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FULL PAPER

PET/CT-guided treatment planning for paediatric cancer patients: a simulation study of proton and conventional photon therapy

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Objective: To investigate the impact of including fluorine-18 fludeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) scanning in the planning of paediatric radiotherapy (RT).

Methods: Target volumes were first delineated without and subsequently re-delineated with access to ¹⁸F-FDG PET scan information, on duplicate CT sets. RT plans were generated for three-dimensional conformal photon RT (3DCRT) and intensity-modulated proton therapy (IMPT). The results were evaluated by comparison of target volumes, target dose coverage parameters, normal tissue complication probability (NTCP) and estimated risk of secondary cancer (SC).

Results: Considerable deviations between CT- and PET/CT-guided target volumes were seen in 3 out of the 11 patients studied. However, averaging over the whole cohort, CT or PET/CT guidance introduced no significant

difference in the shape or size of the target volumes, target dose coverage, irradiated volumes, estimated NTCP or SC risk, neither for IMPT nor 3DCRT.

Conclusion: Our results imply that the inclusion of PET/CT scans in the RT planning process could have considerable impact for individual patients. There were no general trends of increasing or decreasing irradiated volumes, suggesting that the long-term morbidity of RT in childhood would on average remain largely unaffected.

Advances in knowledge: ¹⁸F-FDG PET-based RT planning does not systematically change NTCP or SC risk for paediatric cancer patients compared with CT only. 3 out of 11 patients had a distinct change of target volumes when PET-guided planning was introduced. Dice and mismatch metrics are not sufficient to assess the consequences of target volume differences in the context of RT.

Owing to the rapid technological development during the last two decades, the importance of radiotherapy (RT) in curative regimens of many childhood and adolescent cancers has increased.^{1,2} One of the key advancements is the implementation of intensity-modulated RT modalities, which enable a highly conformal dose distribution to the target volume. The improved conformity usually results in lower doses to organs at risk (OARs) in the proximity of the target volume, at the cost of a larger proportion of healthy tissue receiving low doses of radiation. As the dose gradient between the target volume and the immediate surrounding tissue is steeper, the necessity of including all malignant tissue in the target volume increases. Therefore, diagnostic information from imaging techniques such as

positron emission tomography (PET) and MRI have become valuable complements to CT imaging, which is still the basis for RT planning and dose calculation.^{3–7}

In cancer diagnostics and tumour staging, PET and PET/CT performed using fluorine-18 fludeoxyglucose (¹⁸F-FDG) has been shown to provide valuable information about local tumour extent, lymph node involvement and potential distant metastases, supplementing the anatomical information from a CT scan.^{4,8–13} For adult patients, several studies indicate that PET/CT may influence RT planning and increase the agreement between physical tumour extent (determined from biopsies) and the volume delineated on diagnostic images (compared with CT only).^{14,15}

This has led to an increasing interest in and use of combined PET/CT in paediatric radiation oncology as well.^{16–27} However, conclusions drawn from adults regarding the impact of PET on target volume delineation, and the resulting risks of RT-induced side effects, may not be accurate for paediatric patients owing to differences in body constitution and internal anatomy.^{28–30} Theoretically, ¹⁸F-FDG PET information may cause an increase of target volume, by indicating that the primary tumour is more extensive than that seen on CT, or lead to a changed stage of the disease, owing to detection of involved locoregional lymph nodes or metastatic spread. This may possibly lead to increasing the total volume of irradiated tissue (*i.e.* increasing the integral dose), causing a higher risk of normal tissue complications. On the other hand, when areas of suspected malignancy on CT images are ¹⁸F-FDG negative and/or when the tumour volume is challenging to define using CT only, the ¹⁸F-FDG PET data could lead to a diminished target volume (if the tissue can be determined as clearly non-malignant), which in turn would lead to a reduction of the irradiated normal tissue volume. The latter is often the case for patients with lung cancer, where ¹⁸F-FDG PET helps to tell tumour growth apart from atelectasis.³¹

Children are more sensitive to radiation-induced toxicity than are adults and have a longer life expectancy, in which radiation-induced damage can develop and potentially compromise quality of life. It is of uttermost importance to minimize the irradiated volume of healthy tissue as well as to reduce the dose to tumour-adjacent healthy organs for paediatric cancer patients. Consequently, there is an increasing demand for highly conformal RT techniques, such as proton therapy (PT), for paediatric cancer patients. As PT often provides even sharper dose gradients than does highly conformal photon therapy, correct target volume delineation will most likely be even more critical.^{32–38}

In this study, we examine the impact of the information from ¹⁸F-FDG PET scans on the size and shape of target volumes of paediatric cancer patients. We also study the resulting effect on the RT plans for conventional photon radiotherapy [three dimensional conformal photon RT (3DCRT)] and modern PT by means of treatment planning simulation. We chose to use 3DCRT in our study, as this is available to all modern RT centres and is the most commonly applied RT technique for paediatric patients worldwide. RT plan quality is evaluated using standard metrics derived from treatment planning simulation, as quantitative measures of tumour control probability are not available for most paediatric cancers and is beyond the scope of this study. The CT- and PET/CT-guided treatment plans are evaluated in terms of long-term complication risk, using risk models based on dose–response data from published clinical studies.

METHODS AND MATERIALS

Patients

A total of 51 paediatric patients had been ¹⁸F-FDG PET/CT scanned for staging and RT planning at Rigshospitalet, Copenhagen, Denmark, between 2005 and 2012. Out of these, 25 patients were excluded because of different positioning during the PET/CT scan and/or because different CT scans were ultimately used for the RT planning. Out of the remaining 26 patients, we randomly selected 11 paediatric patients, PET/CT

scanned on a flat tabletop and positioned with the same immobilization devices as would be used in RT delivery, for inclusion in this study (Table 1). The patients represent different primary cancers and anatomical locations, presenting a wide range of RT planning challenges and various treatment plan complexities. The patient with Hodgkin lymphoma was enrolled in a prospective clinical protocol (KF01-178/04) approved by the local scientific ethics committee.

All patients were scanned with Siemens Biograph Sensation 64 (2011), Siemens Biograph Sensation 16 (2005–2007, 2009) or Siemens Biograph 40 (2008) (Siemens Healthcare, Erlangen, Germany). Patients were fasting for at least 6 h prior to the injection of ¹⁸F-FDG, which in turn was administered 60 min before the scan.

