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Review

Personalized radiotherapy treatment planning based on functional imaging

Malgorzata Skórska[a,*], *Tomasz Piotrowski*[a,b]

[a] *Department of Medical Physics, Greater Poland Cancer Centre, Poznan, Poland*
[b] *Department of Electroradiology, University of Medical Sciences, Poznan, Poland*

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ABSTRACT

In recent years, a huge progress in the field of radiotherapy could be observed. From treating patients with kilo-voltage X-rays units to cutting edge technology that can deliver a certain dose with an extreme precision. Modern radiotherapy is characterized, among others, by an individualized approach to the patient. This can be provided by functional imaging which is another step toward a better tumor control. In this paper, we discuss the potential application of functional imaging modalities in personalized radiotherapy planning with emphasis on dose painting. Some limitations of this approach will also be evaluated.

1. Introduction

The year 1895, when Wilhelm Röntgen discovered X-rays, may be assumed as the beginning of radiotherapy. Shortly after this great discovery, first patients were treated. Early applications were done for skin cancers, although neither biological nor physical properties of ionizing radiation were understood.[1,2] Since then, new developments were implemented to improve the quality and precision of radiation delivery.[3–5] One of them was the invention of new imaging techniques e.g. Positron Emission Tomography (PET) or Magnetic Resonance Imaging (MRI). Combining modern diagnostic imaging with a cutting edge radiotherapy technology may bring further improvement.

Such a combination was first suggested by Ling et al.[6] who proposed the concept of integrating physical (which is the state of art nowadays) and biological conformality in radiotherapy. The main idea was to use functional images that may provide additional information on metabolism, physiology or genotype, in the treatment planning process. Knowing the tissue differentiation and biology inside the tumor, the dose distribution could be tailored accordingly. It is well known that hypoxic regions are resistant to treatment and that reduces the chance for recovery.[7] Hence, escalating the treatment dose in that area could increase the local control. Such individual approach to both anatomy and biology of the patient's tumor is called dose painting (DP).

DP is now being thoroughly investigated by many researchers.[8–11] There are still some aspects that need to be solved before implementing this method into clinical practice. Moreover, clinical studies should be carried out in order to prove the therapeutic gain of DP.

* *Corresponding author at*: Department of Medical Physics, Greater Poland Cancer Centre, Garbary 15, 61-866 Poznan, Poland.
E-mail address: malgorzata.skorska@wco.pl (M. Skórska).
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In this article, the summary of the functional imaging in radiotherapy treatment planning will be reviewed with emphasis on the dose painting method. Furthermore, potential limitations and uncertainties are discussed.

1.1. *Dose painting by contours vs. numbers*

Based on functional images, one may determine the functional gross tumor volume (fGTV) which may be homogenously escalated to a higher than typical therapeutic dose. The level of dose prescription in this region is equal for all voxels in the fGTV region.[6] This is called Dose Painting by Contours (DPBC). A more sophisticated method of dose painting is when the dose inside fGTV is prescribed according to the intensity of the functional image signal. This is called Doe Painting by Numbers (DPBN).[12] For example, after PET imaging the fGTV was contoured. For DPBC situation, a dose will be increased for all voxels in this region by "X" Gy. However, for DPBN the prescription dose inside fGTV will vary according to the amount of radiopharmaceutical accumulation. The dose increase in the voxels is correlated with the increase of the PET signal.

The concept of dose painting was introduced by Ling and colleagues[6] in 2000. One year later, these theoretical considerations were realized by Chao et al.,[13] who showed that dose may be increased up to 80 Gy in the hypoxic region located in the head and neck area. Idea of DPBC is clinically feasible and treatment planning is not complicated. Moreover, it can be easily performed using a typical commercial treatment planning software. The drawback of DPBC is that higher boost levels cannot be obtained using this method due to toxicity.[14]

In 2005, Bentzen proposed a new aspect of dose painting by the introduction of DPBN.[12] With this method, higher dose escalation may be obtained. However, this method is far more complex and sometimes special software is required. DPBN planning has previously been proven feasible using volumetric modulated arc therapy,[15] tomotherapy[11,16] and proton therapy.[17]

1.2. *Functional imaging*

Structural imaging (e.g. Computed Tomography (CT) or MRI) creates visual representations of patient's interior. Whereas, functional imaging detects or measures changes occurring inside a certain tissue or organ. Nowadays, CT is a gold standard imaging technique in radiotherapy. However, functional imaging may be a helpful tool in determining tumor volume, efficacy of the treatment or staging.

