RESEARCH ARTICLE

Target volume definition and dosimetric issues in radiotherapy treatment of head and neck disease with FDG-PET/CT: A monocentric experience

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Abstract In previous years FDG-PET/CT has acquired a significant role in radiotherapy treatment of head and neck (H&N) disease. This study focuses on the added value of PET/CT with respect to conventional CT in terms of target delineation and dosimetric implications. **Materials and Methods.** Thirty patients with H&N cancer who underwent FDG-PET/CT examination were analysed retrospectively. Gross tumour volumes were first delineated on CT (CT-GTVs) blinded to PET data and successively on the co-registered PET/CT (PET-GTVs). Both volumes were visible on the fused images. CT and PET/CT volumes were compared. The aim was to understand if tumour regions might be omitted if PET data is not considered in the planning stage. A simulation of a treatment plan was developed based on the CT-GTVs and the dosimetric coverage of PET-highlighted tumour regions were evaluated. **Results.** The mismatching fraction between PET and CT volumes (56%) indicates that PET significantly changes the GTV definition. A simulation of a CT-based treatment plan resulted in 23% of the analysed patients having important underdosages in PET volumes (primary tumour) in the range (-96.5% to -27.4%) while the lymph nodes were underdosaged in the range (-99.1% to -25.1%) for 33% of patients. **Conclusions.** In radiotherapy treatment of H&N disease, PET/CT provides a better target definition and prevents exclusion of pathologic regions. In the population that we analysed here, PET data integrating other conventional diagnostic modalities such as CE-CT, MRI or US avoids significant underdosages of the tumour tissue in 37% of patients.

Keywords: contouring; dosimetry; head and neck; PET/CT; radiotherapy

1. INTRODUCTION

In head and neck (H&N) tumours, computed tomography (CT) and magnetic resonance imaging (MRI) are used for standard examinations, for staging and for follow up. Both modalities provide anatomic information about the tumour and metastases [1,2].

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In previous years FDG-PET/CT has proved to be more accurate than conventional staging [3,4,5]. Moreover, in radiotherapy treatment planning, FDG-PET/CT has become an important tool in terms of target volume delineation [6,7]. The added value of FDG-PET/CT in H&N disease was demonstrated by identification of the occult primary tumour in patients with cervical node metastasis and the detection of distant metastases [8,9,10]. As demonstrated in many studies, the use of PET imaging in radiotherapy treatment planning changes delineation of the target volumes with respect to conventional anatomical imaging [11-17].

Consequently, the use of PET imaging in radiotherapy treatment might change the dosimetric tumour coverage with respect to a conventional CT-based treatment plan. How different the dosimetric tumour coverage in a PET/CT-based treatment plan is compared to a CT-based treatment plan is the overall question that we attempted to answer in this study as applied to H&N disease.

2. MATERIALS AND METHODS

2.1. Patient population

We performed a retrospective analysis of 30 patients with histological diagnosis of H&N cancer from June 2014 to December 2016. The patient classifications were: 15 with pharyngeal cancer (11 oropharynx, 2 rhinopharynx, 2 hypopharynx), 6 with laryngeal cancer, 6 oral cavity cancers, 2 with lymph nodes from unknown primary (CUP), 1 patient was excluded since PET revealed distant metastasis. The median age was 66.7 years (range 40-87 years), 27 were men and 3 were women. Pathologic findings confirmed squamous cell carcinoma for all patients. Tumour stage (T) was comprised between T2 and T4. Only 1 patient had T1. These patients underwent iter diagnostics including CT, magnetic resonance (RM), ultrasound (US) and other clinical examinations. After diagnostic staging, the patients were considered eligible for radiotherapy and underwent FDG-PET/CT to be used in radiotherapy treatment planning and also to complete the diagnostic investigation. PET/CT images were acquired on a DISCOVERY TM 710 PET/CT scanner (GE Healthcare) [18]. The images were reconstructed with OSEM 3D algorithms including PSF (Point Spread Function) and TOF (Time of Flight) and corrected for attenuation, scatter and decay. The exam was performed with an individualized thermoplastic mask including external markers as a reference for isocenter localization and patient positioning during the radiotherapy treatment. Of these patients, 29 were treated with intensity-modulated radiotherapy (IMRT) or volumetric modulated arc radiotherapy (VMAT) techniques. The patient with metastasis was excluded from radiotherapy.

2.2. Investigation methodology

In January 2017, we decided to reconsider the FDG-PET/CT examinations of these patients and we attempted to investigate the difference between radiotherapy planning including PET information and a radiotherapy treatment plan ignoring PET data and based on CT only. The methodology we adopted was the following: the PET/CT images were transferred from the archive system (PACS or PET database) to a MIM software workstation [19] usually used for radiotherapy contouring. PET and CT images were assessed separately by a well-trained radiation oncologist followed by analysis of the fused PET/CT images.