Target volume delineation

Gross tumour volumes (GTVs) and clinical target volumes (CTVs) were retrospectively delineated by a team of three senior physicians: one radiologist, one nuclear medicine physician and one radiation oncologist. Targets were defined in accordance with definitions in ICRU 50 and 62,^{39,40} first without and subsequently with access to an ¹⁸F-FDG PET guidance volume, in random patient order. For the PET/CT-based target volumes, the workflow followed the clinical routine at Rigshospitalet:

- (1) A nuclear medicine physician delineated the PET guidance volume in collaboration with a radiologist. No automatic segmentation or thresholding technique was used.
- (2) The GTV was then delineated by a radiologist specialized in RT planning. Depending on the clinical case, information from additional examinations (*e.g.* MRI, ultrasound or palpation) performed prior to RT planning was available as well as the option to consult with other physicians.
- (3) The CTV was delineated by a radiation oncologist, principally following recommendations for RT of soft-tissue sarcoma (CWS-2002P). In general, CTV of the main tumour (CTV-T) was generated by the addition of an isotropic margin of 1 cm to the GTV and modified to ensure that areas with potential subclinical disease were covered as well as tailored around anatomical structures without evidence of tumour infiltration (*e.g.* air cavities and uninvolved bone). Elective CTVs [high-risk (CTV-EH) and low-risk (CTV-EL)] were employed for three patients with head and neck (H&N) tumours.

The same order of work was employed for the CT-based target volumes (TV_{CT}), excluding the first step. All delineations were made by the same three physicians.

For practical reasons, it was considered unfeasible to completely and accurately distinguish between the information in the patients' written records resulting from PET and the information based solely on other examinations such as CT, palpation or ultrasound. Thus, the delineating physicians received the same written clinical information when delineating the TV_{CT} as when delineating the corresponding PET/CT-based target volumes (TV_{PETCT}). Notes explicitly originating from PET scans were removed in both situations. Accordingly, the only difference between the two situations was the presence of the PET guidance volume.

Table 1. Patient information, size (cm³) of target volumes, dice similarity coefficients (DSCs) and prescribed doses

Patient number	Year of treatment	Age (years)	Weight (kg)/height (cm)	Gender	Tumour	¹⁸ F-FDG PET positive	Administered activity ¹⁸ F-FDG (MBq kg ⁻¹)	Gross tumour volume			Clinical target volume			Prescribed dose to planning target volume (Gy _{RBE})
								CT	PET/CT	DSC	CT	PET/CT	DSC	
1	2011	4	16/101	F	Sarcoma (abdomen)	Yes	3.9	72	68	0.88	288	274	0.95	55
2	2009	16	40/158	F	Sarcoma (abdomen/pelvis)	No	7.2	44	44	0.88	201	205	0.95	50.4
3	2009	7	22/122	F	Angiosarcoma (head/neck)	Yes	4.0	28	25	0.89	98	102	0.94	63
4	2007	16	57/171	M	Sarcoma (abdomen/pelvis)	Yes	7.3	143	126	0.89	462	435	0.91	30
5	2006	6	N/A	F	Ewing's sarcoma (head/neck) Ewing's sarcoma (pelvis)	No	N/A	16	17	0.89	96	101	0.94	18 (boost)
								3	3	0.80	51	49	0.90	
6	2005	2	N/A	F	Rhabdomyosarcoma (head/neck)	Yes	N/A	17	17	0.85	71	63	0.90	58
7	2008	10	37/140	M	Hodgkin's lymphoma (head/neck)	Yes	3.1	97	85	0.83	396	379	0.93	19.8
8	2011	16	53/180	M	NSCLC (lung)	Yes	4.3	23	21	0.79	260	212	0.87	66
9	2011	18	100/192	M	B-cell lymphoma (head/neck)	Yes	4.1	13	14	0.86	164	151	0.91	36
10	2007	18	65/186	M	Nasopharyngeal carcinoma (head/neck)	Yes	6.1	112	124	0.80	424	438	0.84	68
11	2006	17	57/170	M	Nasopharyngeal carcinoma (head/neck)	Yes	7.5	57	64	0.80	305	326	0.88	68
Mean														
Median														
Range														

F, female; ¹⁸F-FDG, fluorine-18 fludeoxyglucose; M, male; N/A, not applicable; NSCLC, non-small-cell lung cancer; PET, positron emission tomography.

Two of the patients were PET negative, meaning that the ^{18}F -FDG accumulation was not higher than what would normally be expected. However, this was not a patient exclusion criterion as any knowledge about the PET status may be informative for the physician delineating the target volumes. No PET guidance volumes were defined for these patients, but a new set of GTVs and CTVs (still named “PET/CT-based”) were delineated.

Treatment planning and dose prescription

Planning target volumes [primary PTV (PTV-T), PTV-EH] and PTV-EL] were defined as a 6-mm spatially uniform expansion of corresponding CTVs (see Target volume delineation section), in accordance with the recommendations in CWS-2002P (6 out of 11 patients had been diagnosed with sarcoma).⁴¹ The same margin was used for all patients and treatment modalities regardless of the tumour type, anatomical location or RT modality, to simplify treatment planning and comparisons. There were no indications of skin infiltration in any of the patients, and therefore all PTVs were kept 2–3 mm inside the body contour.

To ensure symmetrical irradiation of the vertebral bodies, and reduce the risk of uneven bone growth, a supplementary target volume was added whenever target volumes were adjacent to, or overlapping with, the vertebral column. This was defined as the spinal column surrounded by a 6-mm margin and prescribed a dose of 20 Gy for both treatment modalities.^{42–44}

RT plans with curative, or locally curative, intent were generated using a commercial treatment planning system (EclipseTM v. 11.0; Varian® Medical Systems, Palo Alto, CA) for 3DCRT and spot-scanned intensity-modulated PT (IMPT). With duplicate sets of target volumes, this resulted in a total of four RT plans per patient. The prescribed therapeutic doses were retrieved from clinical records. For each patient, RT plans for both modalities were prescribed the same cobalt gray-equivalent (CGE or GyE) dose, denoted Gy_{RBE} .⁴⁵ Thus, for the delivery of proton plans, a relative biological effectiveness (RBE) of 1.1 would be accounted for.

The main priority of the treatment planning was target coverage (striving for PTVs to be covered by 95–107% of the prescription dose), unless the OAR was considered to be vital and the doses to the organ would seriously compromise the quality of life or survival of the patient. In order to generate clinically acceptable plans, published organ-specific dose objectives relevant for paediatric RT were used.^{38,46–48} Brain, medulla (with PRV margin of 6 mm), brainstem and skeletal structures were considered in the RT planning process, as were the structures used for risk estimations (Appendix B). All plans were normalized to the mean dose of the PTV.

