Biologically-optimised IMRT based on molecular imaging of tumour hypoxia–the impact of the tracer used

I. Toma-Dasu[1] and A. Dasu[2,3]

[1] Medical Radiation Physics, Stockholm University and Karolinska Institutet, Stockholm, Sweden
[2] Department of Radiation Physics UHL, County Council of Östergötland, Linköping, Sweden
[3] Radiation Physics, Department of Medical and Health Sciences, Faculty of Health Sciences, Linköping University, Linköping, Sweden

Abstract— **One of the most challenging tasks of current radiation therapy is the individualisation of the treatment plans through biological optimisation and adaptation to functional aspects. This study aims to explore the robustness of a newly proposed method of treatment planning optimisation based on patient-specific radiation sensitivity determined by tumour hypoxia. Theoretical three-dimensional tumours with heterogeneous oxygenations were used to investigate the efficiency of various approaches for calculating the optimal dose distribution and the effects of reoxygenation during the treatment duration. The impact of the spatial averaging implied by the imaging method in combination with the binding properties of the tracer used has also been investigated. It has been shown that a newly proposed method for dose prescription based on functional imaging of hypoxia could lead to improved local control for several tracers that could be practically used. The approach for dose prescription appears to have a significant impact for tumours with dynamic hypoxia. Furthermore, the average implied by the imaging method could reduce the effectiveness of the method, but it still has the potential to provide significantly better results than methods employing highly heterogeneous dose distributions. The results showed that planning and optimisation of treatments based on hypoxia information from PET images is feasible and could provide the tool for individualising the planning on biological and molecular bases.**

Keywords— **tumour oxygenation, vasculature, oxygenation, PET imaging, treatment optimisation**

I. Introduction

Tumour oxygenation is one of the important physiological aspects that could be imaged with positron emission tomography (PET). The presence of hypoxia in tumours has been negatively correlated with response to treatment due to the radioresistance it confers to the cells and their malignant selection [1-2]. Several PET markers that are selectively metabolised in the hypoxic regions and become trapped intracellularly are now available for the clinical imaging of tumour oxygenation [3]. The most known tracer is Fluoromisonidazole (FMISO) that has a rather low clearance rate which requires long investigation times. Alternative nitroimidasole tracers like Fluoroetanidazole (FETA) and Fluoroazomycinarabinofuranoside (FAZA) with better clearance have also shown potential for imaging tumour hypoxia, but they have been used on a more limited scale in comparison to FMISO. Non-imidazole tracers for hypoxia like Cu(II)-diacetyl-bis-N-(4)-methylthiosemicarbazone (Cu-ATSM) are also used. There is therefore a great deal of interest in using the information provided by these tracers on the spatial localisation and the severity of the hypoxic regions to target the potentially troublesome hypoxic foci in tumours.

Several approaches have been proposed to include PET-based hypoxia information into treatment planning [4]. The majority of these involve an escalation of the radiation dose to the supposedly radioresistant targets in the tumour according to the intensities of the image pixels without taking into account the binding properties of the tracer used. Besides the dynamics of hypoxia [5] and the resolution of the imaging modality [6], this has been one aspect of concern for the clinical implementation of PET-based hypoxia targeting. A practical method to include hypoxia information from FMISO-PET into treatment planning taking into account the concerns raised above has recently been proposed [7-8]. This study aims to explore the efficiency of the proposed method for other tracers than FMISO through simulations on tumours with realistically heterogeneous oxygenation as well as the issues that might appear at its clinical implementation into an algorithm for biological optimisation.

II. Methods and materials

The principle of the method proposed to optimise treatment plans based on imaging of tumour hypoxia is illustrated in figure 1. PET images of tumour hypoxia could be converted into radiation sensitivity maps using the uptake properties of the tracer. Dose escalation factors required for a preset level of tumour control would then be calculated from the radiation sensitivity maps obtained in the first step. In order to account for heterogeneity and the dynamics of hypoxia, the resultant distributions would have to undergo a

M. Long (Ed.): World Congress on Medical Physics and Biomedical Engineering, IFMBE Proceedings 39, pp. 1742–1745, 2013.
www.springerlink.com

further optimisation step which leads to a simplified dose distribution with homogeneous doses prescribed to the radioresistant subtargets in the tumour [7].

An important step in this complex algorithm that uses imaging information for advanced treatment planning is thus the conversion of the signal intensities in the PET images into radiation sensitivities. It has indeed been shown that the use of empirical conversions could lead to dose levels that might have little relevance or could even be dangerously high [9]. Relevant conversion functions could therefore be obtained from experimental data on tracer uptake in hypoxic conditions. Given the uptake mechanisms of the tracers, a suitable equation for this purpose would be one describing the inhibition of chemical reactions (equation 1).

$$Uptake = A - \frac{B \cdot pO_2}{C + pO_2} \quad (1)$$

where pO_2 is the local oxygen tension and A, B and C are reaction-specific parameters [7].

