 (2.8 - 33.6) and 12.6 (3.3 - 35) %. There was a statistically significant strong positive correlation of %HIF with MHD (R^2 = 0.97, p<.0001), and of %ILF with IL $V18_{Gy}$ (R^2 = 0.99, p<.0001). For the validation cohort, median %HIF and MHD were 3.9 (0.6 – 8) and 2.5 (1.4 - 4.7) Gy. Median %ILF and IL $V18_{Gy}$ were 20.1 (12.4 - 32.0) and 20.9 (12.4 - 34.4) %. The validation cohort confirmed that %HIF and %ILF continue to be predictive surrogates for heart and IL dose during VSim of left and right-sided cases when including the SCF +/- IMN with a 3-field photon technique.

***Discussion*:** The ability to VSim breast radiotherapy (+/- nodal targets) and accurately predict the heart and IL doses on the dosimetric plan, will ensure that tolerance doses are not exceeded, and identify early in the pre-treatment pathway those cases where alternative techniques or modalities should be considered.

Background

Over half a million women are diagnosed with breast cancer every year in Europe [1]. Radiotherapy (RT) is indicated for most patients following breast conservation and for those with T4 or node positive disease post mastectomy; representing a significant proportion of the RT workload [2].

3D CT volume-based planning has largely replaced Virtual simulation (VSim) for many treatment sites. However, VSim remains a common method of tangential field localisation for breast RT as it is effective at; covering the target, avoiding organs at risk (OAR), and providing patient set-up information [3,4]. The VSim fields are three-dimensionally optimised to International Commission on Radiation Units and Measurements (ICRU) 50/62 requirements; ensuring that the dose to the target volumes is homogeneous and that 'hotspots' within the plan are removed [5,6]. However, although heart and ipsilateral lung (IL) doses can be reported, if dose constraints are not met, amendment of the VSim fields may be required.

The ability to predict heart and IL doses at the point of VSim would avoid late-stage changes, streamline the pre-treatment process, and avoid delays to patients starting RT.

For some patients, a tangential technique is not possible due to unacceptably high heart and/or IL dose. This may be more commonly observed when including the internal mammary nodes (IMN) in the target volume [7-9], or for those patients with unfavourable anatomy (e.g. pectus excavatum). Alternative treatment techniques or modalities may be considered, such as intensity modulated arc therapy (IMAT) or proton bream therapy (PBT). Despite IMAT and PBT facilitating superior target coverage with lower heart and IL doses in such patients [10], the additional cost, resource demands, and low dose bath (IMAT) [11], support why they are not the primary technique or modality selection. Identifying the cases early in the pre-treatment pathway which would result in an undeliverable tangential photon plan, will improve efficiency and reduce treatment delays.

We aimed to identify surrogates predictive of heart and IL dose during the VSim of tangential breast RT, to aid optimal field placement and treatment modality selection.

Methods

Model-Building Cohort

50 patient datasets were retrospectively selected for analysis. To ensure a wide range of heart and IL doses, the eligibility for selection was patients referred for left breast or chest wall RT prior to 2017, when all patients were treated in free-breathing (FB), and not the current standard of deep inspiration breath hold (DIBH), which reduces both heart and IL dose [10].

Patients were positioned supine on a 15 degree inclined breast board with both arms up and supported in a wing-board cradle. They were scanned in 2.5 mm slice thickness from mid neck to the bottom of the lungs.

The target volumes (tumour bed, whole breast or chest wall) and OAR (heart, IL) were manually contoured and fields virtually simulated by advanced breast therapeutic radiographers. Plans were generated using the Varian Eclipse treatment planning system (TPS) and calculated with AAA algorithm v13.7. The prescribed dose was 40.05 Gy in 15# delivered with 6 or 10 MV tangential

photon fields and a non-divergent posterior field border. Fields were optimised to meet ICRU 52/60 planning criteria [5,6] using a combination of wedges and segment fields.

