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Short Communication

Axillary radiotherapy for nodal lymphoma: What CTV expansion is required to account for absence of pre-chemotherapy treatment position FDG PET-CT?

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ABSTRACT

Involved site lymphoma radiotherapy clinical target volumes (CTV) require expansion in the absence of treatment-position pre-chemotherapy PET-CT. This prospective imaging study evaluates CTV contouring for axillary lymphoma using diagnostic imaging compared with co-registered treatment-position PET-CT. Generous expansion axially and cranio-caudally is required to encompass pre-chemotherapy disease without treatment-position pre-chemotherapy PET-CT.

1. Introduction

There has been considerable progress in reducing radiotherapy target volumes in lymphoma patients to minimise late complications whilst maintaining local control [1–3]. The concept of involved node radiotherapy (INRT) was developed with the aim of treating only prior sites of lymph node involvement [1]. INRT requires the acquisition of a pre-chemotherapy Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography – computed tomography (PET-CT) scan in the radiotherapy treatment position with the use of the relevant radiotherapy immobilisation devices and subsequent co-registration to the post-chemotherapy radiotherapy planning CT scan. However, few centres routinely acquire a pre-chemotherapy FDG PET-CT in the potential radiotherapy treatment position [4]. The concept of involved site radiotherapy (ISRT) has been developed by the International Lymphoma Radiotherapy Oncology Group (ILROG) [2,3]. The ILROG guidelines provide guidance on delineating a clinical target volume (CTV) to encompass pre-chemotherapy disease, modified to anatomical boundaries, with an additional expansion to account for any uncertainty in defining pre-chemotherapy disease (including the quality and position of pre-chemotherapy imaging, response to chemotherapy, knowledge of potential subclinical extent, volume changes since imaging, proximity to critical structures) with modification to anatomical boundaries. This CTV expansion is essentially based upon clinical judgement [4]. The UK National Cancer Research Institute Lymphoma Radiotherapy Group [5] also developed ISRT guidelines and attempted to quantify the required CTV expansion specifying 1.5 cm craniocaudally in the direction of lymphatic spread with no axial expansion.

There is little data to guide the necessary CTV expansion to account for the absence of pre-chemotherapy imaging in the radiotherapy position. We have performed a prospective imaging study aiming to quantify the required CTV expansion, and have previously reported results for patients requiring head and neck radiotherapy [6]. Axillary radiotherapy is a less common scenario although CTV delineation is particularly challenging compared with the head and neck region, with differences in arm position between scans and less well defined anatomical landmarks. Here, we report data from patients in our imaging study with axillary nodal disease.

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2. Methods

2.1. Study outline

This is a report on patients with axillary nodal disease included within a prospective single centre imaging study. Inclusion criteria were: age ≥18 years old, histologically proven Hodgkins Lymphoma (HL) or high grade non-Hodgkins Lymphoma (NHL), World Health Organization Performance status 0–2, Ann Arbor Stage I/II disease based upon clinical examination and any radiology investigations previously performed, residual disease in situ after biopsy, PET-CT staging not yet performed, clinical decision that sequential chemotherapy and radiotherapy will be the recommended treatment if stage I/II disease is confirmed on subsequent PET-CT staging. This study was approved by the Research Ethics Committee. Trial registration: ISRCTN Registry: ISRCTN46587767.

A total of 19 patients provided written informed consent and were recruited between October 2013 and January 2016; 3 of the patients who subsequently received chemotherapy and radiotherapy had axillary nodal disease.

2.2. PET-CT imaging

A 5-point thermoplastic immobilisation mask was fabricated prior to PET-CT acquisition, with arms by sides. FDG PET-CT imaging was performed as previously described [6]. A diagnostic half-body PET-CT with arms up on a soft head support was initially performed 60 min following a 400 MBq injection of FDG intravenously; if patients were not able to tolerate the arms up position an arms down position was used. A dedicated contrast-enhanced PET-CT of the axillary region was then acquired with the immobilization mask in place with a radiotherapy head rest, arms down (3–4 bed positions, 2 min per bed position).