For each patient and modality, the RT planning strategy was identical in terms of field set-up (e.g. gantry angles, wedges, blocks etc.) as well as basic OAR priority order for both TV_{PETCT} and TV_{CT} . More details on the treatment plans are available in Appendix A.

Evaluation of target volumes

The dice similarity coefficient (DSC) was the primary method used to compare the different target volumes [Equation (1)]. For the sets A and B, the DSC is calculated by dividing the

intersection of the two sets by their union, which in this study translates into dividing the volume shared by the TV_{CT} and the TV_{PETCT} by the sum of the two target volumes. A DSC of zero implies that there is no overlap at all, and a value of one indicates perfect agreement.

DSC quantifies the overlap between volumes but does not describe how they overlap, for example, which one expands beyond the other. Therefore, another helpful quantity was also used: the mismatch (MM), which shows whether adding the PET scan information causes unanimous change of the target volumes.¹⁴ In situations with distinct size differences, the MM reveals if the smaller volume is entirely within the larger volume [Equation (2)]. For the two types of target volumes in this study, the MM of TV_{CT} to TV_{PETCT} is the size of the part of TV_{CT} not included in TV_{PETCT} , divided by the absolute TV_{PETCT} . The result describes the percentage by which TV_{PETCT} would have to increase in order to cover the TV_{CT} . If the entire TV_{CT} is inside the contours of the TV_{PETCT} , the MM between TV_{CT} and TV_{PETCT} is zero (the numerator becomes zero, as there is no TV_{CT} that is not included in TV_{PETCT}) indicating that TV_{PETCT} does not need to increase to include TV_{CT} .

$$\text{DSC} = \frac{2|\text{TV}_{\text{CT}} \cap \text{TV}_{\text{PETCT}}|}{|\text{TV}_{\text{CT}} \cup \text{TV}_{\text{PETCT}}|} \quad (1)$$

$$\text{MM} = \frac{|\text{TV}_{\text{CT}} \setminus \text{TV}_{\text{PETCT}}|}{|\text{TV}_{\text{PETCT}}|} \quad (2)$$

Statistical analysis

Statistical analyses were performed using Wilcoxon signed-rank tests (IBM SPSS® Statistics v. 20; IBM Corporation, Armonk, NY) comparing the different quantitative metrics. In this exploratory analysis, unadjusted p -values <0.05 were considered to indicate statistically significant differences.

Plan quality

Target coverage for the PTV was evaluated in terms of homogeneity index, defined as the ratio of the PTV receiving $\geq 95\%$ and $\leq 107\%$ of the prescribed dose.

The volume of irradiated healthy tissue, defined as the entire patient volume excluding all PTVs receiving a dose $>0.001 \text{ Gy}_{\text{RBE}}$, was also assessed.

Risk estimations

Normal tissue complication probability

A thorough literature search resulted in non-cancer normal tissue complication probability (NTCP) models for 11 end points relevant for the patients in this study (Appendix B). Although considerable effort was made, adequate studies on paediatric patients were not available for all organs of interest. For these sites, data from adult patients representing the most radiosensitive model were used. Doses per fraction ranged between 1.8 and $3.0 \text{ Gy}_{\text{RBE}}$. However, since the absolute risks were not of interest in this study, merely the relative risks between the plans optimized for TV_{PETCT} and TV_{CT} , respectively, no fractionation correction was applied.

Secondary cancer

Models describing the excess hazard ratio of contracting localized solid secondary cancers (SCs) in the breast, lung, ventricle and thyroid have been previously published.^{61,62} These models account for parameters such as age at exposure and attained age and gender, and allow for estimation of the lifetime cumulative risk of developing the respective SC.

RESULTS

Evaluation of target volumes

The sizes of all target volumes and all DSCs are presented in Table 1 and Figure 1 (the PTVs and the elective target volumes are presented in Appendix D). For some patients, the introduction of PET introduced large variations, but there was no general impact for the whole cohort on average.

The TV_{CT} were generally slightly larger than their PET/CT-based counterparts: the ratio between CT-based and PET/CT-based GTVs was on average 1.02 (median, 1.02; range, 0.88–1.14) and the corresponding ratio for CTVs was 1.04 (median, 1.04; range, 0.93–1.23).

The mismatched volume showed that the CT-based CTV on average would have to increase by 7.1% (median, 5.5%; range, 1.4–19.6%) in order to cover the PET/CT-based CTV. The PET/CT-based CTV would have to increase by 11.5% (median, 11.7%; range, 3.1–25.4%) in order to cover the CT-based CTV (all mismatched volumes are presented in Appendix D). In other words,

Figure 1. The volume of CT-based and positron emission tomography (PET)/CT-based gross tumour volumes (GTVs) (red) and clinical target volumes (CTVs) (turquoise) (12 of each). Circles are target volumes located in head and neck (H&N) region, square icons are non-H&N target volumes (located in the abdomen, pelvis or thorax). Median GTV changes were found in Patients 6 and 5, for which CT-based GTV was 1.2% and 3.7% larger than PET/CT-based GTV, respectively. Median CTV changes were found in the same patients, CT-based CTV was 4.3% and 4.5% larger. For colour images please see online: www.birpublications.org/doi/full/10.1259/bjr.20140586.

Comparison of CT- and PET/CT-based target volumes

none of the CT-based CTVs was entirely within the corresponding PET/CT-based volumes, and vice versa.

Whether PET data have added additional information to the tumour delineation is difficult to determine from merely comparing the GTVs. Instead, this was assessed by whether or not the PET guidance volume was entirely within the CT-based GTV (obviously, the PET guidance volume was always within the PET/CT-based GTV). For 3 of the 11 patients, the PET guidance volume was not entirely within the CT-based GTV, and therefore PET may be considered to truly have had an impact on the target volume delineation (presented in Figure 2a).

The PTVs, which drive the RT optimization and the resulting dose to OARs, were also studied. For 3 out of the 11 patients, there were striking differences between the CT-based and the PET/CT-based PTVs (Figure 2b). They were the same as the patients presented in Figure 2a (Patients 4, 10 and 11), indicating that the impact of PET on GTVs remains noticeable in the PTV. The differences were visually less striking for other patients, such as Patient 9 (Figure 3), where the small visual differences were supported by rather high DSC (0.93). On the other hand, the target volumes of this patient had rather large mismatched volumes (Appendix D).