(1) First, the radiation oncologist contoured the primary tumour and the lymph nodes on the CT images blinded from PET data but comparing CT with all the other diagnostic imaging types (MRI, US, etc) and taking into account the clinical examinations. We considered the contoured volume obtained from this first delineation as the CT-GTV (CT-based gross tumour volume).

(2) Successively, PET images were fused to CT. On the fused images, the radiation oncologist delineated the most active tumour region as highlighted by the FDG uptake. This volume is defined as the biological target volume (BTV). Delineation of BTV was performed for both the primary tumour (BTV_T) and lymph nodes (BTV_N) using an adaptive thresholding method based on the source to background ratio. Contouring thresholds were calculated as a percentage of the maximum value of the Standard Uptake Value (SUVmax) and depended on the SUVmax/background ratio. The method was previously validated in phantom to obtain a specific calibration for our PET scanner as described in [20]. As concerns the lymph nodes, the radiation oncologist included in the target volume those appearing positive on PET (also assessed on CT or RM) and those negative on PET but suspected on CT and/or RM according to the criteria indicated in [21, 22]. Since PET imaging is affected by partial volume effects, in particular for small lesions, lynph nodes positive on PET with a diameter < 5mm were assessed also in CT and/or RM and included in the target if they presented a significant clinical suspicion.

We point out that target contouring was performed by only one radiation oncologist with considerable expertise in radiotherapy to avoid inter-observer variability.

The GTVs for the primary tumour and the lymph nodes were contoured on CT according to the DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG and TROG radiotherapy guidelines [23,24,25]. At completion of the contouring section, we performed a volumetric and a dosimetric analysis.

2.3. Analysis of the target volumes

CT-GTVs were compared with PET-GTVs using the methodology suggested in [26]. The following quantities were considered (Figure 1 a,b,c):

- the overlapping volume OV between PET-GTV and CT-GTV.
- the encompassing volume EV
- the overlap fraction OV-PET (ratio between OV and the PET-GTV)
- the overlap fraction OV-CT (ratio between OV and the CT-GTV)
- the overlap fraction OV-TOT (ratio between the OV and the encompassing volume EV)
- the discrepancy index DI (ratio between the EV and the OV; DI=1 in case of total overlap between PET/CT contours and CT contours and DI=∞ in case of total mismatch)
- the mismatch fraction MF-PET = (1 − OV − PET)
- the mismatch fraction MF-CT = (1 − OV − CT)
- the total mismatch fraction MF-TOT = (1 − OV − TOT)

The SUVmax values and the contouring thresholds were also reported.

2.4. Dosimetric analysis

For the dosimetric analysis, we developed a simulation treatment plan as explained below. CT-GTV was considered as the reference volume to be irradiated while the PET/CT-GTV, the BTV_T and the BTV_N were considered as 'ghost' volumes receiving a dose as a consequence of the CT-GTV irradiation.

In particular, we were interested to evaluate the dose received by the $BTV_{T/N}$ since it represents the most aggressive tumour region. For this purpose, we developed a radiotherapy treatment plan ad-hoc with a 3-D conformal technique using two opposed beams of 6 MV with isocenter in the CT-GTVs (Figure 2).
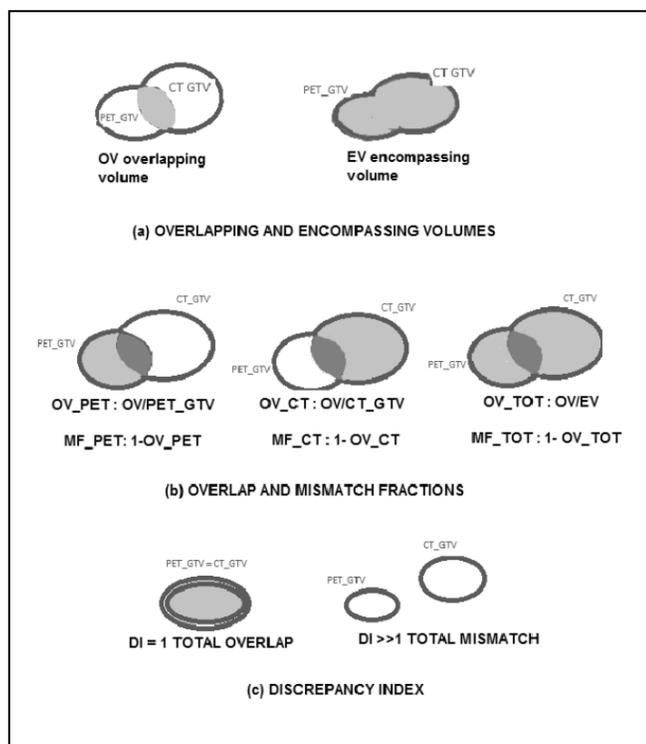
Figure 1. PET/CT and CT volume analysis.
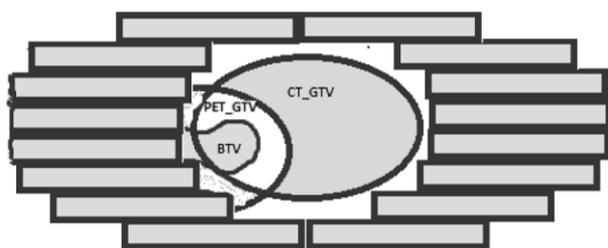
Figure 2. Layout of a 3-D conformal treatment plan.

