

# Radiotherapy treatment planning based on functional PET/CT imaging data

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**Key words:** PET/CT, radiotherapy, segmentation, dose painting, personalized treatment

Nuclear Med Rev 2012; 15, suppl. C: C43–C47

## Abstract

Modern radiotherapy (RT) techniques allow a highly precise and flexible deposition of the radiation dose in the tumor. As a consequence, high conformal tumor doses can be reached while sparing critical organs at risk. Hence, it seems to be very beneficial to increase the dose in the tumor according to functional and molecular information assessed by combined PET/CT imaging. Such functional image guided dose escalation is called dose painting. Two different dose painting approaches have been described to date: dose painting by contours (DPC) and dose painting by numbers (DPBN). DPC consists of delineating an additional functional target volume on the PET/CT images and prescribing this volume homogeneously to a higher dose, whereas DPBN integrates the functional image information directly into the treatment planning process in order to shape the dose in a locally varying manner according to the PET information.

Before dose painting strategies can be applied routinely in clinical practice, a number of factors that potentially affect the accuracy and effectiveness of dose painting, such as image acquisition and reconstruction protocols as well as image quantification will have to be investigated in the future. Nevertheless, integration of functional PET/CT imaging seems to be the cornerstone for advancing RT towards personalized patient-based treatment approaches.

## Introduction

Current state-of the art radiotherapy (RT) consists of applying a homogeneous radiation dose to the tumor volume delineated on the basis of a computed tomography (CT) scan acquired without the use of contrast agent [1]. In the last decade, technological innovations, such as the invention of intensity modulated radiation therapy (IMRT), made a highly precise radiation application possible [2]. As a consequence, high conformal radiation doses can now be given to the tumor while sparing organs at risk and normal tissues. Nevertheless, in a number of tumor entities, such as for example head-and-neck cancer (HNC), control rates remain as low as 50% [3].

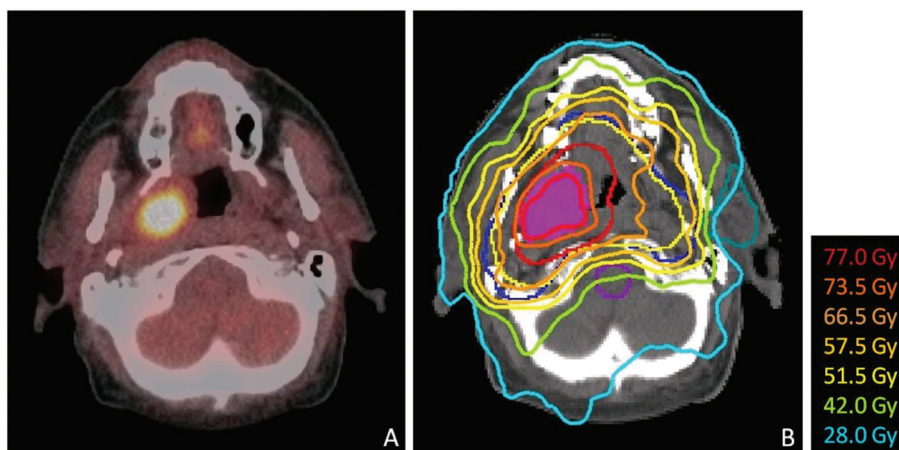
Positron emission tomography (PET) allows visualizing functional and molecular characteristics of a tumor by using dedicated PET tracers [4]. Metabolic activity of tumors can be examined using the PET tracer [<sup>18</sup>F]-Fluorodesoxyglucose (FDG) [5, 6], whereas tumor hypoxia can be imaged with [<sup>18</sup>F]-Fluoromisonidazole (FMISO) [7, 8], [<sup>18</sup>F]-FAZA [9] or [<sup>64</sup>Cu]-ATSM [10]. The PET tracer [<sup>18</sup>F]-3'-fluoro-3'-deoxy-L-thymidine (FLT) has been shown to enable for proliferation imaging in HNC [11].

It may be highly beneficial in terms of patient care and therapy outcome to use the functional PET information in order individualize RT accordingly. Hence, RT adaptation concepts where functional PET/CT data are integrated into the RT planning process are very promising. Different concepts with increasing levels of complexity have been developed in the last years [12].

In terms of radiation dose prescription, different concepts have been proposed in the past. A first idea is dose escalation, where additional radiation dose is given to the functionally abnormal tumor regions as identified on PET/CT images [13]. In contrast, another concept, referred to as dose redistribution, consists of giving more radiation dose to the PET positive regions whereas reducing the dose in the surrounding parts of the tumor with the aim of keeping the integral dose to the tumor constant [14].

