

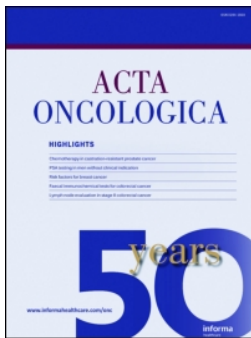
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## Interobserver delineation uncertainty in involved-node radiation therapy (INRT) for early-stage Hodgkin lymphoma: on behalf of the Radiotherapy Committee of the EORTC lymphoma group

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ORIGINAL ARTICLE

## Interobserver delineation uncertainty in involved-node radiation therapy (INRT) for early-stage Hodgkin lymphoma: on behalf of the Radiotherapy Committee of the EORTC lymphoma group

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### ABSTRACT

**Background and purpose:** In early-stage classical Hodgkin lymphoma (HL) the target volume nowadays consists of the volume of the originally involved nodes. Delineation of this volume on a post-chemotherapy CT-scan is challenging. We report on the interobserver variability in target volume definition and its impact on resulting treatment plans.

**Materials and methods:** Two representative cases were selected (1: male, stage IB, localization: left axilla; 2: female, stage IIB, localizations: mediastinum and bilateral neck). Eight experienced observers individually defined the clinical target volume (CTV) using involved-node radiotherapy (INRT) as defined by the EORTC-GELA guidelines for the H10 trial. A consensus contour was generated and the standard deviation computed. We investigated the overlap between observer and consensus contour [Sørensen-Dice coefficient (DSC)] and the magnitude of gross deviations between the surfaces of the observer and consensus contour (Hausdorff distance). 3D-conformal (3D-CRT) and intensity-modulated radiotherapy (IMRT) plans were calculated for each contour in order to investigate the impact of interobserver variability on each treatment modality. Similar target coverage was enforced for all plans.

**Results:** The median CTV was 120 cm<sup>3</sup> (IQR: 95–173 cm<sup>3</sup>) for Case 1, and 255 cm<sup>3</sup> (IQR: 183–293 cm<sup>3</sup>) for Case 2. DSC values were generally high (>0.7), and Hausdorff distances were about 30 mm. The SDs between all observer contours, providing an estimate of the systematic error associated with delineation uncertainty, ranged from 1.9 to 3.8 mm (median: 3.2 mm). Variations in mean dose resulting from different observer contours were small and were not higher in IMRT plans than in 3D-CRT plans.

**Conclusions:** We observed considerable differences in target volume delineation, but the systematic delineation uncertainty of around 3 mm is comparable to that reported in other tumour sites.

This report is a first step towards calculating an evidence-based planning target volume margin for INRT in HL.

### ARTICLE HISTORY


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## Introduction

Radiotherapy (RT) for Hodgkin lymphoma (HL) has changed dramatically during the past decades. When RT was the primary treatment modality, very extensive treatment fields were used to encompass not only the macroscopic lymphoma but also possible microscopic disease. Total or subtotal nodal irradiation encompassing all the major lymph node areas was used routinely in early stage disease. With the advent of effective chemotherapy, it became clear that these large prophylactic treatment fields were no longer needed [1] and involved-field RT (IFRT), including only regions with involved lymph nodes, became the standard [2]. Soon after, studies of patients treated with chemotherapy alone showed

that recurrences occurred most often at the site of initial macroscopic lymphoma involvement [3]. Using FDG-PET to identify this initial involvement, and modern 3-dimensional (3D) conformal treatment planning to target it, it became possible to reduce the treatment volume even further. The EORTC (European Organisation for the Research and Treatment of Cancer) Lymphoma Group pioneered this limited RT for early stage HL, called involved-node radiotherapy (INRT) [4,5]. With INRT, the clinical target volume (CTV) includes only the volume of initially involved lymph nodes, as identified on PET/CT before chemotherapy is administered, without compromising the effectiveness of the treatment [6–8].