A field contour was manually delineated on the axial slice at the superior and inferior field extent, and interpolated to create a 3D volume. This was modified to exclude any areas where multi-leaf collimators (MLC) were present. The heart and IL contours were automatically duplicated and cropped to remove any part of the volume outside of the VSim fields according to the field contour (Figure 1). This added 2 minutes per case to the VSim process. These were re-labelled HIF and ILF. Percentage of heart-in-field (%HIF) and percentage of IL-in-field (%ILF) were calculated and recorded for each patient. Mean heart dose (MHD) and IL $V18_{Gy}$ (volume of the IL receiving 18 Gy) were recorded from the optimised treatment plan, as reported by the TPS.

Pearson's correlation coefficients and linear regressions were performed between; %HIF and MHD, and between %ILF and IL $V18_{Gy}$. Two-tailed statistical significance was set at $p \leq 0.05$. A strong correlation is defined when r is greater than 0.5 [12]. The shared variance is reported using r squared (R^2) [13].

Validation Cohort

10 left and 10 right-sided cases which included an anterior supraclavicular fossa (SCF) field; and 10 left and 10 right-sided cases including the internal mammary nodes (IMN) using a wide tangential technique and anterior SCF field, were selected from patients referred between August 2019 to August 2020.

The method described above was repeated and the validation data was plotted against the linear regressions of the model-based cohort.

VSim Threshold Values

The upper 95% confidence interval (CI) for the gradient and offset of the corresponding model-building linear regression, were used to calculate maximum point values for %HIF and %ILF to be used during VSim to ensure that MHD and IL $V18_{Gy}$ do not exceed commonly used tolerance doses.

Results

Model-Building Cohort (n50)

The median %HIF was 2.6 (0.4 – 16.7). Median MHD was 2.3 (1.2 - 8.0) Gy.

A statistically significant strong positive relationship was found between %HIF and MHD with R^2 = 0.97, p<.0001. For MHD, the gradient was an increase of 0.4 Gy (95% CI 0.37 - 0.41) per 1%HIF with an offset of 1.2 Gy (95% CI 1.08 - 1.3) (Figure 2).

The median %ILF was 12.1 (2.8 – 33.6). Median IL $V18_{Gy}$ was 12.6 (3.3 to 35) %.

A statistically significant strong positive relationship was found between %ILF and IL $V18_{Gy}$ with R^2 = 0.99, p<.0001. For IL $V18_{Gy}$, the gradient was an increase of 1.03% (95% CI 1.01 - 1.05) per 1%ILF with an offset of 0.3% (95% CI -0.03 - 0.62) (Figure 3).

Validation Cohort (n40)

Due to the implementation of a DIBH technique for all left-sided cases, the number of patients with HIF was lower than for the model-building cohort. 5 of the 10 left-sided cases with an anterior SCF field had HIF, with a median %HIF and MHD of 4.4 (1.1 - 6.3) and 2.6 (1.4 - 4.0) Gy. 4 of the 10 left-sided cases including the IMN within a wide tangential technique and an anterior SCF field, had HIF, with a median %HIF and MHD of 1.4 (0.6 - 8.0) and 2.0 (1.5 - 4.7) Gy.

The median %ILF and IL $V18_{Gy}$ was 20.1 (12.4 - 32.0) and 20.9 (12.4 - 34.4) %.

Plotted along the linear regression of the corresponding model-building cohort, the validation cohort was consistent. This confirms that %HIF and %ILF are predictive surrogates for MHD and IL $V18_{Gy}$ during VSim of left and right-sided cases when treating with; tangentials alone; tangentials with an anterior SCF field and wide tangentials including the IMN and an anterior SCF field.

VSim Threshold Values

To provide maximum point values for %HIF and %ILF during VSim to ensure that tolerance doses for heart and IL are not exceeded, the upper 95% CI for the gradient and offset for each linear regression was used for a number of clinically relevant dose levels (Table 1).