2.3. Radiotherapy CT planning scan

The thermoplastic mask fabricated for the pre-chemotherapy PET-CT scan was fitted to assess whether the fit remained optimal. If this was not the case, a new thermoplastic mask was made attempting to maintain a similar neck position. The CT planning scan was acquired with intravenous contrast and 2 or 3 mm slice thickness (dependent upon institutional protocols at the time).

2.4. CTV contouring

Contouring was performed by an experienced radiation oncologist with access to clinical data and diagnostic imaging. To minimise recall, a minimum two week interval was mandated prior to contouring for each individual patient using different methods.

2.5. Contouring using side-by-side assessment of PET-CT acquired in diagnostic position ($CTV_{diagPET}$)

A post-chemotherapy CTV aiming to encompass initially involved lymphoma tissue was contoured using the pre-chemotherapy diagnostic position PET-CT by side-by-side assessment (blinded to treatment position PET-CT), taking into account changes in lymphoma volume and anatomical changes, whilst accounting for anatomical boundaries. To allow quantification of the 'errors' introduced by contouring without optimal co-registered imaging, no additional CTV expansion was undertaken ($CTV_{diagPET}$).

2.6. Contouring using co-registration of PET-CT acquired in radiotherapy position to planning CT scan (CTV_{INRT})

Contouring was performed according to the principles of the ILROG guidelines [2,3] and as previously described [6] (CTV_{INRT}). The contrast-enhanced pre-chemotherapy PET-CT acquired in the radiotherapy position was used to manually contour a gross tumour volume (GTV). Manual rigid registration was undertaken matching to the chest wall and local soft-tissue in the region of the delineated GTV using Mirada RTx v1.4 software (Mirada Medical, Oxford, UK).

3. Data analysis

3.1. Assessment of superior and inferior CTV extent

Distance between the superior slices of the CTV_{INRT} and $CTV_{diagPET}$ was recorded. Distance was similarly recorded for inferior slices.

3.2. Positional analysis

Positional metrics were used to compare CTVs in the axial plane as previously described [6,7]. The most superior and inferior overlapping slices of the CTVs (CTV_{INRT} and $CTV_{diagPET}$) were defined as the limits of the volume, excluding differences in the superior-inferior CTV length from influencing positional metrics. Positional metrics were calculated using ImSimQA software (v3.1.5, OSL, Shrewsbury, UK): Mean distance to conformity (MDC); Centre of gravity distance (CGD); DICE index; conformality index (CI); sensitivity index (Se. Idx). For the CTV_{INRT} and $CTV_{diagPET}$ axial plane comparison, the Se. Idx. calculated the overlap between $CTV_{diagPET}$ and CTV_{INRT} as a percentage of the volume of CTV_{INRT}.

3.3. Statistics

Linear mixed effects models were used to determine the significance of the differences between CTV_{INRT} and $CTV_{diagPET}$ [8]. A significant ρ-value was considered to be $\rho < 0.05$.

4. Results

3 patients who entered the study subsequently received axillary radiotherapy. Patients 1 and 3 had Hodgkin's lymphoma and patient 2 diffuse large B cell lymphoma; age range 21–70 years; mean pre-chemotherapy GTV 78 cm^3 (range 33–141). Each patient had received chemotherapy prior to planning for radiotherapy. Patient 1 had the diagnostic PET-CT scan arms down due to discomfort maintaining an arms-up position. (Fig. 1 provides an example of CTV_{INRT} and $CTV_{diagPET}$ in axial and coronal images.)

4.1. Intra-observer variation in CTV generation

Intra-observer variation in delineating CTV_{INRT} and $CTV_{diagPET}$ on 3 occasions for each patient are summarised in Table 1. Variation CTV extent was large for $CTV_{diagPET}$, with a mean of 7 mm superiorly and 13 mm inferiorly. By contrast, CTV_{INRT} varied by only a single CT slice (2–3 mm) superiorly and inferiorly. Similarly, CTV_{INRT} was significantly more reproducible in the axial plane compared with $CTV_{diagPET}$ for all positional metrics.