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Conformal radiotherapy makes precise target definition essential in all treatment sites. In HL, and in other types of lymphomas as well, these issues are particularly challenging because of the highly variable anatomical disease localizations among patients and because of the inherent difficulty of defining the pre-chemotherapy lymphoma volume on a post-chemotherapy planning CT-scan. In addition, the CTV also includes volumes looking suspicious on CT but not PET positive. Genovesi et al. [9] reported variations in CTV volumes of up to 1000 cm<sup>3</sup> among observers contouring IFRT in supra-diaphragmatic HL without information from FDG-PET scans and in the absence of contouring guidelines. Piva et al. [10] reported similar results in a case of primary mediastinal B-cell lymphoma, despite using deformable image registration to fuse pre- and post-chemotherapy images. Though these reports have raised awareness about the challenges of delineation in HL, they do not reflect a 'best case scenario' context in which INRT can be applied, namely having the pre-chemotherapy PET/CT scan performed in treatment position in order to minimize the geometric uncertainties related to image fusion with the post-chemotherapy planning CT-scan.

In this study, we report on the interobserver variability in target volume delineation in close to optimal pre- and post-chemotherapy imaging conditions as defined by the published INRT guidelines [4] and using the expertise from the Radiotherapy Committee of The EORTC Lymphoma Group. We also investigate whether the dosimetric impact of this interobserver variation is greater for more conformal techniques [such as intensity-modulated radiotherapy (IMRT) than for 3D-conformal (3D-CRT)].

## Materials and methods

### Patient material

In order to test the EORTC-GELA (Groupe d'Etude des Lymphomes de l'Adulte, presently known as the Lymphoma Study Association or LYSA) contouring guidelines for INRT as applied in the H10 trial [6], two cases, typical of early stage HL, were selected. Case no. 1 (male) had clinical stage (CS) IB disease in the left axilla and was treated with four cycles of ABVD (Adriamycin, Bleomycin, Vinblastine and Dacarbazine) followed by INRT. Case no. 2 (female) had CS IIB disease in the mediastinum and bilateral neck and was treated with six cycles of ABVD followed by INRT.

The patients were scanned as recommended in the INRT guidelines [4]. Both patients were staged using whole body 18F-Fluorodeoxyglucose (FDG) PET/CT-scans performed before chemotherapy (from now referred to as 'the pre-chemo PET/CT scan'). The pre-chemo PET/CT scans were acquired on a Siemens Biograph 40 (Siemens Healthineers, Erlangen, Germany) exactly 1 hour after injection of 400 MBq of FDG. Care was taken to acquire these images on a flat table top and in the same position as would later be used for the radiotherapy planning CT scan performed after chemotherapy (referred to as 'the post-chemo CT scan'). The initial PET-positive volume was defined by visual evaluation of the FDG uptake, and was contoured on the pre-chemo PET/CT-scan by a nuclear medicine specialist as was standard practice in the host institution.

### Contouring process

Contouring on the post-chemo CT scan and radiotherapy planning were carried out using the Eclipse® software from Varian Medical Systems (Palo Alto, CA). Scans and information were all anonymized and all contouring was performed at the institution where the patients were treated.

Eight individual radiation oncologists, each highly experienced in contouring for HL, participated in this study met at the host institution in order to contour on separate computers over the course of a single day and were blinded both to each other's contours and to the contours used for the patients' treatment. One of them (Observer 2) contoured in collaboration with an experienced radiologist, as was standard practice in their institution. All observers contoured the initially involved volume on the pre-chemo PET/CT-scan with the help of the already contoured PET-positive volume. The decision as to which lymph nodes were involved initially was made on the basis of all available information including clinical and radiological information, the post-chemo CT-scan and published guidelines [11]. The pre-chemo images were then fused with the post-chemo CT-scan. Each observer then modified the contours of the initially involved volume on the post-chemo CT-scan to allow for shrinkage of tissues from pre- to post-chemo scans, and to allow for uncertainties as deemed necessary. The resulting volume, defined as the tissue volume that contained the initially involved lymph nodes, was named the CTV and defined the tissue volume that each observer considered as needing irradiation.