Two different strategies for dose painting based on functional PET/CT imaging have been proposed so far: Dose Painting by Contours (DPC) and Dose Painting by Numbers (DPBN). The

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**Figure 1 A.** [ $^{18}\text{F}$ ]-FMISO PET/CT acquired 4h pi. A hypoxic volume was delineated based on this image by applying a 40% threshold relative to the maximum SUV. This contour was then registered to the RT planning CT and prescribed with 110% of the conventional dose (77 Gy). **B.** Corresponding slice of the RT planning CT with the FMISO PET based hypoxic target volume overlaid in pink. Resulting IMRT dose distribution of a homogeneous dose escalation by 10% is shown. Regions of interest: PTV70 (red), PTV60 (yellow), PTV54 (blue), left parotid gland (dark green), brain stem (purple)

DPC concept consists of using the PET information for delineating an additional functional planning target volume (f-PTV) which is then prescribed with a higher radiation dose level [15], whereas DPBN uses the local PET intensities in order to create accordingly locally varying dose distributions [12, 13, 16, 17].

### Dose painting by contours

The basic idea of DPC has been described for the first time by Ling et al. in 2000 [15]. It basically consists of delineating an additional functional target volume, often referred to as f-PTV on the basis of functional or molecular imaging techniques such as PET or magnetic resonance imaging (MRI). In a second step this f-PTV is prescribed to a higher radiation dose level than the surrounding tumor tissue. In terms of treatment planning and radiation application, the DPC concept can be realized using a simultaneously integrated boost (SIB) technique where the higher dose to the f-PTV is applied simultaneously in a fractionated concept.

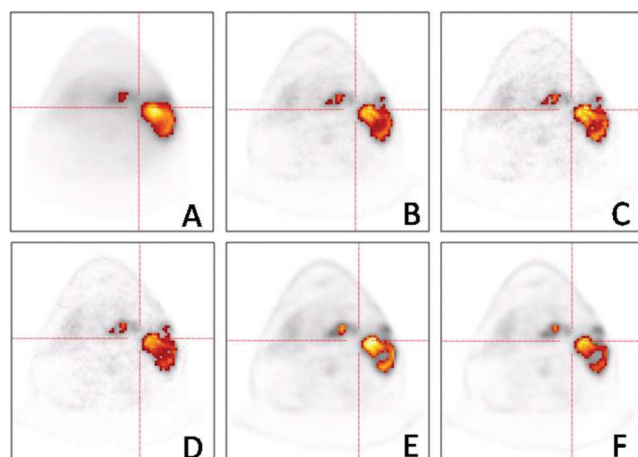
The main difficulty in the DPC approach lies in the accurate delineation of the f-PTV on the functional PET or MRI volume data set. Manual delineation of the PET-based volumes was shown to be subject to large inter-observer variations [18]. As a consequence, automatic algorithms may reduce variability and provide a higher level of objectivity. In the last years, a number of different automatic PET-based contouring algorithms have been developed especially to derive RT target volumes for functional PET data [19].

In Figure 1 an example of a DPC IMRT treatment plan is shown. Figure 1A shows an axial PET/CT slice acquired with the hypoxia tracer FMISO 4h post injection (pi). Based on this PET/CT data set, a hypoxia tumor volume has been delineated using a 40% threshold relative to the maximum SUV in the tumor. Figure 1B shows the DPC IMRT treatment plan applying a homogeneous dose escalation of 10% to the hypoxic subvolume of the tumor. The DPC IMRT plan has been created using the IMRT treatment planning software Hyperion®, developed at the University of Tübingen, Germany. Note, that the dose distribution meets the demanded 10% increase in dose in the hypoxic region while sparing critical organs at risk (spinal cord and parotid gland).

Threshold-based segmentation approaches are very popular as they are easy to implement and very intuitive as they simply aim for separating regions with high tracer uptake from those with low levels of uptake. Absolute thresholding has been proposed by Paulino et al. [20] where they recommend using a fix standardized uptake value (SUV) of 2.5 as threshold. However, due to various biological and physical factors, the absolute SUV is subject to large variations and as a consequence, absolute thresholding seems to be not very robust [21]. An alternative contouring approach consists of applying a relative threshold according to the maximum SUV observed in the tumor region [22]. Here, percentages around 40–50% of the maximum SUV are often reported, mainly resulting from phantom calibrations. A more complex method of threshold-based segmentation is the iterative thresholding approach which consists of determining a variable threshold value that is adjusted iteratively according to the activity levels in tumor lesion and background [23]. Two different groups have developed PET-based contouring algorithms that individually determine an adaptive threshold value according to the source-to-background ratio [24, 25]. This method is more robust in terms of adjusting the threshold value to the individual background activity but requires a thorough calibration of the method to take into account hardware effects of the imaging equipment.

