ELSEVIER

Seminars in
RADIATION
ONCOLOGY

Molecular Imaging-Guided Radiotherapy for the Treatment of Head-and-Neck Squamous Cell Carcinoma: Does it Fulfill the Promises?

Vincent Grégoire, MD, PhD,[*,†] Daniela Thorwarth, PhD,[‡] and John Aldo Lee, Eng, PhD[†]

With the routine use of intensity modulated radiation therapy for the treatment of head-and-neck squamous cell carcinoma allowing highly conformed dose distribution, there is an increasing need for refining both the selection and the delineation of gross tumor volumes (GTV). In this framework, molecular imaging with positron emission tomography and magnetic resonance imaging offers the opportunity to improve diagnostic accuracy and to integrate tumor biology mainly related to the assessment of tumor cell density, tumor hypoxia, and tumor proliferation into the treatment planning equation. Such integration, however, requires a deep comprehension of the technical and methodological issues related to image acquisition, reconstruction, and segmentation. Until now, molecular imaging has had a limited value for the selection of nodal GTV, but there are increasing evidences that both FDG positron emission tomography and diffusion-weighted magnetic resonance imaging has a potential value for the delineation of the primary tumor GTV, effecting on dose distribution. With the apprehension of the heterogeneity in tumor biology through molecular imaging, growing evidences have been collected over the years to support the concept of dose escalation/dose redistribution using a planned heterogeneous dose prescription, the so-called "dose painting" approach. Validation trials are ongoing, and in the coming years, one may expect to position the dose painting approach in the armamentarium for the treatment of patients with head-and-neck squamous cell carcinoma.

Semin Radiat Oncol 28:35-45

Introduction

Molecular imaging, also known as biological imaging or functional imaging, is the use of noninvasive imaging techniques that enable the visualization of various biological pathways and physiologic characteristics of tumors or normal tissues. In short, it mainly refers (but not only) to positron emission tomography (PET) and magnetic resonance imaging (MRI). Molecular imaging offers the unique opportunity to allow for earlier diagnosis and staging of the disease, to contribute to the selection and delineation of the optimal target volumes before and during (ie, adaptive treatment) radiotherapy and to a lesser extent before surgery, to monitor the response early on during the treatment or after its completion, and to help in the early detection of recurrence. From the viewpoint of experimental radiation oncology, molecular imaging may bridge radiobiological concepts such as tumor hypoxia, tumor proliferation, tumor stem cell density, and tumor radiosensitivity by integrating tumor biological heterogeneity into the treatment planning equation.

Typically, anatomical imaging modalities such as computed tomography (CT) and MRI, have always been the most widely used modalities for radiotherapy planning of head and neck (H&N) tumors. Over the last few years, however, molecular imaging and in particular PET and multiparametric MRI have become increasingly used. Providing appropriate tracers are

*Department of Radiation Oncology, St-Luc University Hospital, Brussels, Belgium.
†Department of Molecular Imaging, Radiotherapy and Oncology Unit, Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Brussels, Belgium.
‡Section for Biomedical Physics, Department of Radiation Oncology, University of Tübingen, Tübingen, Germany.
Conflicts of interest: none.
Address reprint requests to Vincent GREGOIRE, MD, PhD, Hon FRCR (UK), Hon FRCR (IE), Radiation Oncology Departement, Cliniques Universitaires St-Luc, 10 Ave Hippocrate, 1200 Brussels, Belgium. E-mail: vincent.gregoire@uclouvain.be

http://dx.doi.org/10.1016/j.semradonc.2017.08.003
1053-4296/

selected, molecular imaging with PET enables the visualization of various molecular pathways including metabolism, proliferation, oxygen delivery and consumption, and receptor or gene expression, all of which may be important in the response to ionizing radiation.[1] On the other hand, diffusion-weighted MRI (DW-MRI) characterizes tissues by probing differences in the random mobility of water molecules related to tissue cellularity and cellular membrane integrity. Dynamic contrast-enhanced MRI provides biological information linked to tumor vasculature (permeability and flow). Proton MR spectroscopy provides information on the relative concentration of chemical substances, which has been shown to represent the chemical signature of tumor, such as an elevated choline-to-citrate ratio.[2]

In this context, this review will focus on the role of molecular imaging with PET and DW-MRI for planning radiotherapy treatment in H&N squamous cell carcinoma (HNSCC). It will successively review the technical and methodological issues related to image acquisition, reconstruction, and segmentation, the benefit of molecular imaging for target volume selection and delineation with FDG-PET and DW-MRI, and the "dose painting" and dose escalation concept. Although in principle covering the complete H&N area, this review will mainly focus on pharyngolaryngeal SCC for which primary radiotherapy is one of the main treatment modalities.