Experimental data on the uptake of hypoxic tracers has been obtained from Lewis et al [10] for FMISO and Cu-ATSM and from Rasey et al [11] for FETA. The conversion function between marker uptake and radioresistance would then be obtained by combining the curve describing the uptake of the marker as a function of local oxygen tension with the relationship between oxygenation and radiosensitivity, like the one proposed by Alper and Howard-Flanders [12].

The result would therefore be an objective relationship between uptake values in the images and the dose modification factors needed to counteract the radioresistance of the cells as it takes into account the particular binding features of each tracer. The conversion of image intensities into dose modifying factors leading to preset values of tumour control is only the first step for robust dose prescription as described in the algorithm proposed by Toma-Dasu et al [7] which takes into account the local heterogeneity in radiosensitivity related to tumour oxygenation and the dynamics of the radioresistant regions. The algorithm proposes that radioresistant subtargets should be defined in the tumour and that homogeneous doses should be prescribed to each subregion in an attempt to combine the advantages of increasing the dose to the radioresistant regions and avoiding the mismatches that could result from heterogeneous dose distributions.

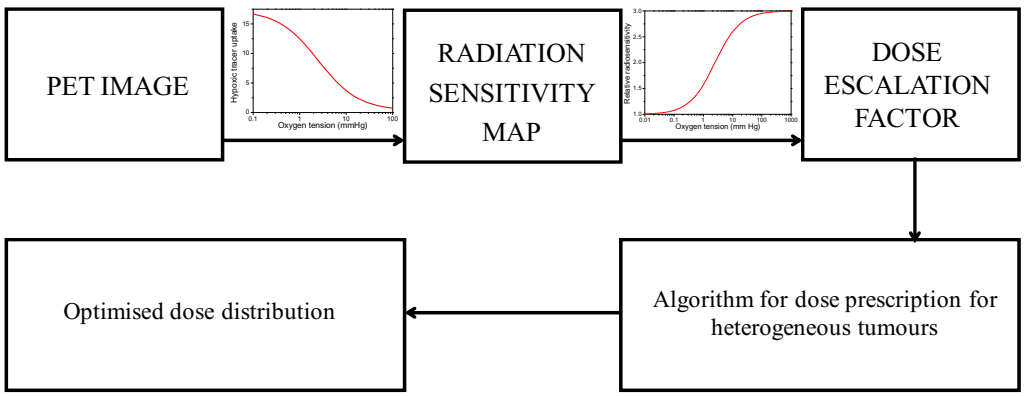

Fig. 1 Schematics of the work-flow for biologically optimised planning based on PET imaged hypoxia. The uptake of the tracer is converted to a map of radiation sensitivity based on a calibration curve for the particular tracer. The sensitivity map is used for determining the dose escalation factors required for a predefined level of survival at the end of the treatment. The calculated doses are used as input for the optimisation functions in the IMRT plans.

The efficiency of the proposed algorithm with respect to the control of the tumour was tested on three-dimensional theoretical tumours with heterogeneous dynamic oxygenation imaged with FMISO, FETA or Cu-ATSM.

Results of a previously developed model to simulate dynamic tissue oxygenation have been used for this purpose as described in Toma-Dasu et al [7]. The focus in this study has been on the averaging effects of the imaging method using different hypoxia tracers and the possible interaction with the binding properties of the tracer used. For this purpose, the uptake curves for the hypoxia tracers, FMISO, FETA or Cu-ATSM, have been used to simulate their selective binding in the hypoxic areas of the tumour.

III. Results and Discussion

Figure 2 shows the relationships between marker uptake and local oxygen tension for three of the most used markers for PET imaging of tumour hypoxia, FMISO, Cu-ATSM and FETA.

The results show that the three markers have different discrimination powers that would be reflected in the distribution of signal intensities in PET images. Thus, it appears that FETA is the most efficient tracer to image the extreme levels of hypoxia, while FMISO and Cu-ATSM could also image cells at intermediate oxygen tensions. This suggests that segmentations on images obtained with the latter two markers would provide a more conservative definition of the radioresistant regions in the tumours. At the same time, such an approach could overestimate the amount of hypoxia in tumours. Furthermore, the results for FETA indicate that some cells could be more able than others to metabolise the tracer at intermediately low oxygen levels. Thus, these results indicate that a generic conversion curve may not be suitable for all the available tracers for imaging hypoxia and for all the tumours.