The most common molecular images used for tumor volume delineation and assessment of pathophysiological characteristics of tissue are PET data. Depending on the tracer used, different information is visualized. The most popular and understood tracer is fluorine-18 fludeoxyglucose (FDG) that provides metabolic and functional information useful during the radiotherapy process. It was already used in some clinical trials where dose escalation was based on FDG avid area inside the tumor volume.[18–20]

A lot of research was done also with other PET tracers. Particularly, with those that visualize tumor hypoxia which was associated with treatment failure. It is well documented that hypoxic microenvironment makes cancer cells more aggressive and resistant to treatment.[21] For this reason, patients with hypoxic regions could potentially benefit from escalating the radiation dose in those regions. However, quantification of tumor hypoxia based on PET still needs to be standardized. There have been several studies that used surrogates for hypoxia but most of them used different approach for thresholding – from visual, standardized uptake value (SUV) to kinetic analysis.[22–24]

Another important aspect is the selection of the appropriate PET tracer. There are several hypoxia tracers, e.g. 18F-fluoromisonidazole (18F-FMISO), 18F-fluoroazomycin-arabinoside (18F-FAZA) or copper(II)-diacetyl-bis(N(4)-methylthiosemicarbazone) (Cu-ATSM). However, all of them have different characteristics and there is no particular hypoxia tracer that is superior to others.[25]

For many types of tumors, proliferation of cancer cells was also linked to treatment failure. Thus, a PET tracer that is a proliferation marker, e.g. 18F-fluorothymidine (FLT), may be used for dose painting[26] or radiotherapy adaptation.

Only a few studies have been found in the literature regarding dose painting based on MR images. In some of them, dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) was employed. This is another method used for estimation of tumor oxygenation[27] and it was shown that it may be a good estimator of local control for some tumors.[28] Søvik et al.[29] and Chen et al.[30] have used this imaging modality for escalation of therapeutic dose with DPBN in head and neck and brain tumors, respectively. However, acquisition and interpretation of DCE-MRI data should be made carefully because it is very challenging.[31]

Diffusion-weighted MRI (DW-MRI) is another technique that may be applied in the personalized radiotherapy treatment planning. DW-MRI is used as an estimate of tumor cell density.[31] Dirix et al.[32] showed a potential role of this method for dose painting in the head and neck region. Moreover, Thorwarth et al.[33] showed that combining DW-MRI with other functional images may be helpful during tailored radiotherapy planning.

There were also studies based on magnetic resonance spectroscopic imaging (MRS) which can identify regions of abnormal metabolic activity.[34] van Lin et al.[35] showed that DPBC escalation up to 90 Gy in prostate cancer patients is feasible. The authors have used both DCE-MRI and MRS for determination of the boost area. Whereas, Deviers et al.[36] showed that MRS may be a future tool to define additional biological target volumes for DP in patients with glioblastoma multiforme.

1.3. *Limitations and uncertainties*

Personalized radiotherapy treatment planning based on functional imaging requires some features during the whole chain of radiotherapy preparation to be maintained. First of all, the patient must be positioned the same way during imaging and treatment, which may be sometimes cumbersome, e.g. dedicated coils for MR imaging. As a result, the table top should be flat and the ability to mount fixations e.g. thermoplastic masks must be enabled.

When it comes to fGTV delineation, some compromise must be adopted. The main limitation would be the voxel size of functional imaging which for PET is 3–5 mm. This value seems to be enormous when biological effects are considered, e.g. hypoxia cells can be observed in a micrometer scale. Due to this fact, some hypoxic cells may not be detected and, as a result, not included in the treatment planning. Moreover, in one voxel several biological processes may take place so the signal will be averaged.[37] Another limitation would be the image noise which is present in all types of functional imaging due to reconstruction algorithms. These imperfections of functional imaging may have an impact on DPBN where each voxel is attributed to different dose level and, hence, the above mentioned limitations may play a significant role. However, this aspect is controversial and probably clinical trials will help solve it.

Another aspect that is raised by the radiotherapy community is that the dependence of signal intensity of functional imaging and therapeutic dose is unknown. Until now, a vast majority of papers concerning DPBN assumed a linear relationship.[8–11,15,16] However, this assumption is theoretical and no evidence of this hypothesis has been proven in the literature.

In the case of treatment plan evaluation, the typical methodology is insufficient. In standard treatment planning the goal is to achieve a homogenous and conformal dose to the target volume and at the same time spare organs at risk. However, in DPBN, the dose in fGTV is not homogenous – it is intentionally heterogeneous. Hence, new methods of plan evaluation have been proposed in the literature. One of them is the new parameter – quality factor and quality-volume histogram proposed by Vanderstraeten et al.[10] Park et al. introduced the index of achievement and the index of hotness and coldness.[38]

Geometrical uncertainties is another limitation of DPBN. Since the dose distribution is very sophisticated, it is vulnerable to patient positioning as proven by Korreman et al.[15] However, lately, Sterpin et al.[39] and Witte et al.[40] have proposed some solutions of that problem.

Even though there are some concerns regarding DP, some clinical trials are now in progress, e.g. in Ghent, Belgium,[8,9,20] Copenhagen, Denmark,[41] and Amsterdam, the Netherlands.[19] All of them refer to the head and neck cancer and are based on the FDG PET.

2. Conclusion

DP based on functional imaging is an example of an individualized approach to treatment that seems to be very promising. However, as discussed in this review, there are some concerns regarding the usage of functional imaging in DP radiotherapy treatment planning. Much research still needs to be done and, hopefully, ongoing clinical trials will provide some new findings.

Conflict of interest

All authors have no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

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