Radiotherapy treatment plans were developed using an ONCENTRA treatment planning system [27]. The dose to CT-GTV was 20 Gy for all patients. It was our choice to consider a simplified treatment planning technique and the same irradiation dose for all patients aimed to obtain a dosimetric evaluation independent from a patient-specific prescribed dose and treatment plan features. All treatment plans were developed by the same operator to avoid any inter-operator variability.

The dose delivered to the $BTV_{T/N}$ was determined from dose-volume histograms according to the following quantities:

1. Dose covering 95% of the BTVs ($D_{95\%}$)
2. Minimum and average dose to the BTVs (D_{min} and D_{av})

We considered that BTVs received an optimal irradiation if the following conditions were satisfied:

1. $D_{95\%} \geq$ 95% of the dose released to CT-GTV
2. D_{min}: 95% of the dose released to CT-GTV (at least)
3. D_{av}: 100% of the dose released to CT-GTV (at least)

Deviations from these conditions were calculated as:

1. $\Delta D_{95\%}$ difference between $D_{95\%}$ and the actual dose covering the 95% of the BTV
2. ΔD_{min} difference between D_{min} and the actual minimum dose to BTV
3. ΔD_{av} difference between D_{av} and the actual average dose to BTV

2.4. Statistical analysis

For descriptive statistical analysis we considered the minimum, maximum, median, mean and standard deviation values. Comparison between CT and PET/CT volumes were performed using the Wilcoxon signed-ranks test since these quantities are not normally distributed.

3. RESULTS

3.1. Target volume analysis

For each patient we evaluated the SUVmax values of the lesions identified on PET images, the PET-GTVs, the BTVs and CT-GTVs. SUVmax values were spread between 3.3 g/mL and 52 g/mL, the mean patient background was about 1 g/mL. Contouring thresholds were in the range 20-41% of SUVmax for primary lesions and 20-50% for lymph nodes. The BTV_T mean volume for primary lesions was 29.9±30.8 mL; while for lymph nodes, mean volume was 29.5±92.6 mL. The large mean value and standard deviation of lymph node volumes were caused by three patients having abnormally expanded lymph nodes (BTV_N mean value excluding these patients was 2.4±3.9 mL). Comparison of PET-GTVs and CT-GTVs shows that the mean functional GTV is smaller than the mean anatomical GTV (75.3 mL versus 92.7 mL). Since PET/CT volumes are more precisely delineated around the FDG-avid tumour region, the mean fraction of OV-PET (see Figure 1.b) results were larger than the OV-CT (0.71 versus 0.54 with one-sided level of significance α=0.5% from the Wilcoxon Signed Rank Test). The mean fraction of OV-TOT was 0.44 and the mean fraction of MF-TOT was 0.56. The DI (5.4±10) was statistically significant with a one-sided level of significance α=0.5% from the Wilcoxon Signed Rank Test. The high values of MF-TOT and DI attest that there is a relevant discrepancy between PET/CT volumes and CT volumes. Table 1 resumes the descriptive parameters for the clinical cases.

Parameter	Min	Max	Median	Mean	S.D.
BTV_primary volumes (mL)	1.7	120	16.5	**29.9**	30.8
BTV_lymph node volumes (mL)	0.2	420	1.4	**29.5**	92.6
CT-GTV volumes (mL)	0.3	420	79.5	**92.7**	89.1
PET-GTV volumes (mL)	1.2	420	42.3	**75.3**	92.7
OV-PET	0	1	0.87	**0.71**	0.33
OV-CT	0	1	0.54	**0.54**	0.35
OV-TOT	0	1	0.37	**0.44**	0.33
MF-PET	0	1	0.13	**0.29**	0.33
MF-CT	0	1	0.46	**0.46**	0.35
MF-TOT	0	1	0.63	**0.56**	0.33
DI	1	61	2.7	**5.40**	10.4

Table 1. Descriptive parameters for the clinical cases.