4.2. Comparison of CTV_{INRT} and $CTV_{diagPET}$: Superior and inferior extent

Table 2 summarises CTV volumes and differences in the superior and inferior boundaries of CTV_{INRT} and $CTV_{diagPET}$. Overall vol-

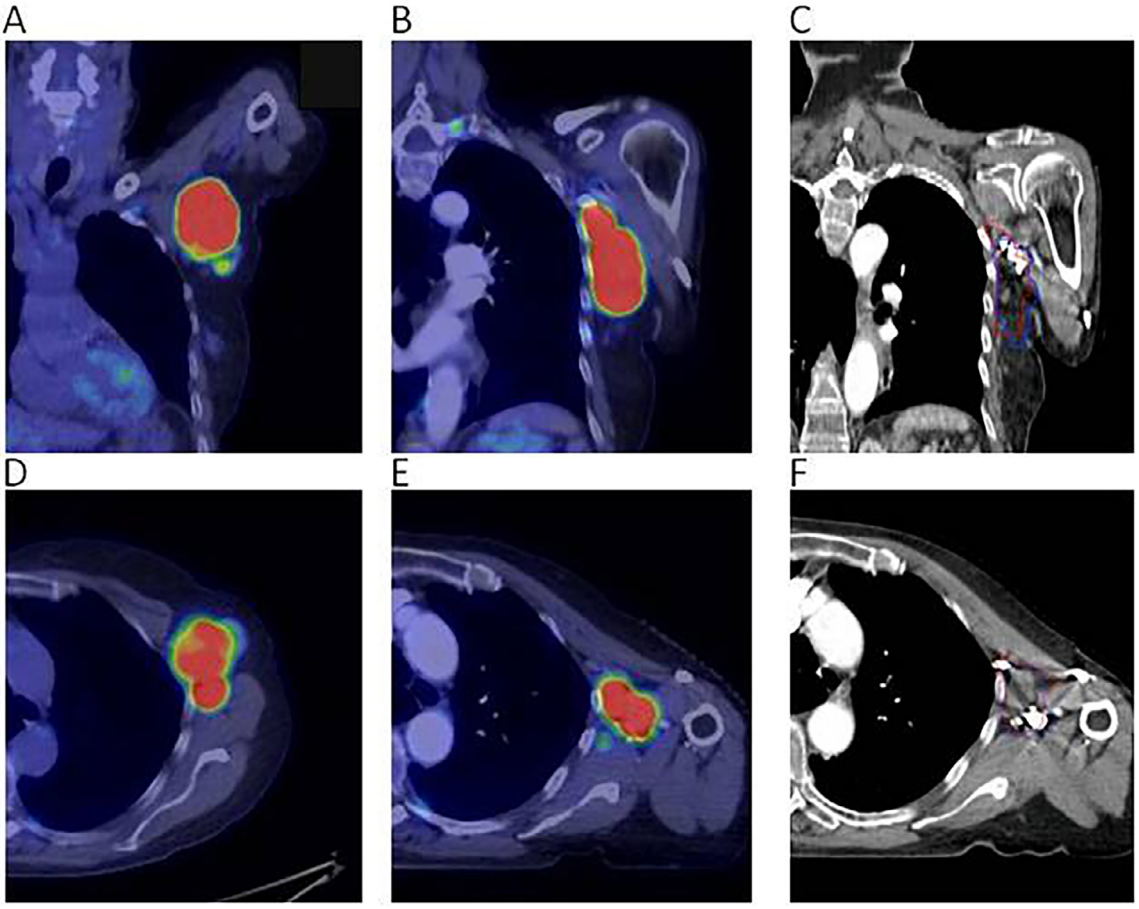

Fig. 1. Comparison of cranio-caudal length of CTV_{INRT} and $CTV_{diagPET}$ in the coronal plane in a patient with stage I diffuse large B cell lymphoma of left axilla treated with 3 cycles of chemotherapy followed by radiotherapy. In coronal plane A) represents pre-chemotherapy FDG PET-CT acquired in the routine arms up diagnostic position, B) represents pre-chemotherapy PET-CT in treatment position with a radiotherapy mask, C) planning CT scan with CTV_{INRT} (blue) (contoured using co-registered pre-chemotherapy radiotherapy treatment-position PET-CT) and $CTV_{diagPET}$ (red) (contoured using side-by-side assessment of diagnostic PET-CT). In the axial plane D) and E) show pre-chemotherapy FDG PET-CT in arms up diagnostic position and treatment position arms down respectively, E) planning CT scan with CTV_{INRT} (blue) and $CTV_{diagPET}$ (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Intra-observer variation in the delineation of CTV_{INRT} and $CTV_{diagPET}$.