### Assessment of the interobserver variability

The CTV and planning target volume (PTV) from all observers were reported for each case. In order to facilitate the presentation of the data, a consensus contour was generated using an expectation-maximization algorithm for simultaneous truth and performance level estimation ('STAPLE' [12]) integrated in the publicly available research environment CERR [13] with a confidence level of 80% (chosen after visual evaluation). This algorithm has previously been used for the assessment of interobserver variation in radiotherapy [14,15]; in principle, the algorithm considers the whole collection of submitted CTV contours and generates a probabilistic estimate of the 'true' CTV contour. The overlap between observer and consensus contour was investigated using the Sørensen-Dice similarity coefficient (DSC) [16,17], defined as:

$$DSC = \frac{2(A \cap B)}{A + B}$$

The magnitude of gross deviations between the surfaces of the observer and consensus contour was investigated using the Hausdorff distance [18] defined as:

'Hausdorff distance' ( $H_d$ ) or the maximum separation between two contours:  $H_d(X, Y) = \max_{x \in X}(\min_{y \in Y} d(x, y))$ .

In the context of radiotherapy, the Hausdorff distance can be thought of as reflecting the difference in beam aperture designed for different target volumes.

An ideal agreement between the surfaces of contours would then translate into a DSC of 1 and Hausdorff distance of 0 mm.

**Table 1.** Volume and overlap data for Case 1. Sørensen-Dice coefficients (DSC) and Hausdorff distances are calculated for the CTV volumes with respect to the consensus contour.

Observer	CTV (cm <sup>3</sup> )	PTV (cm <sup>3</sup> )	DSC	Hausdorff (mm)
1	215	615	0.73	28.1
2	99	347	0.69	29.9
3	162	449	0.80	17.4
4	128	405	0.80	18.5
5	206	544	0.88	11.0
6	84	364	0.64	14.9
7	112	354	0.74	35.1
8	21	373	0.24	47.5
Median	120	389	0.74	23.3
Consensus	176	544	ref	ref

All metrics were computed using the freeware 3D Slicer version 4.4 ([www.slicer.org](http://www.slicer.org) [19]) and the extension SlicerRT [20].

The interobserver variation can be handled as a geometric uncertainty and included in the PTV margin using a margin recipe as a systematic geometric error [21]. In order to derive the systematic uncertainty resulting from the interobserver variation in this study, an in-house matlab script was designed to calculate the SD between the surfaces of the observer contours in 6 directions (anterior, posterior, superior, inferior, right and left). Using the margin recipe described by van Herk [22], the SD can then be multiplied by 2.5 in order to provide a margin estimate accounting only for the interobserver variation (i.e. assuming other geometric uncertainties such as organ motion or patient set-up are equal to 0).

### Treatment planning

In more conformal techniques such as IMRT, interobserver variability may have a larger impact on the resulting dose distribution compared to simple forms of 3D-CRT (e.g. two opposing fields). In order to test this hypothesis, treatment plans were made based on each contour from the eight observers, using the current standard CTV-to-PTV margins recommended in the International Lymphoma Radiation Oncology Group (ILROG) guidelines [23]: a 1 cm isotropic margin was added, except for the case with mediastinal involvement (Case 2) where a 1.5 cm margin was added in the superior-inferior direction, as is recommended to account for respiration motion. All PTVs were then retracted 5 mm under the skin. For each set of contours, a 3D-CRT plan and an IMRT plan were generated. 3D-CRT plans often consisted of two opposing fields, with the addition of smaller fields to improve the dose homogeneity ('field-in-field'). IMRT plans used 4–5 different beam angles chosen to minimize entry through the organs at risk. The dose to the PTV was specified as 30.6 Gy in 17 fractions, 5 fractions per week. A total of  $2 \times 2 \times 8$  treatment plans were calculated using the Analytic Anisotropic Algorithm (version 13, Varian Medical Systems). Similar target coverage was enforced for all plans, so that 95% of the PTV received at least 95% of the prescribed dose. The maximum dose accepted in the PTV (or any part of the body) was 107% of the prescribed dose. For IMRT plans, constraints were applied on the heart, lungs and female breasts (for Case 2) to achieve 'as low as possible' a dose to those organs. The resulting mean doses to the heart and lungs, as well as the percentage of body volume receiving over 95% of the prescribed dose (V95%), were estimated for both