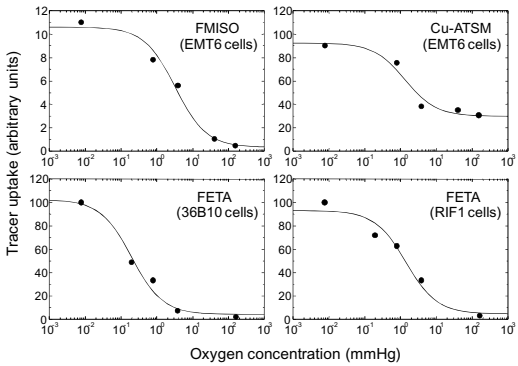

Fig. 2 Uptake curves for the hypoxic tracers in various cell lines as a function of the oxygen concentration.

An important issue for the clinical implementation of the proposed method is the averaging over large tissue volumes that is characteristic to many imaging modalities and PET in particular. Indeed, hypoxic regions could exist on a microscopic scale [6,13,14] that would not be rendered correctly with the resolution available to modern imaging systems. This would consequently be reflected in the heterogeneity of the image signals and has the potential to affect the efficiency of the proposed dose prescription method [7].

Simulations were performed to investigate whether the impact of the PET image resolution is the same for all the hypoxic markers. Thus in order to simulate the effect of limited measurement resolution, tracer uptake maps in the simulated tumours were convoluted with the same Gaussian function and the resultant maps of radiosensitivity related parameters were then used as input for the dose prescription algorithm. The predicted results for all the hypoxic tracers considered are shown in figure 3.

As suggested in Toma-Dasu et al [7], it appears that averaging could reduce the effectiveness of the prescribed doses. However, the magnitude of this effect differs according to the uptake properties of the tracer used for imaging. Thus, it appears that averaging has the least effect on the tracers most efficient in imaging the extreme levels of hypoxia (as is the case of FETA in 36B10 cells), while most effect is to be expected for tracers that could bind even at intermediate oxygen tensions (as illustrated by FMISO in EMF6 cells). The explanation for this behaviour could be that the former tracers bind preferentially to the most hypoxic cells and therefore there is not very much heterogeneity in the resulting tracer distribution. In contrast, the latter tracers could cover a broader range of oxygen tensions, with a larger heterogeneity, which could lead to prescribed doses with reduced effectiveness if not imaged accurately.

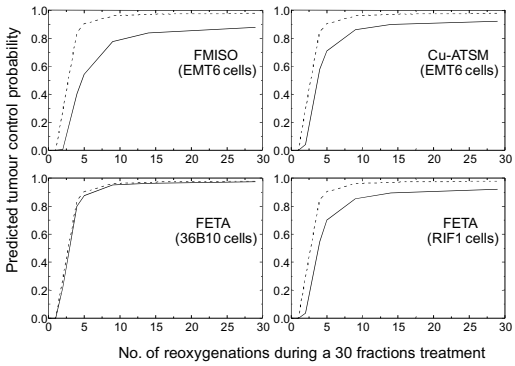

Fig. 3 The predicted tumour control probability as a function of the number of oxygen changes during the course of a radiotherapy treatment delivered in 30 fractions for the ideal situation when the tracer uptake is accurately determined in each cell (dotted line) or is affected by the averaging process as in a PET image (full line).

The results also indicate that the proposed method to account for tumour hypoxia could be successfully used with several tracers even when the resolution of the images used is reduced due to spatial averaging. More extreme averaging could reduce the heterogeneity in the images and would therefore influence the prescribed dose levels. Further investigations on the efficiency of the method for clinical images are therefore warranted. Nevertheless, it appears that the proposed method could account for the effects of hypoxia dynamics and leads to higher control levels than those that could be obtained from highly heterogeneous dose distributions.

The results also indicate that the method proposed by Toma-Dasu et al [7] loses effectiveness for very low reoxygenation rates. This could be a matter of concern for highly hypofractionated treatments that do not provide enough reoxygenation opportunities, but for longer schedules with conventional fractionations this may not be an issue since clinical observations of tumour oxygenation indicate that

the patterns of hypoxia change in weekly investigations [5] and preclinical studies indicate even faster reoxygenation rates [15].

Clinical implementation of the conversion function described in this study requires some form of normalisation, since absolute signal intensities measured with PET depend on the injected activity, measurement time and the efficiency of the detectors. This could be achieved in practice by normalising the images to the signal intensity in a region with known or measurable oxygenation, with preferably high tissue oxygenation. The reference region for oxygenation could be a muscle as muscles generally have good oxygenation or to avoid difficulties in identifying muscles or determining the activities in small structures, a large region outside the target with better oxygenation.

