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Original article

Primary tumor delineation based on ^{18}FDG PET for locally advanced head and neck cancer treated by chemo-radiotherapy

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ABSTRACT

Purpose/objective: The use of FDG-PET for target volume delineation has been validated by our group for patients with locally advanced head and neck squamous cell carcinoma (HNSCC) treated by concomitant chemo-radiotherapy providing a strict methodology for image acquisition and segmentation. The aims of this study were (1) to confirm these results in a multicentric setting, and (2) to evaluate the clinical outcome in a prospective series of patients treated with FDG-PET scan-based radiotherapy planning.

Material/methods: Forty-one patients with stage III or IV HNSCC were included in this prospective multicentric study from 2007 to 2009. Before treatment, each patient underwent head and neck endoscopy, contrast enhanced CT or MRI and FDG PET scan. Patients were treated with invert or forward planning IMRT (using dose–volume constraints on PTVs and OARs). Primary tumor GTV_{PET} were automatically delineated using a gradient based method and were registered on the planning CT. A prophylactic (50 Gy) and a therapeutic (70 Gy) primary tumor CTV_{PET} were contoured using GTV_{PET} volume along with data provided by endoscopy and pre-treatment imaging. Nodal CTV were delineated on the planning CT using internationally accepted guidelines. PTV was created by adding a security margin of 4–5 mm around CTV_{PET} (PTV_{PET}). At the end of the inclusion period after a minimal follow-up of 2 years, target volumes (GTV_{CT}, CTV_{CT}, PTV_{CT}) for the primary tumors were re-delineated on the planning CT-scan using anatomic imaging only to perform a volumetric and a dosimetric comparison.

Results: Mean age of the population was 59 years. Oropharynx was the most common tumor location (68%), followed by oral cavity (17%), larynx (7%) and hypopharynx (7%). GTV_{PET} contours were significantly smaller than GTV_{CT} contours in all cases but one (average volume 28.8 ml vs 40.4 ml, $p < 0.0001$). The prophylactic primary tumor target volumes (CTV 50 Gy and PTV 50 Gy) based on PET scan were significantly smaller ($p < 0.0001$) in oropharynx cases. The boost target volumes (CTV 70 Gy and PTV 70 Gy) contoured on PET scan were also significantly smaller than the ones contoured on CT scan in all cases ($p < 0.0001$). The dosimetry comparison showed a significant decrease in parotid and oral cavity mean dose from the PET-based plans. After completion of chemo-radiotherapy, 5 patients had selective node dissection for suspicious lymph nodes on MRI and/or PET scan; only one had a positive pathological node. At a median follow-up of 3 years, the relapse-free and overall survival rates were respectively 32% and 43%. No marginal recurrence (in the CTV_{CT} but outside the CTV_{PET}) was observed.

Conclusion: This study confirms that the use of ^{18}FDG-PET translated into smaller GTV, CTV and PTV for the primary tumor volumes in comparison with the use of CT. PET planning also demonstrated an improvement on dosimetry by lowering dose to certain organs at risk.

Computed tomography (CT) is the most routinely used imaging modality for radiotherapy treatment planning [1]. However, depending on the tumor location, target volume delineation can become difficult and highly variable on this type of image because of poor contrast between macroscopic tumor and surrounding soft tissues [1]. This is particularly true in head and neck radiotherapy where complex anatomic structures are closely related to organs at risk. Furthermore, with intensity modulated radiotherapy (IMRT) planning, because it creates steep dose gradients between those organs at risk and target volumes [2], precise delineation then

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becomes mandatory by the fact that contours impreciseness can lead to inadequate dose distribution. Also, inter-observer variability in target volume delineation is a major obstacle to IMRT standardization in clinical and research setting [3]. The use of a less variable imaging method may become handy.

Unlike anatomic imaging, positron emission tomography with ^{18}F-Fluorodeoxyglucose (^{18}FDG-PET) takes into account the biological differences of radiopharmacological uptake between the tumor and the surrounding tissues, making it a potentially useful tool for target volume delineation in head and neck cancers. The subject has been addressed in several studies [4–10]. It has been previously shown by our group that the use of ^{18}FDG-PET scan has an impact on volume delineation, providing that an adequate image acquisition and segmentation method was used [11,12]. In a planning study on patients with pharyngo-laryngeal tumors, PET-based delineation led to significantly smaller gross tumor volumes (GTV), clinical target volumes (CTV) and planning target volumes (PTV) compared to traditional CT-planning. In the same planning study, it was also retrospectively demonstrated that PET-based delineation could have translated into a different dose distribution compared to CT-based plans [13].

In this framework, this present phase II trial was designed to prospectively assess the volumetric and dosimetric benefits of ^{18}FDG PET scan-based delineation in a multicentric setting and to evaluate the clinical outcome in terms of local control and overall survival in a cohort of stage III or IV HNSCC patients.