3.2. Dose-volume histogram implications for the Biological Target Volumes

Dosimetric implications for the $BTV_{(T/N)}$ in case of a CT-based treatment plan were evaluated from dose-volume histograms. The differences between the actual doses released to BTVs and the optimal irradiation conditions considered for this study and reported in the previous section were calculated and shown in Table 2. The Δ95% dose differences for $BTV_{(T/N)}$ are shown in Figures 3-4.
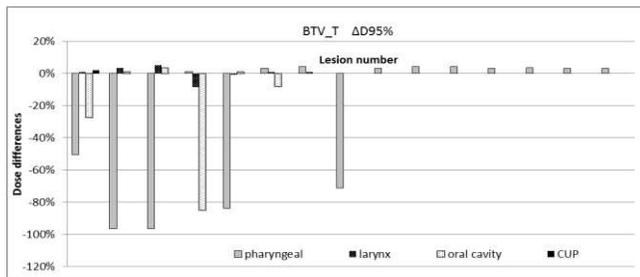
Figure 3. Dose differences for BTV$_T$.
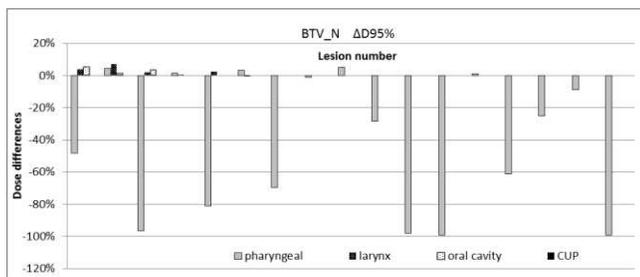
Figure 4. Dose differences for BTV$_N$.

The dosimetric findings for $BTV_{T/N}$ obtained from the simulated CT-based treatment plan is resumed as follows:
- 23% of the patients had underdosages on the BTV_T with $\Delta D_{95\%}$ in the range of (-96.5% to -27.4%)
- 33% of the patients had underdosages on the BTV_N with $\Delta D_{95\%}$ in the range of (-99.1% to -25.1%)

- 37% of the patients had underdosages on the BTV_T or BTV_N with $\Delta D_{95\%} \leq$ -25%
- ΔD_{av} of $BTV_{(T/N)}$ was < -10% in 30% of the patients
- In pharyngeal cancer, $\Delta D_{95\%}$ of the BTV_T is in the range (0 to -96.5%; mean -24.3%) and $\Delta D_{95\%}$ of the BTV_N is in the range (0 to -99.1%; mean -41.2%).
- In oral cavity cancer, $\Delta D_{95\%}$ of the BTV_T is in the range (0 to -84.8%; mean -19.1%), while for the BTV_N no significant underdosages were reported probably because the number of malignant lynph nodes in these patients was low.

Considering the lesion numbers (29 primary/CUP cancer lesions and 29 lynph nodes):
- 23% of the BTV_T lesions have underdosages with $\Delta D_{95\%}$ in the range (-27.4 to -96.5%)
- 34.5% of the BTV_N lesions have underdosages with $\Delta D_{95\%}$ in the range (-25.1% to -99.1%)

Pharyngeal (rhino-oro-hypo pharyngeal) cancer (15 patients)		
BTV$_T$ mean dose difference (%)		
$\Delta D_{95\%}$	ΔD_{min}	ΔD_{av}
Mean -24.3	-35.6	-5.8
S.D. 41.8	44.0	16.3
Min -96.5	-97.5	-55.2
BTV$_N$ mean dose difference (%)		
$\Delta D_{95\%}$	ΔD_{min}	ΔD_{av}
Mean -41.2	-54.3	-20.3
S.D. 42.3	43.4	33.6
Min -99.1	-99.1	-98.7
Oral cavity cancer (6 patients)		
BTV$_T$ mean dose difference (%)		
$\Delta D_{95\%}$	ΔD_{min}	ΔD_{av}
Mean -19.1	-31.1	-2.3
S.D. 34.2	44.3	5.3
Min -84.8	-94.7	-13.0
BTV$_N$ mean dose difference (%)		
$\Delta D_{95\%}$	ΔD_{min}	ΔD_{av}
Mean 2.5	0.4	1.0
S.D. 2.4	4.2	2.1
Min 0.0	-5.3	-0.8
Laryngeal cancer (6 patients)		
BTV$_T$ mean dose difference (%)		
$\Delta D_{95\%}$	ΔD_{min}	ΔD_{av}
Mean 0.4	-5.7	0.5
S.D. 4.3	5.3	2.1
Min -8.4	-14.0	-2.8
BTV$_N$ mean dose difference (%)		
$\Delta D_{95\%}$	ΔD_{min}	ΔD_{av}
Mean 2.1	2.1	1.8
S.D. 2.6	2.9	2.7
Min -0.8	-2.2	-2.3

Table 2. Mean dose differences for BTV$_T$ and BTV.