Moreover, the clinical implementation of the proposed method involves further aspects that should be accounted for and which are beyond the purpose of the present study. Thus, the method requires that all the tumour cells are exposed to the hypoxic marker in order to metabolise it according to their oxygenation level. This could be a matter of concern for the transiently hypoxic cells around the blood vessels with limited perfusion, but investigation times are generally longer than the timescale of perfusion-related reoxygenation and therefore the impact of this aspect might be rather limited. The metabolic properties of the cells in the target volume could be another matter of concern as different uptake rates have been observed for various cells (figure 3). This is particularly relevant for cases when the target volume is a mix of tumour and stroma cells and observational studies are required to study the impact of this aspect. The results in figure 3 though indicate that the predicted differences in outcome may be rather small and this comes in support of the studies that showed good correlations between hypoxia measurements with PET and other methods [16].

IV. Conclusions

The results showed that the recently proposed method for dose prescription based on functional imaging of hypoxia [7] could lead to improved local control for several tracers that could be practically used. The average implied by the imaging method could reduce the effectiveness of the method, but it still has the potential to provide significantly better results than methods employing highly heterogeneous dose distributions. Clinical implementation of the method has to be performed in parallel with observational studies aimed at investigating the impact of clinically-specific aspects of hypoxia imaging with PET.

Acknowledgment

Financial support from the Cancer Research Funds of Radiumhemmet and the County Council of Östergötland is gratefully acknowledged.

References

1. Höckel M, Knoop C, Schlenger K et al. (1993) Intratumoral pO2 predicts survival in advanced cancer of the uterine cervix. Radiother Oncol 26:45-50
2. Brizel DM, Dodge RK, Clough RW et al. (1999) Oxygenation of head and neck cancer: changes during radiotherapy and impact on treatment outcome. Radiother Oncol 53:113-117
3. Apisarnthanarax S, Chao KS (2005) Current imaging paradigms in radiation oncology. Radiat Res 163:1-25
4. Thorwarth D, Alber M (2010) Implementation of hypoxia imaging into treatment planning and delivery. Radiother Oncol 97:172-175
5. Eschmann SM, Paulsen F, Bedeshem C et al. (2007) Hypoxia-imaging with (18)F-Misonidazole and PET: changes of kinetics during radiotherapy of head-and-neck cancer. Radiother Oncol 83:406-410
6. Busk M, Horsman MR, Overgaard J (2008) Resolution in PET hypoxia imaging: voxel size matters. Acta Oncol 47:1201-1210
7. Toma-Dasu I, Dasu A, Brahme A (2009) Dose prescription and optimisation based on tumour hypoxia. Acta Oncol 48:1181-1192
8. Toma-Dasu I, Uhrdin J, Antonovic L et al. (2011) Dose prescription and treatment planning based on FMISO-PET hypoxia. Acta Oncol
9. Toma-Dasu I, Uhrdin J, Dasu A et al. (2009) Therapy optimization based on non-linear uptake of PET tracers versus "linear dose painting". in: WC 2009, IFMBE Proceedings 25/I, edited by Dössel O, Schlegel WC. Springer, 221-224
10. Lewis JS, McCarthy DW, McCarthy TJ et al. (1999) Evaluation of 64Cu-ATSM in vitro and in vivo in a hypoxic tumor model. J Nucl Med 40:177-183
11. Rasey JS, Hofstrand PD, Chin LK et al. (1999) Characterization of [18F]fluoroetanidazole, a new radiopharmaceutical for detecting tumor hypoxia. J Nucl Med 40:1072-1079
12. Alper T, Howard-Flanders P (1956) Role of oxygen in modifying the radiosensitivity of E. Coli B. Nature 178:978-979
13. Dasu A, Toma-Dasu I, Karlsson M (2003) Theoretical simulation of tumour oxygenation and results from acute and chronic hypoxia. Phys Med Biol 48:2829-2842
14. Dasu A, Toma-Dasu I (2008) Vascular oxygen content and the tissue oxygenation--a theoretical analysis. Med Phys 35:539-545
15. Chaplin DJ, Olive PL, Durand RE (1987) Intermittent blood flow in a murine tumor: radiobiological effects. Cancer Res 47:597-601
16. Gagel B, Reinartz P, Dimartino E et al. (2004) pO(2) Polarography versus positron emission tomography ([(18)F] fluoromisonidazole, [(18)F]-2-fluoro-2'-deoxyglucose). An appraisal of radiotherapeutically relevant hypoxia. Strahlenther Onkol 180:616-622

Address of the corresponding author:

Author: Iuliana Toma-Dasu
Institute: Medical Radiation Physics
Stockholm University and Karolinska Institutet
City: 171 64 Stockholm
Country: Sweden
Email: iuliana.livia.dasu@ki.se