Statistical analysis

The statistical analyses did not reveal any significant volumetric change between the CT-based and PET/CT-based GTVs ($p = 0.476$), CTVs ($p = 0.326$) or PTVs ($p = 0.346$). Separating the patients into H&N (7 target volumes) and non-H&N (5 target volumes) did not reveal any significant changes either (H&N: GTVs, $p = 0.673$; CTVs, $p = 0.866$ and PTVs, $p = 0.866$; non-H&N: GTVs, $p = 0.109$; CTVs, $p = 0.138$ and PTVs, $p = 0.136$).

Despite the lack of statistically significant differences between TV_{CT} and TV_{PETCT} for the whole cohort, some trends could be detected. The GTVs became smaller or remained of the same size with the inclusion of PET for patients with tumours outside the H&N region. The PET/CT-based CTVs and PTVs in this group were also generally reduced, with one exception in Patient 2, where the CTV increased by 4 cm³ (2%) and the PTV increased by 6 cm³ (2%).

No such trends were seen for the target volumes of patients with tumours in the H&N region.

Plan quality

Target coverage for PTV-T is presented in terms of homogeneity index (Figure 4). For CT-based PTV-T, average target coverage was 0.93 (median, 0.93; range, 0.87–0.99) and 0.98 (median, 0.98; range, 0.94–1.00) for 3DCRT and IMPT, respectively. For the PET/CT-based PTV-T, corresponding numbers were 0.92 (median, 0.93; range, 0.84–0.99) and 0.97 (median, 0.98, range, 0.94–1.00). All homogeneity indexes are presented in Appendix C.

The largest target coverage difference was seen in the 3DCRT plans for Patient 10, where the homogeneity index decreased from 0.87 to 0.84 when going from CT- to PET/CT-based PTV. The CT-based PTV was 35 cm³ smaller than was the PET/CT-based PTV (535 and 570 cm³), and the differences were mainly

Figure 2. (a) From top: Patient 4 (sarcoma), Patient 10 (carcinoma) and Patient 11 (carcinoma). Contours: cyan = positron emission tomography (PET) guidance volume, orange = CT-based gross tumour volume (GTV), pink = PET/CT-based GTV. (b) From top: Patient 4 (sarcoma), dice similarity coefficient (DSC) = 0.92. Patient 10 (carcinoma), DSC = 0.87. Patient 11 (carcinoma), DSC = 0.91. Contours: red = PET/CT-based planning target volume (PTV), turquoise = CT-based PTV. These are the same patients as in (a), albeit slightly different CT-slice images. DSCs for the PTVs of all patients are presented in Appendix D. For colour images please see online: www.birpublications.org/doi/full/10.1259/bjr.20140586.

in towards the medulla (Figure 2b). In the IMPT plans, homogeneity index for CT- and PET/CT-based PTVs were 0.97 and 0.95, respectively. For the PTVs of the remaining patients, homogeneity indexes differed by ≤ 0.02 in the 3DCRT plans with and without PET, and by ≤ 0.01 in the IMPT plans.

The average volume of irradiated healthy tissue (entire patient volume minus all PTVs) for the photon modality was $10,692 \text{ cm}^3$ (median, $10,540 \text{ cm}^3$; range, $4333\text{--}17,495 \text{ cm}^3$) and $10,771 \text{ cm}^3$ (median, $10,572 \text{ cm}^3$; range, $4277\text{--}17,535 \text{ cm}^3$), for TV_{CT} and TV_{PETCT} respectively. The corresponding numbers for IMPT were 2540 cm^3 (median, 2542 cm^3 ; range, $1157\text{--}4837 \text{ cm}^3$) and 2622 cm^3 (median, 2808 cm^3 , range, $1199\text{--}4767 \text{ cm}^3$) indicating a slight increase in irradiated volume for the PET/CT-based plans (Figure 4).

Risk estimations

The risk models are presented in detail in Appendix B, and a summary of the dose estimations used in the dose–response models is presented in Appendix C.

NTCP and SC risks are presented in Figures 5 and 6, respectively. In these figures, risk estimates $<3\%$ are not shown (NTCP $<3\%$

and SC risk $<3\%$). As seen, the risks were only marginally affected by the inclusion of PET. Although the impact of PET on RT-induced risks overall was minor and comparable for both 3DCRT and IMPT, the risks were reduced with IMPT compared with 3DCRT for most patients, with three exceptions: for Patients 10 and 11, the doses to thyroid gland and the risk of hypothyroidism was lower with 3DCRT than with IMPT, in the plans optimized for TV_{CT} as well as TV_{PETCT} . For both patients, target coverage was clearly superior with IMPT plans, especially in the elective PTVs, which involved most parts of the thyroid (Appendix C). The superior target coverage in IMPT plans may partially be the reason for the higher NTCP.

DISCUSSION

We performed this treatment planning study on a heterogeneous group of children and adolescents with different tumour location and histology. The objective was to evaluate the impact of including PET in the target definition process of paediatric RT planning. Our primary interest was the effect on target volumes and the risk of RT-induced complications estimated from the resulting treatment plans with conventional photon RT and modern PT. Similar to the approach in Fogliata *et al*,³³ the

Figure 3. Patient 9 (lymphoma), dice similarity coefficient = 0.93. Contours: red = positron emission tomography/CT-based planning target volume (PTV), turquoise = CT-based PTV. For colour images please see online: www.birpublications.org/doi/full/10.1259/bjr.20140586.

patients in our cohort represent varying treatment complexity in terms of diagnosis and anatomical considerations. Our hypothesis was to reveal existence of general tendencies, such as whether the information from a PET scan generally leads to increased or decreased target volumes, irrespective of primary diagnosis.

Target volumes

As seen in Figure 2a,b, for some patients, the shape of the target volume was distinctly altered with the inclusion of PET, which in turn impacts the treatment plans, in terms of the distribution of curative dose. For the patients in this study, the target volume alterations were mainly noticeable in cases where the accumulation of ^{18}F -FDG added information about whether or not lymph nodes should be included in the target volume. Although not investigated in this study, this could in turn affect the stage of disease, potentially leading to an altered treatment regimen.