Image Acquisition, Reconstruction and Segmentation With PET and MRI

PET and PET/CT have been routinely used as a diagnostic tool to detect and stage lesions for quite some time in oncology.[3] In radiotherapy, there is a growing trend to use PET in treatment planning, either to delineate the target volumes or to further investigate their heterogeneity.[4] These new usages have, however, much stronger requirements for image quality to reach acceptable quality. PET comes indeed with a couple of appealing characteristics, related to its functional nature, as well as intrinsic limitations, such as a rather low spatial resolution and a high level of noise.[5] For several physical and technical reasons, spatial resolution of PET is typically around half a centimetre, whereas (anatomical) CT and MRI do not exceed 1 mm.[3] This explains the blurry aspect of PET images. As PET is an emission modality, the activity of the injected tracer must be limited for obvious radioprotective reasons; this restricts the number of emitted and detected photons and thus leads to rather noisy images.[5]

When target delineation or heterogeneity assessment are aimed at resolution and noise should be carefully optimized when selecting or designing acquisition protocols and reconstruction procedures.[4] For instance, it is recommended to acquire images in 3-dimensional (3D) mode (not in 2D) and to correct for scatter, attenuation, random events and dead time.[3] If available, the use of time-of-flight measurements also increase quality.[5,6] New crystal scintillators and silicon photomultipliers improve both time and space resolution in recent PET systems.[6] Regarding reconstruction, iterative (statistical) algorithms are now the standard option.[3] Depending on hardware specificities, most vendors develop their own adapted reconstruction software. In some PET systems, resolution recovery is a feature that can compensate (partly) for blur.[7] Reconstruction speed is no longer an issue thanks to modern central and graphical processors.[6] In summary, there is a trade-off to attain between the injected tracer dose, the acquisition duration, patient comfort, and image quality.[3]

Depending on reconstruction options, PET images can be further processed afterwards, with denoising or deblurring filters.[8,9] Denoising reduces spurious random oscillations in the image, which can affect contrast. When image quality is essential as it is for automatic segmentation, edge-preserving filters are preferred to usual Gaussian smoothing, which degrades spatial resolution.[4] Image deblurring aims at resolution recovery and partial volume effect correction.[10] It restores sharp edges between regions of low- and high-tracer uptake. To some (limited) extent, deblurring methods can also recover some of the uptake heterogeneities occurring within the tumor. Such methods, however, require an accurate knowledge of the resolution characteristics of the PET camera.

Accurate delineation of the tumor volume and shape from PET images remains an open challenge.[4,11,12] Manual delineation by experienced physicians in nuclear medicine or radiation oncology remains widespread, although such methodology appears highly debatable. Variability in image display and interobserver or intraobserver variability are the most prominent caveats.[4,11,12] On the other hand, highly trained physicians can develop an expertise that can be difficult to translate into an automatic method. Multimodal delineation (PET fused with CT or MR) makes the process even more complicated to describe and formalize.

Variability in manual delineation has motivated the development of automatic delineation methods that are supposedly more objective and reproducible.[4,11,12] The simplest method relies on a fixed uptake threshold to separate tumor and surrounding healthy tissues. It can be expressed as an absolute value, in standardized uptake values (SUVs) for instance, or in a relative way, like the maximal uptake within the tumor (SUV_{max}) or some more elaborate statistic (SUV_{peak}). Common values are 2.5 SUV or approximately 40% of the SUV_{max}.[4] Using 50% of the FDG SUV_{max} to automatically delineate primary tumors of the H&N region led to volumes that were larger than those delineated with CT in 25% of the cases.[13] However, results from this study have to be taken with caution since the use of a single threshold appears questionable. Another study showed indeed that the threshold required to match macroscopic laryngectomy specimens used as a "gold standard" varied from one specimen to another between 36% and 73% of the SUV_{max}.[14] Such data and the lack of validation studies illustrate that fixed thresholds achieve poor delineation accuracy.

Adaptive thresholding addresses some of the above limitations. The uptake threshold depends then on both the maximum uptake in the tumor and the average uptake in the surrounding background. This method has been shown to be accurate for segmenting PET images in a series of pharyngolaryngeal tumors.[15] Although validated as a reliable