If VSim requires the maximum %HIF or %ILF to be exceeded, where further compromise of target coverage cannot be accepted, the following formulae can be used to estimate MHD and IL $V18_{Gy.}$

MHD (Gy) = (0.4 x %HIF) + 1.2

IL $V18_{Gy}$ % = (1.03 x %ILF) + 0.3

Discussion

Radiotherapy has a significant role in the management of breast cancer, with a large proportion of RT resources assigned to treating this patient group. Small inefficiencies can therefore have a significant negative impact on workload. Optimising the RT pre-treatment pathway by streamlining processes will not only reduce treatment delays, but can release dosimetry, physics and clinician resources for those cases requiring more complex techniques. This was recognised by the Department of Health's Cancer Reform Strategy (2007) [14], and supported the UK-wide implementation of advanced practice therapeutic radiographers [15], with similar strategies emerging globally.

Since the publication by Darby *et* al in 2013 [16], MHD has emerged as an important consideration when planning breast RT. This has been a catalyst for the wide implementation of DIBH for left-sided RT, which is highly successful in keeping MHD to <2 Gy when treating the breast or chest wall alone, as recommended by the RCR [7]. However, with recent changes in the indication to treat the ipsilateral IMN in a subset of high-risk patients, the heart (and IL) has once again become the dose limiting organ [7].

The ability for tangential breast RT to achieve optimum target coverage whilst meeting heart and IL dose constraints can be challenging, particularly (but not exclusively) for patients requiring

irradiation of the IMN, a medial tumour bed, unfavourable anatomy, (pectus excavatum, small lung volume, anterior/lateral heart position), or are unable to perform DIBH.

Various methods are employed during VSim to reduce the amount of heart and IL in the fields such as; reducing the medial and/or lateral tangential field borders, MLC to shield the OAR, or moving the match to be more superior between tangential and anterior SCF fields. However, doing this without a VSim surrogate for heart or IL dose may result in unnecessary compromise to target coverage, or OAR doses exceeding tolerance in the final optimised plan. The latter requires detailed discussion between the dosimetrist and clinical oncologist at the late-stage of plan approval; only days from when the RT course is due to commence. Amending field placement, accepting higher OAR doses, changing to an IMAT technique, or deciding to omit nodal targets, are all possible outcomes which can delay RT starting and will have short-notice resource demands on the clinical oncologist, dosimetrists and physicists. Having OAR dose surrogates during VSim is therefore highly desirable.

Lorenzen *et al* [17] identified a correlation between maximum heart distance and MHD. Despite the linear relationship and R^2 of 0.85, this study did not provide a method for translating this into VSim practice, and is not as accurate at predicting MHD compared to %HIF as identified in our study (R^2 0.97).

Kong et al [18] aimed to define a maximum heart distance threshold for field placement of breast RT. 22 left-sided cases were evaluated, and demonstrated a positive correlation between maximum heart distance and MHD (R^2 0.76). They provided a method to translate these findings during VSim; suggesting that MHD could be approximated as 3 times the maximum heart distance. However, with a smaller R^2 value, this 2-D surrogate is not an accurate predictor of MHD, and may result in either unnecessary compromise to target coverage by the VSim fields, or the optimised plan exceeding MHD tolerance.

Our study has identified %HIF and %ILF as predictive surrogates for heart and IL dose during VSim. With the high R^2 values and narrow confidence intervals for calculating threshold values for %HIF and %ILF, these VSim surrogates will ensure that target coverage compromises will not be made unnecessarily, and that heart and IL tolerances doses will not be unexpectedly exceeded on the final treatment plan. As acknowledged in the RCR guidelines [7], tolerance levels for the OAR are dependent on the extent of the nodal target volumes (+/- SCF, +/- IMN) to be irradiated. We have provided maximum %HIF to achieve MHD tolerance of 2, 4 and 6 Gy (1.7, 6.5 and 11.4%), and maximum %ILF to achieve IL $V18_{Gy}$ of 15%, 25%, 30% and 35% (13.5, 23, 28 and 32.5%). This efficiency-improving addition to the VSim process is easy to implement, adding only 2-minutes per case.