The overall DSCs were high and can only be regarded as within normal inter- and intra-observer variability, with a mean value of 0.85 and 0.91 for GTV and CTV, respectively.⁶³ For most patients, the differences between $\text{TV}_{\text{PET/CT}}$ and TV_{CT} were reduced by the addition of margins, resulting in higher DSCs for CTV than for GTV, and similarly, higher DSCs for PTV than for CTV (Table 1, Appendix D). The mismatched volumes (presented in Appendix D) are not as easily interpreted in this aspect, but highlight that the inclusion of PET does not unanimously lead to increasing or decreasing the target volumes. In other words, adding an ^{18}F -FDG PET scan to target volume delineation can result in removing as well as adding some regions of suspicion.

Neither DSC nor MM takes the shape of the target volume discrepancies into account, which may be very important in the context of RT. The target volumes and target volume discrepancies of Patient 4 in Figure 2 and Patient in Figure 3 are good examples of this. DSC was high for both patients, but for Patient 4, there were obvious differences in the dose distribution in the PET/CT-based and the CT-based RT plan. For Patient 9, the dose distribution was essentially the same, regardless of the inclusion of PET.

The MM indicates a large impact of PET on the target volumes of Patient 9 (Appendix D), but, as already mentioned, the shape of the discrepancies between $\text{TV}_{\text{PET/CT}}$ and TV_{CT} become negligible in the context of RT. This leads to the conclusion that commonly used tools for volume comparisons, such as DSC and MM, do not provide a complete measure of how important the discrepancies will be for a patient's RT, as it does not account for whether the discrepancies are isotropically distributed or confined to a localized region. Lacking better quantitative measures, a qualitative evaluation of target volume and treatment-planning differences remains necessary, although current advances in automated treatment

Figure 4. Left: target coverage in terms of the ratio of planning target volume (PTV)-T receiving $\geq 95\%$ as well as $\leq 107\%$ of the prescribed dose. Right: irradiated healthy tissue (cm^3), defined as the entire patient volume minus all PTVs. Values from radiotherapy (RT) plans optimized for CT-based and positron emission tomography (PET)/CT-based target volumes (TVs), for three-dimensional conformal photon RT (3DCRT) (blue icons) and intensity-modulated proton therapy (IMPT) (pink icons). Circles are target volumes located in head and neck (H&N) region, square icons are non-H&N target volumes (located in the abdomen, pelvis or thorax). For irradiated volume, the patient with target volumes in both the neck and pelvis is presented as non-H&N. For colour images please see online: www.birpublications.org/doi/full/10.1259/bjr.20140586.

Plan quality parameters

Figure 5. Estimated normal tissue complication probability (NTCP) in radiotherapy (RT) plans generated for CT-based and positron emission tomography (PET)/CT-based target volumes (TVs) with three-dimensional conformal photon RT (3DCRT) (blue) and intensity-modulated proton therapy (IMPT) (pink). Circles are target volumes located in head and neck (H&N) region, square icons are non-H&N target volumes (located in abdomen, pelvis or thorax). Risk estimates <3% are not shown. For more information about the risk models and complications, see Appendix B. Note the different scales on the y-axes. For colour images please see online: www.birpublications.org/doi/full/10.1259/bjr.20140586.

planning may provide tools that could make trying to estimate the impact on dose distribution from a change in target volume more practical.

Plan quality and risk estimations

Despite the changed shape of the target volumes caused by the inclusion of PET, overall it was possible to maintain the same target coverage without notably affecting the risk of normal tissue complications for both the conventional photon therapy technique and PT. The long-term risks attributable to RT were overall only marginally affected by the use of TV_{CT} or TV_{PET/CT}.

PT plans were associated with a reduction in NTCP and SC risk compared with 3DCRT. The conventional photon therapy resulted in much lower target coverage for H&N tumours

located near critical organs such as the brain stem and medulla. Reducing the dose to these organs and thereby avoiding high risk of unacceptable complications, occasionally required compromises to dose coverage of PTV and CTV, as our intention was to generate clinically acceptable RT plans.

Another interesting observation is the volume of irradiated healthy tissue. For each modality separately, this parameter is not notably affected by the inclusion of ¹⁸F-FDG PET, but it is worth noting that the volume is about three times larger for 3DCRT than for IMPT. We chose to study the volume receiving >0.001 Gy_{RBE}, in accordance with the linear-no-threshold model, which assumes that any non-zero dose can potentially induce a future malignancy.

Radiation exposure from positron emission tomography/CT scans

A PET-CT is a rather costly procedure (approximately 2700 USD/1600 GBP) and involves an extra radiological burden for young patients. Hence, the use of PET/CT should be carefully considered in this population with respect to both resources and dose exposure.

Regarding the dose and risk attributable to the ¹⁸F-FDG PET and CT scan of paediatric patients, we refer to a study that showed that ¹⁸F-FDG PET adds very little to the long-term risks in comparison with the dose from the CT scan, and even less in relation to the dose from RT.⁶⁴ For the 11 patients in the study at hand, effective PET/CT doses were on average 30 mSv and the ¹⁸F-FDG PET contributed with approximately 25–30% of that. Regardless, unnecessary radiation dose should always be avoided, and it is

Figure 6. Estimations of lifetime cumulative secondary cancer (SC) risk for radiotherapy (RT) plans generated for CT-based and positron emission tomography (PET)/CT-based target volumes (TVs) with three-dimensional conformal photon RT (3DCRT) (blue) and intensity-modulated proton therapy (IMPT) (pink). Circles are target volumes located in head and neck (H&N) region, square icons are non-H&N target volumes (located in the abdomen, pelvis or thorax). Risk estimates <3% are not shown. Note the different scales on the y-axes. For colour images please see online: www.birpublications.org/doi/full/10.1259/bjr.20140586.

therefore important to thoroughly assess the value as well as the risks of including ^{18}F -FDG PET in radiotherapy planning. Every effort should be made to minimize the risk of radiation-induced complications for paediatric patients, from diagnostic as well as therapeutic exposure. We believe that this can best be carried out when choosing treatment modality and radiation type, rather than by avoiding ^{18}F -FDG PET scanning for RT planning.

Limitations of the study

The risks presented for normal tissue complications and SCs are attributable to large uncertainties, especially considering the varying life expectancy of paediatric patients with different diagnoses. We fully acknowledge the limitations of the models used and stress that they may have limited validity for estimating absolute risks in individual patients. However, the risk estimations do allow for rough relative comparisons between the CT and PET/CT cases and to some extent between treatment modalities. The small changes in estimated NTCP and SC risks between using TV_{CT} or $\text{TV}_{\text{PET/CT}}$ were negligible in comparison to the underlying model uncertainty.