	Patient	CI	MDC (mm)	CGD (mm)	DICE	Superior and inferior extent variation (mm)	
						Superior	Inferior
CTV_{INRT}	1	0.59	4.60	3.24	0.78	0	2
	2	0.61	4.72	3.32	0.83	3	3
	3	0.65	3.86	1.30	0.80	2	0
	Mean	0.62	4.39	2.62	0.80	1.7	1.7
$CTV_{diagPET}$	1	0.47	7.78	9.12	0.70	12	24
	2	0.47	7.36	3.86	0.72	9	15
	3	0.61	4.26	2.68	0.77	4	4
	Mean	0.52	6.47	5.22	0.73	7.3	13.3
P-value (CTV_{INRT} vs. $CTV_{diagPET}$)		0.001	<0.001	0.01	<0.001	–	–

CTV = clinical target volume; CoG = centre of gravity distance; CI = conformality index; MDC = mean distance to conformity; Se.Idx = sensitivity index.

umes were similar for patients 2 and 3, although $CTV_{diagPET}$ was larger for patient 1. For the superior CTV extent, $CTV_{diagPET}$ varied by +2 to 21 mm beyond CTV_{INRT}. The inferior CTV extent, $CTV_{diagPET}$ varied by −27 to +12 mm. Based upon these data, there were considerable discrepancies between the superior and inferior extents of $CTV_{diagPET}$ and CTV_{INRT}; for patient 2 an additional 27 mm was required inferiorly beyond $CTV_{diagPET}$ to ensure that CTV_{INRT} was included.

4.3. Comparison of CTV_{INRT} and $CTV_{diagPET}$: Axial plane

Table 2 shows the positional metrics used to compare CTV_{INRT} and $CTV_{diagPET}$ in the axial plane (data based on CTVs within overlapping lengths). Overall there was considerable differences between CTV_{INRT} and $CTV_{diagPET}$ contours in the axial plane. Mean DICE index was limited at 0.63 (range 0.61–0.65). Mean differences in CGD was 5 mm (range 2.5–10.0). Mean Se.Idx was 0.68 (range

Table 2
CTV_{INRT} and $CTV_{diagPET}$ volumes and their variation in superior and inferior extent.

Patient	Variation in superior-inferior CTV extent						Comparison of CTVs in axial plane				
	Volume (cm^3)			CoG (mm) (Sup-Inf direction)	Margins from CTV_{INRT} to $CTV_{diagPET}$ (mm)*		CI	MDC (mm)	CGD (mm)	DICE	Se.Idx
	CTV_{INRT}	$CTV_{diagPET}$	Difference (%)		Superior	Inferior					
1	67	110	+66	4.3	2	12	0.40	9.74	10.07	0.63	0.79
2	109	114	+5	3.0	21	-27	0.43	12.06	3.69	0.61	0.63
3	54	53	−2	1.1	12	0	0.48	6.43	2.45	0.65	0.63
Mean	76	92	+21	2.8	9	-2	0.44	9.41	5.40	0.63	0.68
Stdev	34	29	–	1.6	6	15	0.04	2.83	4.09	0.02	0.09

CTV = clinical target volume; CoG = centre of gravity distance; CI = conformality index; MDC = mean distance to conformity; Se.Idx = sensitivity index.
* '−'indicates undercontouring and '+' indicates overcontouring over $CTV_{diagPET}$ compared with CTV_{INRT}.

0.63–0.79), indicating that a mean of 68% of CTV_{INRT} was contained within $CTV_{diagPET}$ in the axial plane. MDC includes both over- and underlap of contours. Mean and maximum MDC undercoverage (areas of undercoverage of CTV_{INRT} by $CTV_{diagPET}$) were 4 and 16.4 mm respectively. Mean and maximum MDC overcoverage (regions of $CTV_{diagPET}$ which are non-overlapping with CTV_{INRT}) was 5.5 and 18.3 mm respectively.