**Table 2.** Volume and overlap data for Case 2. Sørensen-Dice coefficients (DSC) and Hausdorff distances are calculated for the CTV volumes with respect to the consensus contour.

Observer	CTV (cm <sup>3</sup> )	PTV (cm <sup>3</sup> )	DSC	Hausdorff (mm)
1	370	986	0.74	30.8
2	192	653	0.74	19.2
3	336	827	0.87	11.0
4	240	689	0.81	18.1
5	279	780	0.89	13.2
6	157	620	0.67	20.9
7	270	728	0.88	12.6
8	141	874	0.64	17.5
Median	255	754	0.78	17.8
Consensus	298	858	ref	ref

cases. For Case 2, the mean dose to the female breasts, thyroid and carotid artery were also reported.

## Results

### Assessment of the interobserver variability

The volumes of the CTVs defined by the eight observers and their associated PTVs are shown in Tables 1 and 2. The median CTV was 120 cm<sup>3</sup> (IQR: 95–173 cm<sup>3</sup>) for Case 1, and 255 cm<sup>3</sup> (IQR: 183–293 cm<sup>3</sup>). Compared to the consensus contours, this represented variations of –155% to 39% for Case 1 and of –157% to 72% for Case 2. These variations were carried on to the PTV volumes, with differences up to 268 cm<sup>3</sup> for Case 1 and 366 cm<sup>3</sup> for Case 2.

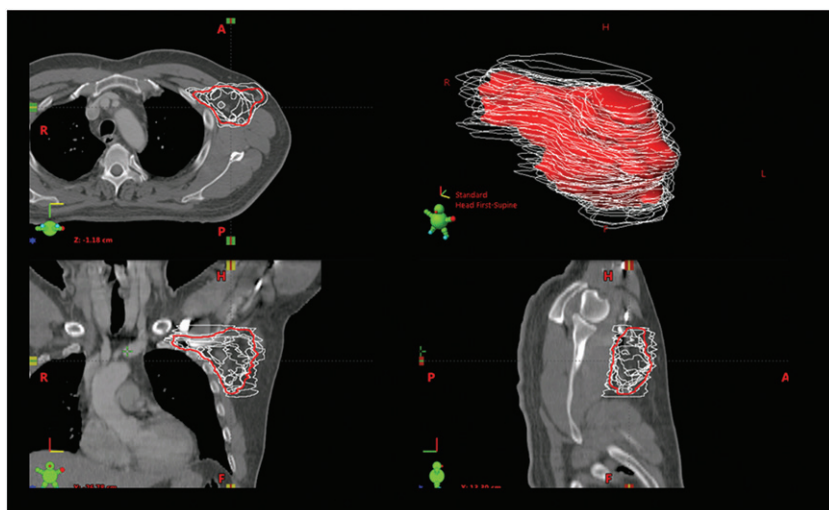
Representative slices with all observer contours as well the consensus contour are shown in Figures 1 and 2. DSC values were generally high (>0.7), and the Hausdorff distances were around 30 mm, with the notable exception of Observer 8 (Case 1), where the CTV was drawn as small 'islands' (visible in Figure 1). This configuration, however, did not lead to a smaller PTV size than for other observers: the PTV for Observer 8 is very close to the median PTV (373 vs. 389 cm<sup>3</sup>) even though the CTV was five times smaller than the median CTV.