Although our validation cohort has a smaller incidence of HIF compared to the model-building cohort (FB tangentials only) due to implementation of DIBH, not only did this provide additional data at the higher range of IL volume, but also demonstrated that these surrogates can be employed when nodal targets are included; be that with an anterior SCF field or wide tangentials that include the IMN.

It is important to acknowledge that in some cases, a modest increase to OAR dose will be accepted before considering target compromise or an IMAT technique. In such cases where the VSim tolerance of %HIF or %ILF is exceeded, the simple formulae provided can estimate the OAR doses to confirm whether to proceed to dosimetric plan production, or if an alternative technique (IMAT) or modality (PBT) should be considered.

Ranger *et al* [10] reported MHD of 2.5 Gy (± 1.0 SD) when using a DIBH wide tangential technique in a planning study of 14 patients. The mean $V36_{Gy}$ (90% prescribed dose) for the IMN PTV was 77.8% (±7.1 SD), with a dose objective of 90%. This may suggest that the wide tangential fields could have been widened further to improve the IMN dose, whilst still keeping MHD <6 Gy as recommended by the RCR [7]. Using %HIF as a predictive surrogate for MHD would facilitate this during VSim of the wide tangential fields, and may avoid unnecessary use of alternative techniques such as IMAT; which, as well as being resource-heavy to deliver, may be associated with greater normal tissue toxicity [11].

For those centres with limited DIBH provision, using %HIF as a predictive surrogate for MHD during VSim will indicate which patients should be allocated the DIBH technique. This will avoid the delay and wasted resources of needing to produce a dosimetric plan on the FB dataset to confirm that the tolerance dose is exceeded.

Conclusion

Our study identified accurate surrogates for heart and IL dose that can be easily and quickly calculated during VSim of breast RT (+/- nodes). This removes the inefficiencies associated with producing dosimetric plans that exceed tolerance doses and require late-stage changes, and also avoids unnecessary compromise to target coverage where heart and IL doses are below tolerance.

The %HIF and %ILF threshold levels presented in this study have been clinically implemented at our institution during the VSim of breast and chest wall RT (+/- nodes) for all patients, to optimise tangential field placement and identify early in the pre-treatment pathway which patients will require IMAT. The parameters of these equations have been generated from local data and other centres should establish the relationship that is valid for their local techniques and planning system.

The validation data for MHD is small as DIBH is effective at reducing HIF, however, when observing the data displayed tightly amongst that of the model-building cohort, this supports %HIF as a strong surrogate for MHD. The extensive %ILF validation data gives reassurance that both %HIF and %ILF are reliable dose surrogates as rely on the same in-field dose relationship.

Future Work

The ability to predict heart and IL dose from the diagnostic staging CT scan for patients most likely to have unacceptably high OAR doses (e.g. those requiring IMN RT or with pectus excavatum), by using %HIF and %ILF, may further optimise radiotherapy pathways, but would need validation. This may be particularly useful to identify eligibility for PBT national referral or clinical trials.