For clinically relevant RT planning, the CTV-to-PTV margin should be adjusted depending on anatomical region as well as treatment modality and verification imaging routine.^{65–73} Therefore, using the same CTV-to-PTV margin for the proton and photon RT plans in this study, might introduce a bias in favour of IMPT. Part of the benefit with IMPT over 3DCRT might be reduced if IMPT would require larger margins, although that investigation is beyond the scope of the present work.

Allowing for deteriorated target coverage in the photon plans may somewhat have lowered the dose to OARs overlapping with the PTV. This may be regarded as causing an underestimation of the differences between risk estimations from 3DCRT and IMPT.

Owing to limitations of the treatment planning system, secondary neutron production within the patient and PT equipment (e.g. treatment head and range shifter) was not included in the NTCP and SC risk estimates. These neutron doses depend considerably on the patient size, with higher neutron doses to patients with smaller body stature.²⁸ Depending on the PT modality and patient size, the organ-specific equivalent doses from neutrons during a course of 70 Gy_{RBE} can be equivalent to about 30 CT scans.²⁸ We do not expect that the addition of secondary neutron doses would change the results of our study.

CONCLUSION

In this study cohort, the information provided by ^{18}F -FDG PET/CT did not systematically alter the target volumes or the average long-term risks attributable to the resulting treatment plans. This was true for both conventional photon therapy and modern PT. Including PET in the radiotherapy treatment planning process did change the shape and extension of the target volume for some individual patients.

A tendency of systematic alterations of target on volumes was observed primarily for the patients with a tumour outside the H&N region. On the other hand, the importance of PET in terms of the inclusion of lymph nodes was most obvious for patients with H&N tumours, which may also alter the staging of the disease.

To validate or dismiss these trends requires a larger and more homogenous data set. Further research is needed in order to determine which paediatric cancer patient subgroups would benefit most from ^{18}F -FDG PET/CT-guided RT planning.

ADDENDUM

As seen for Patient 10 in Figure 2, one of the major discrepancies between the two sets of target volumes was caused by ^{18}F -FDG accumulation in the vertebral body, interpreted as tumour growth. Despite this skeletal metastasis, the patient was treated with RT aiming to be locally curative (68 Gy). The diagnostic imaging performed 5 months after the PET/CT scan revealed local control of the metastasis in C2.

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APPENDIX A

Table A1. Details of the radiotherapy (RT) plans

Patient number	3DCRT	IMPT
1	Five + four fields ^a Coplanar Wedges in three + three fields 6X and 18X	Three fields Coplanar 70–250 P
2	Two + four fields ^a Coplanar Wedges in one field + two ^a fields 6X and 18X	Three fields Coplanar 70–250 P
3	Three + three fields ^a Non-coplanar Wedges in three + two fields 6X and 18X	Three fields Coplanar 70–250 P
4	Three fields Non-coplanar Wedges in two fields 6X and 18X	Four fields Coplanar 70–250 P
5 ^b	Three + two fields Coplanar Wedges in three + zero fields 6X and 18X	Two + two fields Coplanar 70–250 P
6	Two + four fields ^c Coplanar Wedges in three fields + one field 6X and 18X	Six fields Non-coplanar 70–250 P
7	Four fields Non-coplanar Wedges in two fields 6X and 18X	Three fields Non-coplanar 70–250 P
8	Four fields Non-coplanar Wedges in three fields 6–18X	Three fields Coplanar 70–250 P
9	Five + three fields ^a Non-coplanar Wedges in five + two fields 6–18X	Four fields Coplanar 70–250 P
10	Six + six fields ^c Non-coplanar Wedges in three + three fields 6–18X	Four fields Coplanar 70–250 P
11	Four + four fields ^c Non-coplanar Wedges in four + four fields 6X	Five fields Coplanar 70–250 P

3DCRT, three-dimensional conformal photon RT; IMPT, intensity-modulated proton therapy.

^aTo ensure symmetric bone irradiation.

^bTwo targets.

^cTo ensure dose coverage of elective volume. 6X and 18X denotes the acceleration potential and corresponds to maximum photon energy of 6 and 18 MeV, respectively. 70–250 P denotes the kinetic energy span of the protons.

APPENDIX B

Table A2. The models used to assess the risk of non-cancer normal tissue complications

Organ	Paediatric patients	End point	Model	Parameters
Heart ⁴⁹	Yes	Congestive heart failure	Linear model $HR = 1 + k \times D_{\text{mean,heart}}$	$k = 0.0554$
		Myocardial infarction		$k = 0.0399$
		Pericardial disease		$k = 0.0530$
		Valvular abnormalities		$k = 0.0672$
Lung ⁵⁰	No	Radiation pneumonitis	Logistic model, mean dose both lungs	$\gamma_{50} = 0.97$ $TD_{50} = 30.8$
Oesophagus ⁵¹	No	Acute oesophagitis, (WHO grade ≥ 2)	LKB model, mean dose	$n = 0.69$ $m = 0.36$ $TD_{50} = 47$
Kidney ⁵²	No	Symptomatic, radiation nephropathy	Logistic model, mean dose both kidneys	$\gamma_{50} = 1.924$ $TD_{50} = 27.84$
Liver ⁵³	No	Radiation-induced liver disease	LKB model, mean dose	$n = 1$ $m = 0.12$ $TD_{50} = 39.8$
Small intestine ⁵⁴	No	Gastrointestinal toxicity (WHO grade 1–4)	LKB model, mean dose	$n = 0.09$ $m = 0.17$ $TD_{50} = 32$
Rectum ⁵⁵	No	Late rectal toxicity or rectal bleeding (grade ≥ 2)	LKB model, mean dose	$n = 0.09$ $m = 0.13$ $TD_{50} = 76.9$
Parotid glands ⁵⁶	No	Xerostomia (25% of original saliva flow)	LKB model, mean dose	$n = 1$ $m = 0.4$ $TD_{50} = 39.9$
Thyroid ⁵⁷	Yes	Hypothyroidism	Logistic model, mean dose	$\gamma_{50} = 0.49$ $D_{50} = 28.41$
Eye ⁵⁸	Yes	Blindness	Linear model $RR = 1 + k \cdot D_{\text{max,eye}}$	$k = 0.34$
Cochlea ⁵⁹	Yes	Ototoxicity (grade 3–4)	Logistic model, mean dose	$\gamma_{50} = 1.74$ $D_{50} = 50.17$

HR, hazard ratio; LKB model, Lyman-Kutcher-Burman model; WHO, World Health Organization.