The systematic uncertainty resulting from interobserver variation, expressed as the SD between all observer contours in each direction, is reported in Supplementary Table S1 and ranged between 1.9 and 3.8 mm, with a median of 3.2 mm.

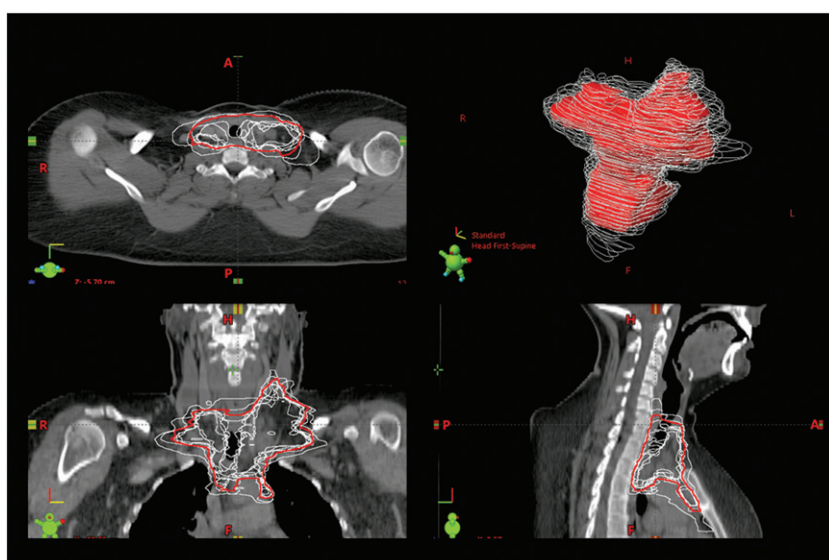
### Impact on treatment planning

All plans satisfied the PTV coverage criterion of 95% of the prescription dose to 95% of the PTV. The maximum dose allowed was kept under 107%, though this condition was difficult to fulfil for 3D-CRT plans and small hot spots of up to 110% were occasionally accepted. The DVHs for the heart and lungs are presented in Figures 3 and 4.

The resulting mean doses to the heart were low; around 0.3 Gy for Case 1 and 0.9 Gy for Case 2 (see Supplementary Tables S2 and S3). For Case 1, variations in mean dose were under 0.2 Gy for the heart and 1.2 Gy for the lungs across the group of observers, considering both treatment modalities. For Case 2, mean heart dose variations were under 0.4 Gy with the noticeable exception of Observer 7. There, the CTV encompassed more tissue in the inferior direction (Figure 2) and consequently led to a noticeably higher dose to the heart (for both modalities) and lungs (for IMRT) as observed by the DVHs in Figure 4. The resulting mean heart dose was



**Figure 1.** Delineations from the eight expert observers (in white) and generated consensus contour (in red) for Case 1. Note the presence of a contour drawn as small 'islands', especially visible in the transverse view (top left).



**Figure 2.** Delineations from the eight expert observers (in white) and generated consensus contour (in red) for Case 2. Note that one observer included more tissue in the inferior direction, towards the heart. This is especially visible in the sagittal view (bottom right).

