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PET-CT in lymphoma

# Evaluation of clinical target volume expansion required for involved site neck radiotherapy for lymphoma to account for the absence of a pre-chemotherapy PET-CT in the radiotherapy treatment position

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ABSTRACT

*Background and purpose:* Involved site radiotherapy clinical target volume (CTV) for lymphoma requires an expansion to account for the absence of radiotherapy treatment-position pre-chemotherapy imaging, which is not widely implemented. This prospective imaging study aims to quantify CTV expansion required for neck radiotherapy.

*Materials and methods:* 10 patients from a prospective single centre imaging study underwent a pre-chemotherapy FDG-PET-CT in both the diagnostic and radiotherapy treatment position, and subsequently received neck radiotherapy post-chemotherapy. $CTV_{INRT}$ and $CTV_{diagPET}$ were delineated on the planning CT, following co-registration of the radiotherapy position PET-CT and side-by-side assessment of diagnostic PET-CT respectively.

*Results:* Intra-observer variability was limited, with delineation of $CTV_{INRT}$ highly reproducible and slightly lower for $CTV_{diagPET}$ (mean DICE 0.88 and 0.8 respectively). Superiorly, $CTV_{diagPET}$ varied by −10 to +15 mm from $CTV_{INRT}$. Inferiorly, $CTV_{diagPET}$ varied by −18 to +6 mm from $CTV_{INRT}$. Comparing $CTV_{INRT}$ and $CTV_{diagPET}$ in the axial plane, the mean DICE was 0.74. Mean sensitivity index was 0.75 (range 0.59–0.91), showing that on average 75% of the $CTV_{INRT}$ was encompassed by the $CTV_{diagPET}$.

*Conclusions:* In the absence of treatment-position PET-CT, CTV expansion cranially and caudally by 10 mm and 18 mm respectively, along with generous contouring in the axial plane, was required to encompass pre-chemotherapy disease.

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Radiotherapy continues to be widely used as part of curative treatment for Hodgkin (HL) and non-Hodgkin lymphoma (NHL). Late treatment-related complications have been highlighted, with second malignancy and cardiac toxicity identified as the most common cause of non-lymphoma deaths in HL survivors [1–3]. Radiotherapy dose to the head and neck region has been shown to increase stroke risk [4]. Multiple studies have demonstrated that complications are related to the irradiated volume [5,6].

Modern lymphoma radiotherapy delivery aims to maintain local control rates whilst minimising radiation dose to normal tissues [7–10]. In 2006 Girinsky et al. [10] introduced the concept of involved nodal radiotherapy (INRT). INRT aims to treat only prior sites of nodal involvement and requires the acquisition of a pre-chemotherapy 2-[$^{18}$Fluorine]-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography – computed tomography (PET-CT) in the radiotherapy treatment position with appropriate radiotherapy immobilisation devices with rigid co-registration to the post-chemotherapy planning CT. However, most centres have been unable to implement the requirement for INRT of a pre-chemotherapy PET-CT in the radiotherapy treatment position [11]. The International Lymphoma Radiation Oncology Group (ILROG) developed widely applicable guidelines for involved site radiotherapy (ISRT) [7,8]. In situations in which radiotherapy is delivered as part of combined modality treatment, the clinical target volume (CTV) is designed to encompass the extent of disease pre-chemotherapy, modified to anatomical boundaries, and expanded to account for any uncertainties in defining the pre-chemotherapy extent of disease, including the quality, position and accuracy of imaging [7,8], depending upon clinical judgement [11]. INRT is regarded as ISRT when pre-chemotherapy PET-CT in the radiotherapy treatment position is available [7].

To date, there has been no data available to directly guide the expansion in CTV to account for the absence of optimal pre-chemotherapy imaging. In this prospective imaging study a series

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of patients underwent a pre-chemotherapy FDG PET-CT in both standard diagnostic and radiotherapy treatment positions. This study aims to evaluate the magnitude of uncertainty introduced into CTV delineation for nodal neck disease in the absence of a radiotherapy-position pre-chemotherapy PET-CT, in order to quantitatively inform on appropriate CTV expansion.