The models for hypothyroidism, ototoxicity and pneumonitis were derived using the same data as in Brodin et al,³⁸ only described according to the definition of a logistic function (with dose as covariate) presented in Bentzen and Tucker.⁶⁰ The models for blindness and cardiac complications are slightly different from the ones presented in Brodin et al^{38,61} but based on the same data. The normal tissue complication probability model for xerostomia is identical to the one used in Brodin et al.³⁸ The models predicting the risk of complications in oesophagus and rectum were found in QUANTEC reports.^{51,55} Models for liver and small intestine were found in other published studies.^{53,54} The risk model for radiation nephropathy was extracted from dose-response data published in Cassady.⁵²

APPENDIX C

Table A3. (a) Dose estimates for patients with non-head-and-neck tumours

Patient number	RT modality		Mean dose, ventricle (Gy _{RBE})	Mean dose, lungs (Gy _{RBE})	Mean dose, heart (Gy _{RBE})	Mean dose, kidneys (Gy _{RBE})	Mean dose, liver (Gy _{RBE})	Mean dose, oesophagus (Gy _{RBE})	Mean dose, small intestine (Gy _{RBE})	Mean dose, rectum (Gy _{RBE})	Homogeneity index, PTV-T/PTV-S
1	3DCRT	CT	21.5	N/A	N/A	36.4	18.9	2.9	53.7	0.7	0.89/1.00
		PET/CT	21.0			35.7	16.9	2.7	53.5	0.6	0.91/0.99
	IMPT	CT	9.1			32.3	4.9	<0.05	44.9	<0.05	0.96/1.00
		PET/CT	9.2			31.6	4.3	<0.05	44.2	<0.05	0.96/1.00
2	3DCRT	CT	<0.05	N/A	N/A	<0.05	<0.05	<0.05	5.3	38.6	0.96/1.00
		PET/CT	<0.05			<0.05	<0.05	<0.05	5.7	39.0	0.97/1.00
	IMPT	CT	<0.05			<0.05	<0.05	<0.05	0.5	30.6	0.99/1.00
		PET/CT	<0.05			<0.05	<0.05	<0.05	0.7	31.2	0.98/1.00
4	3DCRT	CT	<0.05	N/A	N/A	<0.05	<0.05	<0.05	10.3	29.3	0.95
		PET/CT	<0.05			<0.05	<0.05	<0.05	10.9	29.3	0.96
	IMPT	CT	<0.05			<0.05	<0.05	<0.05	6.2	25.1	1.00
		PET/CT	<0.05			<0.05	<0.05	<0.05	6.6	23.1	1.00
5	3DCRT	CT	0.1	0.2	0.1	0.2	0.1	0.8	6.8	6.1	0.98
		PET/CT	0.3	0.2	0.1	0.2	0.1	1.0	6.4	6.1	0.98
	IMPT	CT	<0.05	<0.05	<0.05	<0.05	<0.05	0.3	0.9	1.6	0.99
		PET/CT	<0.05	<0.05	<0.05	<0.05	<0.05	0.5	0.8	1.5	0.99
8	3DCRT	CT	2.0	30.0	31.3	0.2	3.6	27.1	<0.05	<0.05	0.95
		PET/CT	1.7	28.9	30.8	0.2	3.1	26.0	<0.05	<0.05	0.95
	IMPT	CT	<0.05	20.3	11.2	<0.05	0.4	19.8	<0.05	<0.05	0.98
		PET/CT	<0.05	20.2	10.3	<0.05	0.5	20.3	<0.05	<0.05	0.99

3DCRT, three-dimensional conformal photon RT; IMPT, intensity-modulated proton therapy; N/A, not applicable; PET, positron emission tomography; PTV, planning target volume; PTV-S, target volume for symmetrical bone tissue irradiation; PTV-T, primary PTV; RT, radiotherapy.

Patient 8, mean thyroid doses: 3DCRT CT, 1.1 Gy; 3DCRT PETCT, 0.9 Gy; IMPT CT, <0.05 Gy; IMPT PET/CT, <0.05 Gy.

Table A3. (b) Dose estimates for patients with head-and-neck tumours

Patient number	Radiotherapy modality		Mean dose thyroid (Gy _{RBE})	Mean dose parotids (Gy _{RBE})	Maximum dose eyes (Gy _{RBE})	Mean dose cochlea (Gy _{RBE})	Mean dose lungs (Gy _{RBE})	Mean dose heart (Gy _{RBE})	Mean dose oesophagus (Gy _{RBE})	Homogeneity index PTV-T/PTV-EH/PTV-EL
3	3DCRT	CT	65.9	12.6	1.0	1.9	3.4	1.1	26.4	0.87/1.00
		PET/CT	65.7	12.1	1.0	1.9	2.9	0.8	24.2	0.86/1.00
	IMPT	CT	62.1	4.5	<0.005	<0.05	2.4	<0.05	24.3	0.95/1.00
5	3DCRT	PET/CT	61.4	4.6	<0.005	<0.05	2.2	<0.05	22.8	0.96/1.00
		CT	15.6	12.3	2.7	15.9	0.2	0.1	0.4	0.99
	IMPT	PET/CT	15.8	12.6	2.7	16.0	0.2	0.1	0.5	0.99
6	3DCRT	CT	6.5	3.8	<0.05	6.3	<0.05	<0.05	<0.05	0.94
		PET/CT	6.0	4.0	<0.05	6.7	<0.05	<0.05	0.2	0.93
	IMPT	CT	13.6	52.7	2.7	16.7	0.3	0.2	0.2	0.93/0.93
7	3DCRT	PET/CT	13.2	51.1	1.8	10.9	0.3	0.2	0.2	0.92/0.94
		CT	16.3	38.4	28.1	16.0	<0.05	<0.05	<0.05	1.00/0.96
	IMPT	PET/CT	19.3	38.6	22.0	16.9	<0.05	<0.05	<0.05	0.99/0.96
9	3DCRT	CT	21.0	12.1	1.8	15.0	3.5	1.5	7.2	0.87
		PET/CT	20.9	12.2	1.8	15.1	3.6	1.45	7.2	0.87
	IMPT	CT	14.7	12.4	<0.05	2.9	0.7	<0.05	4.3	0.98
10	3DCRT	PET/CT	13.9	12.5	0.1	6.5	0.8	<0.05	4.5	0.98
		CT	5.3	21.1	0.8	13.5	N/A	N/A	1.5	0.93/0.95
	IMPT	PET/CT	5.3	20.1	0.7	13.4			1.5	0.94/0.95
11	3DCRT	CT	0.1	14.3	<0.05	<0.05			<0.05	0.99/1.00
		PET/CT	0.2	12.4	<0.05	<0.05			<0.05	0.99/1.00
	IMPT	CT	30.9	74.1	34.9	67.2	0.9	0.1	7.0	0.87/0.63/0.52
11	3DCRT	PET/CT	23.3	76.4	35.6	70.6	0.7	0.1	5.0	0.84/0.65/0.47
		CT	57.6	57.4	24.1	61.9	0.1	<0.05	4.3	0.97/0.96/0.96
	IMPT	PET/CT	54.2	58.3	22.6	60.0	0.4	<0.05	6.5	0.95/0.95/0.96
11	3DCRT	CT	59.0	68.4	29.7	65.5	4.2	0.4	8.6	0.93/0.64/0.91
		PET/CT	58.2	68.5	33.7	66.3	4.3	0.4	7.4	0.91/0.68/0.96
	IMPT	CT	61.1	47.3	20.2	42.3	0.7	<0.05	3.1	0.97/0.97/0.94
11	3DCRT	PET/CT	60.7	48.8	20.2	44.3	0.7	<0.05	2.9	0.96/0.95/0.95
		CT	60.7	48.8	20.2	44.3	0.7	<0.05	2.9	0.96/0.95/0.95