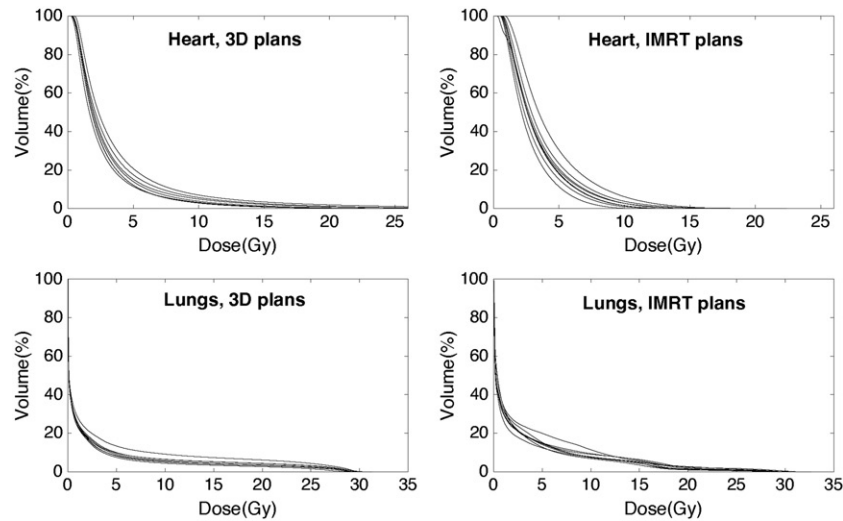
then increased to 4.4Gy (3D CRT) and 3.7Gy (IMRT) in Supplementary Table S3. This increase was also present though less pronounced for the lungs and the breasts (Supplementary Table S4).

## Discussion

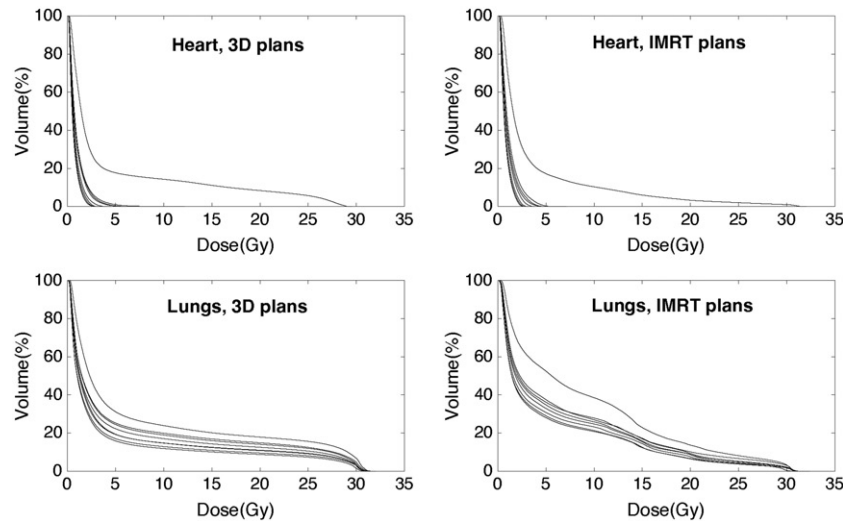
Inter- and intraobserver differences in the contouring of the gross tumour volume (GTV) and CTV have been reported in many tumour types and introduce a systematic geometrical uncertainty that must be taken into account in the subsequent planning process [22]. Quantifying this uncertainty is a difficult process and is usually performed using one or two representative patient examples [9,10,14]. Interobserver studies cannot claim to represent a whole clinical area or reflect the range of complexity of all patient cases. However, such studies offer a baseline for what is achievable, and a benchmark for other institutions developing their own treatment procedures and delineation guidelines. In our study, we chose to present two

typical (as opposed to challenging) HL cases and to include only experts in the group of observers. Combined to the close-to-optimal imaging conditions and INRT approach, we believe it represents a 'best case scenario' situation which is substantially different from the two previously published reports of delineation uncertainty in HL [9,10].

Contouring for radiotherapy in the setting of modern combined modality treatment of early stage HL poses special challenges. In this situation, a volume which contained lymphoma before chemotherapy is contoured on a post-chemotherapy scan where most or all of the initial lymphoma has disappeared, and where shrinkage and deformation of the surrounding normal tissues have happened to varying degrees. This resembles in many ways the situation of post-operative radiotherapy in other tumour types, e.g. in head and neck cancer. In view of these challenges, it is reassuring to observe that the interobserver variability was on the same order of magnitude as has been reported for other indications, such as locally advanced lung cancer (4–5 mm [24]),



**Figure 3.** DVH of the dose received by the heart and for all observer contours in Case 1. Results are shown for 3D conformal plans (left) as well as intensity-modulated radiotherapy plans (right).