Methods

Patients

Three hospital centers included patients in this study: Centre Oscar Lambret, Lille, France (PI: Eric Lartigau), Cliniques Universitaires St-Luc, Bruxelles, Belgium (PI: Vincent Grégoire) and Clinique et Maternité Sainte-Elisabeth, Namur, Belgium (PI: Jean-François Daisne). Eligibility criteria included patients aged 18 years or older, with ECOG performance status $\leqslant$2, controlled diabetes (otherwise glycaemia <1.5 g/l), and measurable T3–T4 squamous cell carcinoma of the head and neck (excluding nasopharynx and sino-nasal cancer) treated with a curative intent by concomitant radiotherapy and chemotherapy or cetuximab. Exclusion criteria included secondary uncontrolled cancer, pregnancy, hypersensibility or allergy to the FDG or any of the excipients and any uncontrolled systemic disease.

Study investigations were conducted after approval by the local Ethics Committee (Nord-Ouest IV Comité de Protection des Patients) on April 10, 2007 and after approval of the French Health Authority (DGS) on April 13th, 2007. Informed consent was obtained from all patients. The study is registered under the number NCT00809016.

Complete medical history and clinical exam of the upper aero-digestive tract were obtained from all patients before inclusion in the trial. Tumor imaging was performed with CT-Scan and/or MRI and metastatic work-up was done according to each participating center's local practice, including at least a lung CT or a whole body FDG-PET CT. Patients were staged using the American Joint Committee on Cancer TNM 6th edition staging system.

Simulation and image acquisition

Patients were immobilized using a thermoplastic mask with an adequate neck support (Civco, The Netherlands). For CT image acquisition, unless contra-indicated, iodine contrast was typically injected in two phases, i.e. a first phase with 60 ml at a rate of 1.5 cc/s, thereafter after a rest period of 120 s, a second phase with 50 ml at a rate of 2.0 ml/s. CT acquisition started immediately after the end of the second injection phase on a GE Lightspeed RT CT-scanner (General Electrics Healthcare, France) or on a 16 detectors row spiral computed tomography (MX 8000 IDT, Philips, The Netherlands) by using a section thickness of 0.75 mm, a reconstruction interval of 1 mm and a pitch of 0.9. The longitudinal field of view (FOV) typically included the sterno-clavicular junction up to the frontal sinuses. Axial images were typically acquired using a matrix of 512 $\times$ 512 pixels, and reconstructed with a full width at half- maximum (FWHM) of 0.52 $\times$ 0.52 $\times$ 1 mm^3 in the x, y and z directions, respectively. PET-image acquisitions were performed on a Siemens Exact ECAT HR + camera (CTI, Knoxville, TN, USA) or on a GE Advance camera (GE medical Systems, France) by using an axial FOV of 155 mm (one bed position centered on the primary tumor). One hundred eighty-five MBq (5 mCi) of FDG diluted into 5 cc of saline was intravenously injected. Emission scan (10 min 3D acquisition) started 50 min (range 50–70 min) after the injection. At the end of the acquisition, a 2D transmission scan of 10 min was performed using external rotating rods of 68 Ge. Images were corrected for dead time, random, scatter and attenuation and then reconstructed using a three-dimensional Ordered Subset Expectation Maximization (3D-OSEM) algorithm. Images were then transferred to the research workstation at St-Luc University Hospital for segmentation.

Volume delineation

Two different sets of contours were obtained for each patient, i.e. PET-based and CT-based contours. Only primary tumor (T) contours were compared in this present study (GTV-T, CTV-T and PTV-T). Since the pathologic nodes could be easily identified and delineated in the different deep spaces of the neck, because of the different density (fat and tumor), nodal GTVs, CTVs and PTVs were contoured using only CT-scan information. For the sole purpose of simplifying the manuscript, GTV, CTV and PTV will be used instead of GTV-T, CTV-T and PTV-T throughout the article. All contours used for treatment were performed by trained radiation oncologists in each participating center. For each patient, PET and CT contours were done by the same radiation oncologist (one per participating institution) to avoid inter-observer variability. For treatment, the nodal GTVs and CTVs were delineated on the planning CT without any use of FDG-PET scans using international guidelines [14,15]; the primary tumor GTVs were automatically delineated on the FDG-PET images ($GTVs_{PET}$) using a gradient-based method previously described [12]; these images were then registered on the planning CT images to delineate the CTVs, and then the PTVs using a mutual information registration algorithm as previously described [16]. Information coming from the H&N fiberoptic examination and the endoscopy under general anesthesia was used as well as from imaging data. For the comparative study, tumor GTVs and CTVs were retrospectively delineated on the planning CT images without any knowledge of the FDG-PET data ($GTVs_{CT}$). These delineations were performed 2 years after the last patient had been treated.

Prophylactic tumor CTVs (i.e. CTV with a prescribed dose of 50 Gy) usually consisted of an arbitrary 15–20 mm margin around the GTV with corrections made to exclude anatomical barriers (e.g. hyo-epiglottic membrane, mandible) or air. It also included specific areas at risk for microscopic spread depending on the primary tumor location (e.g. para-pharyngeal space for tonsil fossa carcinoma and pre-epiglottic space for supra-glottic carcinoma). Therapeutic tumor CTVs (i.e. CTV with a prescribed dose of 70 Gy) were usually delineated by adding an arbitrary margin of 5 mm around the GTV, with corrections made for anatomical barriers and air.

The PTVs were created using a uniform margin of 4–5 mm around the CTVs, depending on local guidelines of each

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