Figures & Tables

Figure 1: Axial, sagittal and coronal views of field, ILF and HIF contours

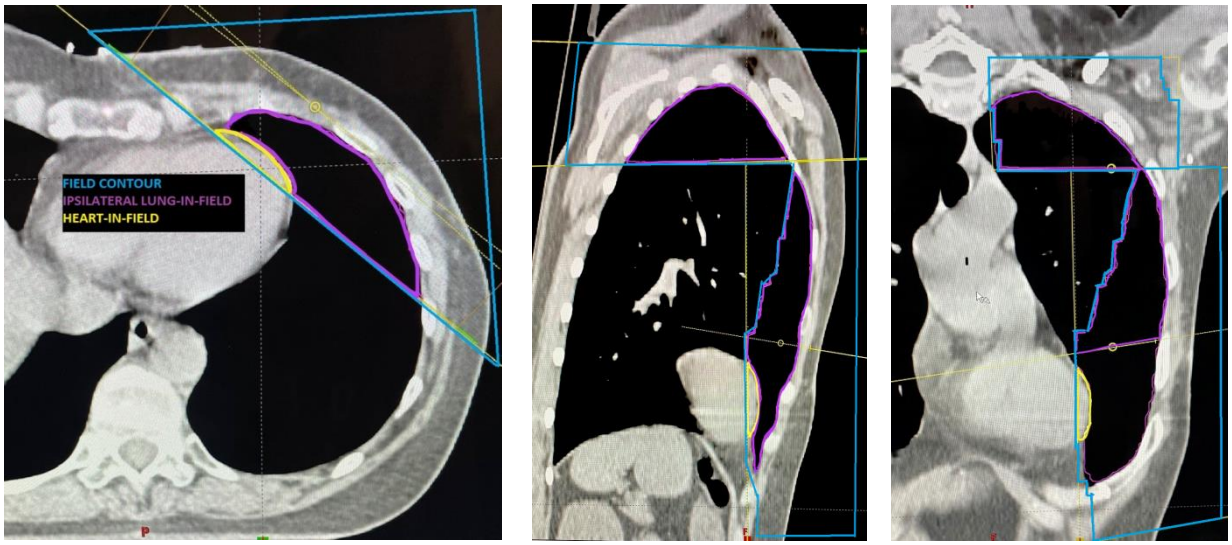


Figure 2: Correlation between Mean Heart Dose (MHD) and percentage of heart in the virtually simulated fields (%HIF).