In contrast to threshold-based approaches, a gradient-based segmentation algorithm has been proposed by Geets et al. [26]. This algorithm combines partial volume effect correction or deblurring of the PET image and a subsequent derivation of the local image gradients. Gradient-based PET segmentation is much more complex and thus difficult to implement. However, recent studies validated the gradient-based segmentation approach and showed superiority to thresholding methods [27, 28]. Nevertheless, a large number of much more sophisticated algorithms are being developed by several research groups, making use of various mathematical concepts, such as fuzzy logic [29], textural analysis [30], etc.

Validation of PET-based segmentation algorithms is very difficult. The gold standard for validation of the accuracy of newly developed algorithms has to be a comparison with pathology [31]. To date, only a few groups have realized a validation of PET-based

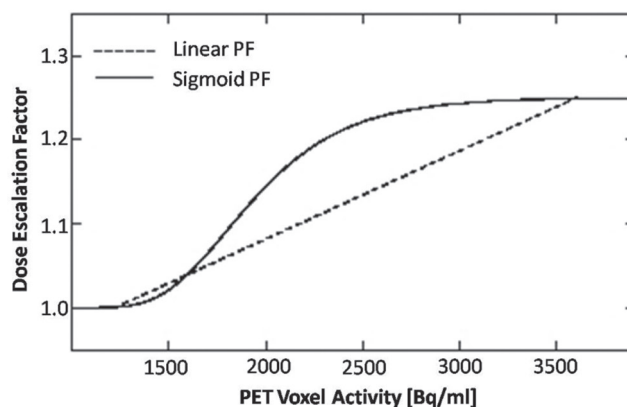


**Figure 2.** FDG PET/CT) data reconstructed using 6 different reconstruction settings: **A.** ordered subsets expectation maximization with 2 iterations 4 subsets (OSEM 2i4s); **B.** OSEM 4i8s; **C.** OSEM 2i24s; **D.** Time-of-Flight (TOF) 2i21s; **E.** Resolution Modeling (RM) 2i24s; **F.** TOF+RM 2i21s. For all data sets, the same delineation method (40% SUVmax) was used. The resulting volumes, displayed in red/orange, are the following: (A) 37.1 ccm, (B) 38.4 ccm, (C) 39.5 ccm, (D) 38.2 ccm, (E) 31.0 ccm, (F) 28.9 ccm

segmentation for RT by comparison with shape and size of surgical specimens [27, 32]. Nevertheless, a validation with respect to pathology is extremely demanding. As a consequence, most studies so far used phantom measurements, statistical approaches or patient data for validation purposes [19, 22–24, 26]. Robustness of the segmentation method is an increasingly important issue especially when it comes to a clinical usage. Manual delineation by experts in the fields of Nuclear Medicine and Radiation Therapy and also interactive or manually assisted algorithms were shown to be very competitive compared to fully automatic ones [19].

In addition to physiologic aspects that depend strongly on the tracer used for the PET/CT examination, there are a number of physical, technical and also logistical aspects that may impact the quality of target volume delineation. First, the acquisition protocol used for the PET/CT examination has a strong influence on the quantitative imaging parameters which consequentially impact target volume segmentation [33, 34]. Also aspects concerning the spatial resolution, blurring effects and intrinsic partial volume effects of PET imaging affect automatic delineation algorithms and may lead to a significant over- or underestimation of the target volume [35]. Moreover, the settings chosen for image reconstruction may have a significant influence on the subsequently delineated RT volume [36]. As a consequence, standardized approaches for image acquisition, reconstruction and interpretation are mandatory for comparable results [37].

Figure 2 illustrates the influence of PET image reconstruction on target volume delineation. One set of FDG PET raw data of a HNC patient was reconstructed using six different reconstruction methods/settings. On each reconstructed PET image, the same delineation method (40% SUVmax) was applied. Note, that a variation in size and shape of the segmented volume of up to 28% is observed

