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Review

Physical radiotherapy treatment planning based on functional PET/CT data

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ABSTRACT

Positron emission tomography (PET) provides molecular information about the tumor microenvironment in addition to anatomical imaging. Hence, it seems to be highly beneficial to integrate PET data into radiotherapy (RT) treatment planning. Functional PET images can be used in RT planning following different strategies, with different orders of complexity. In a first instance, PET imaging data can be used for better target volume delineation. A second strategy, dose painting by contours (DPBC), consists of creating an additional PET-based target volume which will then be treated with a higher dose level. In contrast, dose painting by numbers (DPBN) aims for a locally varying dose prescription according to the variation of the PET signal. For both dose painting approaches, isotoxicity planning strategies should be applied in order not to compromise organs at risk compared to conventional modern RT treatment.

In terms of physical dose painting treatment planning, several factors that may introduce limitations and uncertainties are of major importance. These are the PET voxel size, uncertainties due to image acquisition and reconstruction, a reproducible image registration, inherent biological uncertainties due to biological and chemical tracer characteristics, accurate dose calculation algorithms and radiation delivery techniques able to apply highly modulated dose distributions. Further research is necessary in order to investigate these factors and their influence on dose painting treatment planning and delivery thoroughly.

To date, dose painting remains a theoretical concept which needs further validation. Nevertheless, molecular imaging has the potential to significantly improve target volume delineation and might also serve as a basis for treatment alteration in the future.

In the last decade radiation therapy (RT) has gone through a technological innovation. Advanced techniques such as conventional and helical intensity modulated radiation therapy (IMRT), and proton/ion therapy, allow highly conformal dose distributions. Combined with IGRT, they significantly improve the accuracy of radiation dose delivery. Furthermore, IMRT brings the opportunity to voluntarily deliver heterogeneous dose prescriptions within the target or to multiple targets. Adaptive radiation therapy (ART) was initially defined as "the explicit inclusion of the temporal changes in anatomy during the imaging, planning, and delivery of RT" [1], but this concept could easily be extended to the integration of temporal modifications of the tumor biology occurring during fractionated radiotherapy. The identification of such biological changes might help in adjusting radiation intensity or fields and/or altering the RT regimen, at the time when further treatment optimizations are still possible. This raises the question how to guide the optimal dose distribution. In this regard it was suggested that functional positron emission tomography (PET) imaging might be of additional value. Together with anatomical computed tomography (CT) and magnetic resonance imaging (MRI), PET offers valuable data for tumor and sensitive structures [2].

Integrating molecular imaging information as obtained from PET into RT treatment planning might be highly beneficial for the patient in terms of improved target volume definition and characterization [3–10].

For clinical PET imaging, most often the tracer [^{18}F]Fluorodeoxyglucose (FDG) is used which allows to examine tumor metabolism [11–14]. For individual RT adaptation other specific PET biomarkers such as tracers for tumor hypoxia and proliferation might be of interest [15–21]. Tumor hypoxia can be visualized using different PET tracers such as [^{18}F]Fluoromisonidazole (FMISO) [16], [^{18}F]Fluoroazomycin (FAZA) [15] and Cu-ATSM [17]. In contrast, tumor proliferation can be imaged with [^{18}F]Fluorothymidine (FLT) [22].

Molecular imaging can be used in radiotherapy treatment planning (RTP) with different intentions and levels of complexity:

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(1) PET may be used as any other anatomic imaging modality to define a gross target volume (GTV) which has to be identified using a proper segmentation algorithm [11,23]. This PET-based volume will modify the GTV delineated on CT if an abnormal uptake is found outside that volume. A potential impact of PET is an increased size of the high dose planning target volume (PTV) mainly from additional inclusion of metastatic lymph nodes missed on CT or the reduction of the low-dose PTV due to the exclusion of negative lymph nodes [24,25]. In addition to target selection, additional PET data can also have a high impact on target volume delineation, by either increasing or decreasing the size of the primary GTV [12–14].
(2) The PET signal might also be used to define a subvolume in a CT-derived GTV [26]. In this case the aim of biological image-guided radiotherapy is to modify the dose to particular regions identified by functional imaging, also referred to as dose painting by contours (DPBC). Since the target dose is often restricted by surrounding organs at risk (OAR), the idea is to enhance the tumor control rate by increasing the prescribed dose only to the functional subvolume within the tumor as these regions are considered to be more radioresistant than the rest of the tumor. DPBC can be realized either by giving a simple dose boost to the functional volume during the whole treatment or only to certain fractions or by redistributing the integral dose according to this functional information.
(3) Furthermore, the functional PET image might be used to gradually shape the dose according to the voxel intensities [27–30]. This concept, dose painting by numbers (DPBN), is currently investigated by a number of academic centers. To date DPBN remains a theoretical concept.