**Figure 4.** DVH of the dose received by the heart and for all observer contours in Case 2. Results are shown for 3D conformal plans (left) as well as intensity-modulated radiotherapy plans (right).

breast-conserving radiotherapy (2–8 mm, estimated from [25]) or prostate cancer (1.7–3.5 mm [22]).

It should, however, be noted that this level of confidence can only be achieved with dedicated radiation oncologists, knowledgeable of the disease, as well as an optimal use of imaging. It is strongly recommended to use PET as part of the pre-chemotherapy evaluation when planning to use highly conformal IMRT after chemotherapy, as PET significantly improves the detection of involved sites in patients with HL [26,27]. It is also recommended that the pre-chemotherapy PET/CT-scan be acquired with the patient in the same position as will later be used for RT. Strict adherence to this principle is necessary if fusion of the pre-chemotherapy PET/CT images with the post-chemotherapy planning CT-images is to be used successfully. If this is not achievable, or if in spite of correct positioning the fusion of the pre- and post-chemotherapy images remains sub-optimal (e.g. if the patient loses weight), those additional uncertainties will mandate the use of larger margins to secure coverage of the initially involved volume [23].

In this study, the interobserver variability led to marked differences in CTV volume. These differences are mitigated by the generation of the PTV margin, though large discrepancies remain. For example, for Case 1, the PTV size for Observer 1 is almost double that for Observer 2. The impact of this variability on the dose to OARs appears modest, as the disease location was favourably far from major OARs in both cases. The mean doses to the heart, lung and breasts were slightly higher with IMRT than with 3D-CRT but all remained very low. There is one notable exception: for Case 2, Observer 7, the mean heart dose was about 3.5 Gy higher than for all other observers, even though the corresponding PTV size, DSC and Hausdorff distance were all well within the reported range for other observers. This illustrates two things: (1) that all the mentioned metrics fail to fully represent the variability in doses received by the OARs and (2) that a few millimeters of difference in contouring can have a considerable impact on the dose to neighbouring OARs. This last difference will likely become even more substantial for novel treatment modalities such as proton therapy. Though a

certain degree of variability is inevitable even within an expert group, efforts such as guidelines or 'collaborative' contouring (with at least two observers present at the time of delineation) have been suggested to effectively decrease the risk of outliers and should be encouraged.

Determining the SD between the observer contours is a first step towards calculating an evidence-based PTV margin for INRT in HL. The present results suggest that the systematic delineation uncertainty is around 3 mm, which alone would result in a CTV to PTV margin of almost 8 mm (according to the van Herk's formula [22]), very close to the 10 mm recommended by ILROG. In practice, other uncertainties, such as image fusion and patient set-up, must be included in a thorough margin recipe and can only increase the total PTV margin required. The limitations of our study include the small number of patient cases and relatively small number of observers. The clinical cases selected for this study, though fairly typical of early-stage HL, have smaller target volumes than the cases selected by Genovesi et al. [9] and Piva et al. [10], which could limit the comparison between these three studies in addition to the differences in imaging conditions already stated. Finally, all observers in this study were experienced with contouring for INRT for HL, and this might not reflect the experience of less experienced centres, or of centres using Involved Site radiotherapy (ISRT). Even bearing these limitations in mind, we believe that those results illustrate the potential of guidelines and standardization, both for pre- and post-chemotherapy imaging as well as for delineation of the CTV.

## Conclusions

CTV volumes varied considerably between observers in both clinical cases. However, the systematic delineation uncertainty was around 3 mm and is comparable to that reported in other clinical situations. Results suggest that the dosimetric impact of interobserver variation is not larger for IMRT than for 3D-CRT. This study demonstrates that contouring target volumes for conformal INRT in HL can be performed with the same interobserver variability as can be achieved in other tumour types.

## Disclosure statement

The authors have no conflict of interest regarding the data presented in this manuscript.

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