## Methods

### *Study outline*

This is a prospective single centre imaging study in patients with HL or high grade NHL with clinical ± radiological (pre-PET-CT) stage I/II disease potentially suitable for treatment with sequential chemotherapy and radiotherapy (pending PET-CT staging outcome). The imaging protocol incorporates a pre-chemotherapy FDG-PET-CT acquired according to standard diagnostic protocols and, using the same FDG injection, acquisition of an additional FDG-PET-CT scan with intravenous contrast with limited coverage of the head and neck region in the radiotherapy treatment position using radiotherapy mask immobilisation. Treatment was delivered according to institutional clinical protocols.

### *Patient selection and recruitment*

Inclusion criteria were: age $\geq$18 years old, male or female, histologically proven HL or high grade NHL, World Health Organisation (WHO) 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 were recruited between October 2013 and January 2016. All patients provided informed written consent. 12/19 patients subsequently underwent treatment with chemotherapy followed by radiotherapy. 10 of these patients underwent radiotherapy to the neck region and form the basis of this report.

### *PET-CT imaging*

A 5-point thermoplastic immobilisation mask was fabricated prior to PET-CT acquisition, with arms by sides; neck position was determined by the anatomical location of known disease and was either extended or neutral. FDG PET-CT imaging was performed on a 64-section GE Discovery 690 PET-CT system (GE Healthcare, Amersham, UK) with a flat couch top. A standard diagnostic half-body PET-CT with arms up on a soft head support was performed 60 min following a 400 MBq injection of FDG intravenously. A dedicated PET-CT of the head and neck 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) from skull vertex to carina. The CT component of the head and neck acquisition was obtained after a 25 s delay following a bolus of 100 ml of iodinated contrast (Niopam 300, Bracco Ltd, High Wycombe, UK) injected at 3 ml/s using the following settings; 120 kV, variable mA (min 10, max 600, noise index 12.2), tube rotation 0.5 s per rotation, pitch 0.969 with a 2.5 mm slice reconstruction.

### *Radiotherapy CT planning scan*

For patients who were subsequently treated with radiotherapy following chemotherapy 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).

### *CTV contouring*

Contouring was performed by radiation oncologists in a single centre specialising in the treatment of lymphoma, with access to clinical history and findings of clinical examination. When contouring using side-by-side assessment the clinician was blinded to the treatment position PET-CT. To minimise potential for recall, a minimum two week interval was mandated prior to generating contours for each individual patient using different methods.

### *Contouring using co-registration of PET-CT acquired in radiotherapy position to planning CT scan*

Contouring was performed according to the principles of the ILROG guidelines [7,8]. The contrast-enhanced pre-chemotherapy PET-CT acquired in the radiotherapy position was used to manually contour a gross tumour volume (GTV) based on the morphology of the CT and a GTV based upon the PET images, using predefined window and colour settings (SUV scale 0–7, volcano colour scale for overlayed images). Rigid registration over the whole image was undertaken using Mirada RTx v1.4 software (Mirada Medical, Oxford, UK). All registrations were assessed for clinical suitability by a radiation oncologist. The post-chemotherapy CTV ($CTV_{INRT}$) was contoured, taking into account the co-registered pre-chemotherapy GTV and changes in lymphoma volume and anatomical position, whilst accounting for anatomical boundaries.

### *Contouring using side-by-side assessment of PET-CT acquired in diagnostic position*

This simulates a situation in which optimal pre-chemotherapy PET-CT imaging in the treatment position is not available ($CTV_{diagPET}$). 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, 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.

### *Data analysis*

#### *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.

#### *Positional analysis*

Positional metrics were used to compare CTVs in the axial plane. 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 also used