PET/CT-based radiotherapy planning has been extensively studied during the last years. Cases are reported in which FDG PET [27], FMISO PET [17] or FAZA PET [15] imaging have been used for guiding therapy and for hypoxia-directed IMRT. Several authors have shown the theoretical feasibility of a dose escalation to the PET-based hypoxic GTV which might improve the loco-regional control without exceeding the normal tissue tolerance [16,18,19,31–34]. The only clinical dose painting trial so far has been reported by Madani et al. [33]. The trial has demonstrated the feasibility of FDG PET imaging for focused dose escalation.

However, PET imaging has some important drawbacks. One of the main limitations for biological image-guided radiotherapy is the limited spatial resolution of 5–7 mm and the related partial volume effects [35,36]. This results in an underestimation of activity and an overestimation of the size of small objects. This effect becomes even more important when PET is used for dose painting in subvolumes of the tumor as these are likely to have small diameters of only a few millimeters. One possible solution which has been proposed recently is to apply a recovery technique during image reconstruction [37,38]. In addition to the limited inherent resolution of PET, the reconstruction algorithms introduce signal noise. Hence an accurate definition of the geometric tumor extension is very difficult. Different segmentation methods have been suggested [11,23] to find a standardized delineation method but the issue is still under investigation and needs more validation studies.

Recently, a few studies were published where the temporal and spatial stability of PET signals before the start of RT were investigated from multiple examinations [20,39,40]. For a potential clinical realization of dose painting in the future, spatial and temporal stability of PET images are major requirements. Even with the advent of PET/CT, image registration is not an outdate problem. It is necessary to take into account that the acquisition times for PET and CT are different, which can lead to misregistration effects caused by patient movement or breathing motion. In some institutions, the CT used for treatment planning is acquired separately from the PET/CT which requires subsequent image registration. In that case, in order to guarantee the reproducibility of patient positioning, laser localization, positioning aids such as masks and vacuum pillows, and a flat tabletop are necessary.

Dose painting strategies

Dose painting by contours

A first concept of integrating functional image information into treatment planning has been proposed in 2000 by Ling et al. [26]. According to this strategy, a functional PET image acquired before the start of therapy is used to delineate an additional sub-region of the PTV which shows the respective functional characteristics. This functional part of the target volume may be defined as the metabolically active volume in the GTV as assessed by an FDG PET scan [28,41] or the hypoxic fraction of the tumor imaged with dedicated hypoxia PET tracers such as FMISO [20], FAZA [15] and Cu-ATSM [21]. Dose painting by contours (DPBC) consists of applying a higher, homogeneous dose to the functional part of the PTV. The rationale for this strategy is to overcome the specific local radioresistance induced by the functional abnormality as assessed from the PET data. A major requirement for the definition of a functional PTV is the temporal and spatial stability of the respective PET images [20].

DPBC can either be realized by prescribing additional dose to the functional parts of the PTV [21] or by dose redistribution which basically means to escalate the dose to a sub-region of the PTV while keeping the mean dose to the whole PTV constant [42]. In general, treatment application and also planning for DPBC can be realized using the simultaneous integrated boost (SIB) technique. Cautious decisions have to be taken considering the question of a safety margin around the functional subvolumes. In addition, the resulting dose distribution (DD) will present with steep dose gradients. Those finite gradient regions should be carefully placed within the PTV during the planning process. One possible strategy would be a combination of positioning errors and location of the dose gradient. In other words, placing the dose gradient outside the PET-based functional target volume may have synergistic effects considering the eventual patient motion during RT.

Figure 1 shows an example of an HNC patient where FDG PET/CT was used in order to delineate the PTV of first order (PTV66). In this case, three different GTV areas were identified: the central primary tumor mass ($GTV66_C$), a lymph node on the right ($GTV66_R$) as well as on the left side ($GTV66_L$). Each of those volumes was delineated automatically with three different techniques, a 40% isocontour technique ($GTV66_{40\%}$), a 50% isocontour ($GTV66_{50\%}$), and a signal-to-background-based algorithm ($GTV66_{SB}$). The respective PTVs were generated by extending the clinical target volume (CTV) by 3 mm, whereas the CTV resulted from a 5 mm extension of the GTV. The treatment plan has been optimized for the volumes drawn with a 50% PET signal intensity threshold ($PTV66_{R50\%}$, $PTV66_{L50\%}$, $PTV66_{C50\%}$, $PTV60_{50\%}$). The planning system Eclipse vs. 8.1 was used for radiation treatment planning with the pencil beam (PB) dose engine. The resulting dose distribution (DD) as shown in Figure 1 was then evaluated for the three different sets of PET-based PTVs by comparing the corresponding dose volume histograms (DVHs). Table 1 summarizes the DVH statistics as well as the different volume sizes in detail. It was observed that the level of dose coverage did not vary significantly for all the three delineation techniques. The results suggest that the choice of employed threshold value is not so crucial for small volumes, which may be different for larger PET-based target volumes.