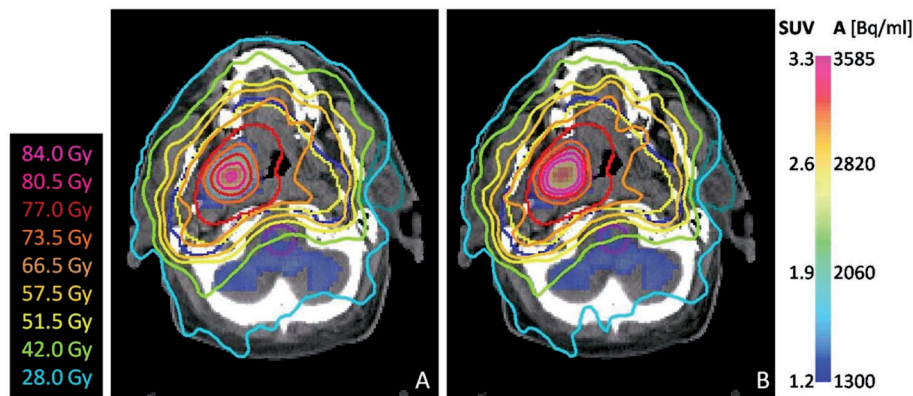


**Figure 3.** Linear and non-linear prescription function (PF) relating the PET voxel activity to a local dose prescription for Dose Painting by Numbers (DPBN)

### Dose painting by numbers

A further trend to the idea of the dose painting is the concept of dose painting by numbers (DPBN). DPBN aims at shaping the dose in a locally varying manner according to the local distribution of the functional imaging parameters derived from PET or MRI. In contrast to DPC, DPBN treatment planning requires a prescription function that relates the single voxel parameter values to individual dose values. As such, DPBN requires new approaches for treatment planning and also plan evaluation. A possible approach for DPBN IMRT optimization might be to generate a sensitivity map for the target volume based on the PET data that enables to derive local dose prescriptions. This sensitivity map can then be integrated directly into the optimization process during inverse treatment planning. For DPBN treatment plan evaluation, the usage of effective dose volume histograms (eDVH) has been proposed [13]. An eDVH is determined by weighting each voxel dose with the assigned sensitivity value and evaluate this parameter in a histogram. In other words, this means simply to compare for each voxel the local prescription dose with the planned dose.

In addition to the factors mentioned above, there is a whole chain of factors that need to be taken into account for DPBN. First, the influence of tumor biology and structure on PET signal formation has to be extremely well understood to assess its effect on DPBN. Furthermore all aspects of imaging physics including acquisition protocols, resolution and reconstruction effects crucially impact the accuracy of the PET-derived parameter map that is taken as a voxel-basis for DPBN. The choice of the parameter is of major relevance for DPBN as it should reflect radiobiological characteristics of the individual tumor. Also the prescription function used to translate the PET image or parameter map into a local dose distribution is of major importance. Different prescription functions may completely change the appearance of the resulting dose distribution for the same underlying functional image (cf. Figure 3) [38]. Inherently, this means that integrating functional imaging into RT requires highly reliable image quantification, higher than current diagnostic requirements are. The technical and also clinical feasibility of both, DPC and DPBN could be shown by different studies [17, 39].



**Figure 4.** Dose Painting by Numbers (DPBN) according to the local FMISO intensities 4h pi for the two different prescription functions shown in Figure 3: Linear PF (A), Sigmoid PF (B). The FMISO PET acquired 4h pi is overlaid to the planning CT in color. Regions of interest: PTV70 (red), PTV60 (yellow), PTV54 (blue), left parotid gland (dark green), brain stem (purple)

Figure 4 shows two different DPBN IMRT plans for a HNC patient created on the basis of FMISO PET/CT image data acquired 4h pi. For those DPBN plans, two different prescription functions as shown in Figure 3 were used (linear vs. sigmoid) to translate the same functional image (FMISO PET 4h pi) into a locally varying dose distribution. For both plans, a maximum dose escalation factor of 1.25 was requested which translates to a prescription dose of up to 87.5 Gy for a standard target prescription of 70 Gy. Note that the resulting DPBN IMRT plans for the two different prescription functions are extremely different in the hypoxic tumor area.

## Conclusion

Individually adapted RT based on functional PET/CT information seems to be highly beneficial in terms of improved patient care and potentially increased outcome rates. Recent technological advances both in imaging technology as well as in high precision RT could in the near future lead to a promising new therapy approach: functional image guided RT.

Different studies showed that both approaches, DPC and DPBN can be technically and also clinically realized. Nevertheless, a clinical realization of dose painting imposes high requirements in terms of imaging standards and treatment planning. Also the daily application of such individually adapted treatment plans necessitates accurate patient positioning with e.g. daily on-board imaging techniques. Also anatomical and volumetric changes during therapy should be assessed thoroughly. For this purpose, dedicated deformable image registration methods have to be developed in the future. Clinical studies are needed to validate the benefit of dose painting strategies and to derive the required dose escalation levels.

The integration of functional and molecular imaging using PET/CT and in the future also PET/MR into treatment planning of high-precision RT has been shown to bear a great potential to advance RT towards a personalized patient-based treatment approach.

## Acknowledgments

DT is financially supported by the Ministry of Science, Research and the Arts Baden Württemberg and the European Social Fund.

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