3DCRT, three-dimensional conformal photon RT; IMPT, intensity-modulated proton therapy; N/A, not applicable; PET, positron emission tomography; PTV, planning target volume; PTV-EH, high-risk PTV; PTV-EL, low-risk PTV; PTV-T, primary PTV.

APPENDIX D

Table A4. (a) Size (cm³) of planning target volume (PTV) and dice similarity coefficients (DSCs)

	Patient number	1	2	3	4	5		6	7	8	9	10	11	Mean	Median	Range
PTV	CT	488	335	152	708	185	114	92	617	477	295	675	535	389	406	92–708
	PET/CT	465	341	145	685	194	110	82	600	412	275	716	570	383	377	82–716
	DSC	0.96	0.96	0.94	0.92	0.95	0.92	0.91	0.95	0.91	0.93	0.87	0.91	0.93	0.93	0.84–0.95

PET, positron emission tomography.

Table A4. (b) Size (cm³) of elective target volumes, dice similarity coefficients (DSCs) and prescribed doses

Patient number	CTV-EH			CTV-EL			PTV-EH			PTV-EL			Prescribed dose to PTV-EH (Gy _{RBE})	Prescribed dose to PTV-EL (Gy _{RBE})
	CT	PET/CT	DSC	CT	PET/CT	DSC	CT	PET/CT	DSC	CT	PET/CT	DSC		
6	138	130	0.90	N/A	N/A	N/A	213	194	0.91	N/A	N/A	N/A	50	N/A
10	809	858	0.86	984	1052	0.87	1203	1259	0.90	1406	1497	0.91	60	50
11	555	586	0.88	758	725	0.88	943	974	0.92	1140	1141	0.92	60	50

CTV, clinical target volume; EH, elective high risk; EL, elective low risk; N/A, not applicable; PET, positron emission tomography; PTV, planning target volume.

Table A4. (c) Mismatched volumes

Patient number	GTV-T (%)	CTV-T (%)	CTV-EH (%)	CTV-EL (%)	PTV-T (%)	PTV-EH (%)	PTV-EL (%)
1							
a	9.3	2.8	N/A	N/A	1.7	N/A	N/A
b	15.2	8.1			6.5		
2							
a	12.3	5.9	N/A	N/A	4.5	N/A	N/A
b	12.0	4.2			2.8		
3							
a	5.7	1.4	N/A	N/A	3.6	N/A	N/A
b	17.5	11.2			9.0		
4							
a	5.0	5.9	N/A	N/A	6.1	N/A	N/A
b	18.6	12.2			9.7		
5							
a1	14.9	8.7	N/A	N/A	7.3	N/A	N/A
b1	7.1	3.1			2.2		
a2	17.2	7.8			5.8		
b2	22.9	12.5			9.9		
6							
a	13.7	4.3	6.7	N/A	3.7	4.5	N/A
b	15.6	17.2	12.8		15.7	15.0	
7							
a	10.6	5.0	N/A	N/A	4.0	N/A	N/A
b	25.1	9.9			7.0		
8							
a	16.9	3.0	N/A	N/A	2.1	N/A	N/A
b	25.2	25.4			17.8		
9							
a	18.0	4.7	N/A	N/A	3.4	N/A	N/A
b	11.0	13.9			10.6		
10							
a	27.1	19.6	17.0	18.0	16.7	12.6	13.0
b	14.3	12.3	10.6	8.5	9.8	7.6	6.1
11							
a	28.9	16.0	15.7	9.9	13.0	10.3	7.9
b	12.6	8.2	9.4	14.7	6.1	6.8	7.9
Mean							
a	15.0	7.1	13.1	14.0	6.0	9.1	10.5
b	16.4	11.5	10.9	11.6	8.9	9.8	7.0

(Continued)

Table A4. (Continued)

Patient number	GTV-T (%)	CTV-T (%)	CTV-EH (%)	CTV-EL (%)	PTV-T (%)	PTV-EH (%)	PTV-EL (%)
Median							
a	14.3	5.5	15.7	–	4.3	10.3	–
b	15.4	11.7	10.6	–	9.4	7.6	–
Range							
a	5.0–28.9	1.4–19.6	6.7–17	9.9–18.0	1.7–16.7	4.5–12.6	7.9–13.0
b	7.1–25.2	3.1–25.4	9.4–12.8	8.5–14.7	2.2–17.8	6.8–15.0	6.1–7.9

a, mismatch TV_{PETCT} to TV_{CT}; b, mismatch TV_{CT} to TV_{PETCT}; CTV-T, primary clinical target volume; EH, elective high risk; EL, elective low risk; GTV-T, primary gross tumour volume; N/A, not applicable; Patient 5: 1, TV in the head and neck; 2, TV in the pelvis; PET, positron emission tomography; PTV, planning target volume, TV, target volume.