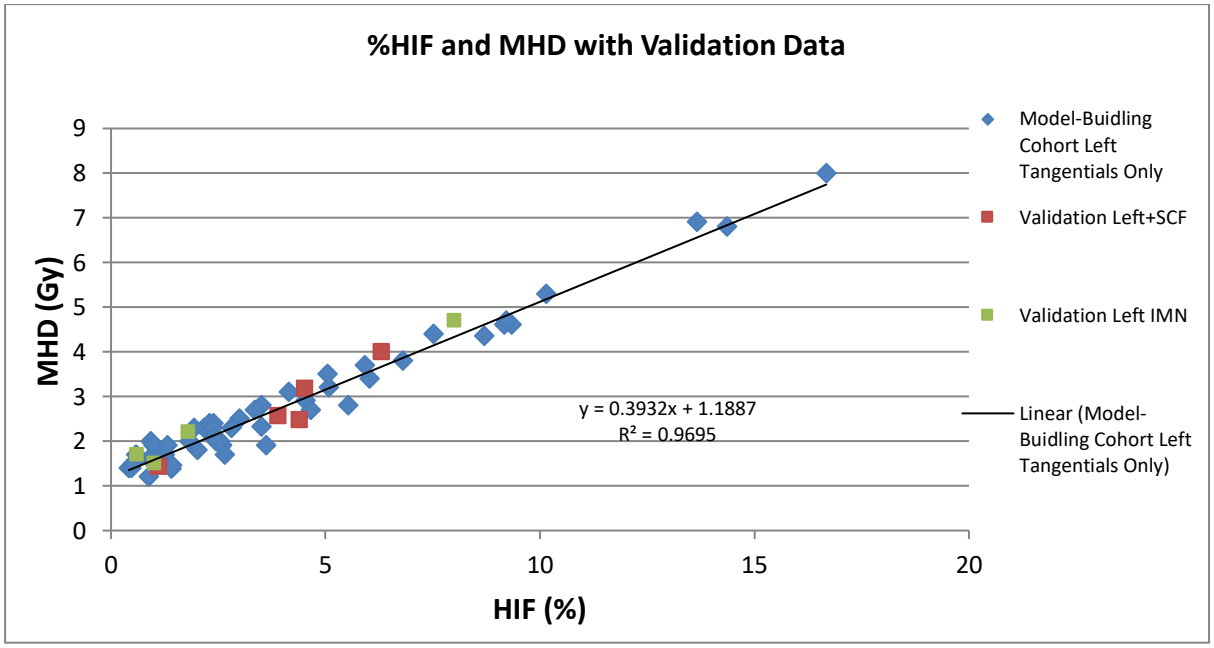
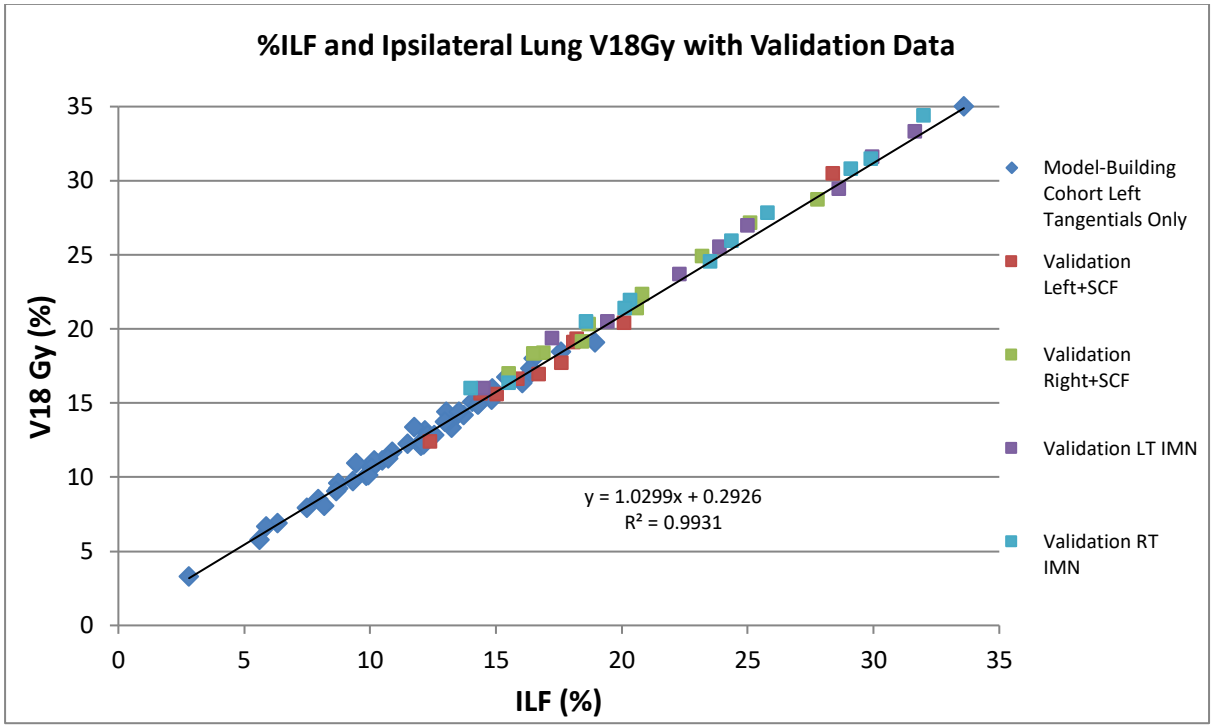


Figure 3: Correlation between Volume of Ipsilateral Lung Receiving 18 Gy ($V18_{Gy}$) and percentage of ipsilateral lung in virtually simulated fields (%ILF)



Tables

Table 1: Maximum point values for %HIF and %ILF during VSim for MHD and IL V18 $_{Gy}$ tolerance doses

MHD Tolerance (Gy)	Maximum %HIF
2.0	1.7
4.0	6.5
6.0	11.4
IL $V18_{Gy}$ Tolerance (%)	Maximum %ILF
15	13.5
25	23.0
30	28.0
35	32.5

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