5. Discussion

No previous studies have evaluated the CTV expansion required for axillary radiotherapy. The treatment position FDG PET-CT in this prospective study allows the generation of INRT CTVs which represent a 'gold standard' for comparison with CTVs contoured using non-registered diagnostic non-treatment position PET-CT. This report aims to evaluate differences in $CTV_{diagPET}$ compared with CTV_{INRT} to inform on appropriate CTV margin expansions for ISRT for axillary radiotherapy.

Intra-observer variability was assessed to provide a guide to the reproducibility CTV contouring. Variation in the cranio-caudal CTV extent was low for CTV_{INRT} (maximum of 3 mm superior-inferior variation) but higher for $CTV_{diagPET}$ (maximum 24 mm superiorly and 12 mm inferiorly). Similarly, CTV_{INRT} was significantly more reproducible in the axial plane based on assessment of all positional metrics.

CTV_{INRT} and $CTV_{diagPET}$ were compared in craniocaudal extent and in the axial plane. The maximum distance of 'under-contouring' of the $CTV_{diagPET}$ compared with the 'gold-standard' CTV_{INRT} was 27 mm inferiorly. The maximum 'over-contouring' of the $CTV_{diagPET}$ was 21 mm superiorly and 15 mm inferiorly. There was only limited conformality between CTV_{INRT} and $CTV_{diagPET}$ in the axial plane, with a mean DICE of 0.63 (range 0.61–0.65). The mean Se.Idx was 0.68 (range 0.63–0.79) meaning that in the axial plane a mean of 68% of the CTV_{INRT} was encompassed by the $CTV_{diagPET}$, implying a significant risk of geographical miss with the $CTV_{diagPET}$ if an appropriate CTV expansion is not added to account for this inaccuracy. The maximum MDC under coverage was 16.4 mm (mean 4 mm). These data are despite modification to anatomical boundaries and suggest a generous approach is required in the axial plane. One patient in this study (patient 1) had the diagnostic PET-CT with arms down due to discomfort maintaining the arms up position. It might be considered that this would assist in contouring the $CTV_{diagPET}$, although it is notable that there remained considerable cranio-caudal differences and similar positional metrics in the axial planes to the other two patients.

These data indicate the potential inaccuracy of contouring an axillary CTV in the absence of treatment-position PET-CT. As only 3 patients from our imaging study had axillary disease, this analysis cannot explore the extent of variability in CTV contouring between patients with small/large volume disease and different sites within the axilla. However, analysis shows high intra-observer variability, considerable craniocaudal over- and under-contouring, and limited conformality in the axial plane for $CTV_{diagPET}$. Contouring of $CTV_{diagPET}$ in patients with axillary disease appears considerably less accurate than for neck disease based on our prior data [6]. This is likely to relate to the large positional differences between anatomy in the axilla depending upon arm position and the lack of obvious anatomical landmarks by comparison with the neck.

Our practice has been to deliver axillary radiotherapy arms down with a 5-point thermoplastic mask which we have found to optimise of reproducibility of shoulder/arm position and allow simpler treatment of adjacent neck if required. Other treatment positions are feasible e.g. arms up on a wing board which may offer some separation of target volume from the lungs; this can match the pre-chemotherapy arms up PET-CT position although unless identical immobilisation devices are used positions will still differ. Clearly these data cannot be directly applied to different treatment positions. However, the variability shown highlights the importance attempting to obtain optimal treatment-position imaging pre-chemotherapy. In the absence of optimal pre-chemotherapy imaging clinical judgement is necessary in CTV construction based upon ease in re-constructing the pre-chemotherapy extent of disease. These data demonstrate the difficulty of accurate tumour reconstruction in the axilla and the need to carefully consider margins to avoid geographic misses.

In summary, our small cohort demonstrated that a generous CTV expansion is required cranio-caudally and in the axial plane to ensure the pre-chemotherapy extent of axillary disease is encompassed. Centres should attempt to acquire pre-chemotherapy PET-CT as close to the treatment position as possible to improve the accuracy of contouring and allow smaller CTVs.

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Conflicts of interest

We have no conflicts of interest to declare.

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