4. DISCUSSION AND CONCLUSIONS

The results of the volumetric analysis showing that the mean PET-based GTV is smaller than the mean CT-based GTV is consistent with other studies reported in the literature. In the pioneering investigation of Daisne *et al.*, it was demonstrated that GTV delineated from ^{18}F-FDG PET was closest to the pathologic volume from surgical specimens, and smaller than GTV delineated by CT and MRI [11]. Schinagl *et al.* [28] and Figuereido *et al.* [29] also showed that CT-based GTV was larger than a PET-based GTV obtained with a source to background segmentation method.

However, Schinagl *et al.* in the same study demonstrated that the volume and shape of PET-GTV heavily depends on the segmentation algorithm. So far, to our knowledge, a standardized segmentation method to obtain GTVs from PET data is not yet available; but as indicated in [11-13], an automatic segmentation tool is highly recommended. In this work, we used a thresholding segmentation method - based on source to background ratio - to delineate the biological target volume. Our choice to use an adaptive thresholding segmentation was supported by the fact that the method was previously validated in a phantom study that obtained a specific calibration for our PET scanner [20].

The high values of MF-TOT (0.56) and DI (5.44) resulting from the present work confirms a discrepancy between PET-based GTVs and CT-based GTVs. These findings might attest that PET identifies tumour regions missed with CT. However, it is important to underline that PET has two main limitations: the inability to detect small lesions (< 5 mm in diameter) and false positive findings due to peritumoral inflammation. Lesions with dimensions lower than PET resolution could therefore be underestimated and the mismatch between PET and CT volumes could represent a geographical miss of CT-GTV, but also a false positive PET finding due to inflammation.

Unfortunately, without a comparison with pathology specimens, we are not able to establish which contour is the most reliable. In literature studies, comparing PET, MRI and CT scans with the histopathology of resected tumour specimens shows that none of these three imaging modalities is 100% accurate. However, PET appears to be the most accurate of the three. Tumour volume determined by PET tends to be smaller on average than the volume determined by the other modalities, but most closely approximates the true tumour volume [11].

The discrepancy between PET-GTVs and CT-GTVs also affects dosimetric issues related to the radiotherapeutical treatment. We demonstrated by simple simulation that the BTV_T/BTV_N might result in underdosage in a treatment plan which is CT-based. The most severe underdosages of $BTV_{T/N}$ were observed in pharyngeal and oral cancer; while in laryngeal cancer no significant dose differences (within ± 5%) were reported. 23% of the analysed BTV_T and 34.5% of the analysed BTV_N had underdosages less than -25%. These results may be explained by the fact that the overlapping between CT volumes and PET volumes are similar to those represented in Figure 2. Here the BTV_T/BTV_N are not visible on CT alone and therefore they risk being partially or totally obscured by the multileaf collimator in a CT-based treatment plan. These dosimetric findings emphasize the importance of a reliable PET segmentation tool for the correct identification of BTVs. We are conscious that these results are limited to the restricted and heterogeneous population analysed in this work.

Other limitations are represented by the poor PET resolution and the false positive findings. In spite of these pitfalls, we are reasonably confident that: (1) incorporation of PET information in the GTVs delineation translates to a reduction of the high dose volumes and helps in sparing the surrounding tissues as already asserted in [17]; (2) PET data might identify a tumour region not clearly visible on CT and prevent it from geographical missing, especially in pharyngeal or oral cavity disease, while improving the dosimetric coverage of the tumour extent.

Following these considerations, we have decided to include an FDG-PET/CT examination in the clinical protocol of patients with H&N disease that are candidates for radiotherapy and to integrate all the information deriving from clinical examinations and from other diagnostic modalities such as CT or CE-CT, MRI and US.

ETHICAL CONSIDERATION STATEMENT

An informed consent about the use of the clinical data in retrospective studies was signed by all patients considered in this study.

CONFLICTS OF INTEREST

None of the authors has any conflicts of interest to declare.

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