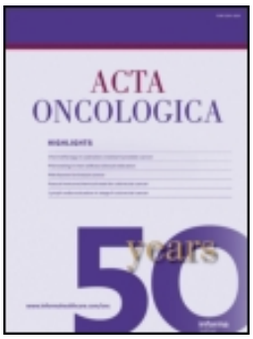

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ORIGINAL ARTICLE

Dose prescription and treatment planning based on FMISO-PET hypoxia

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Abstract

Purpose. The study presents the implementation of a novel method for incorporating hypoxia information from PET-CT imaging into treatment planning and estimates the efficiency of various optimization approaches. Its focuses on the feasibility of optimizing treatment plans based on the non-linear conversion of PET hypoxia images into radiosensitivity maps from the uptake properties of the tracers used. *Material and methods.* PET hypoxia images of seven head-and-neck cancer patients were used to determine optimal dose distributions needed to counteract the radiation resistance associated with tumor hypoxia assuming various scenarios regarding the evolution of the hypoxic compartment during the treatment. A research planning system for advanced studies has been used to optimize IMRT plans based on hypoxia information from patient PET images. These resulting plans were compared in terms of target coverage for the same fulfilled constraints regarding the organs at risk. *Results.* The results of a planning study indicated the clinical feasibility of the proposed method for treatment planning based on PET hypoxia. Antihypoxic strategies would lead to small improvements in all the patients, but higher effects are expected for the fraction of patients with hypoxic tumors. For these, individualization of the treatment based on hypoxia PET imaging could lead to improved treatment outcome while creating the premises for limiting the irradiation of the surrounding normal tissues. *Conclusions.* The proposed approach offers the possibility of improved treatment results as it takes into consideration the heterogeneity and the dynamics of the hypoxic regions. It also provides early identification of the clinical cases that might benefit from dose escalation as well as the cases that could benefit from other counter-hypoxic measures.

The technological revolution in imaging methods during the last decades has significantly improved cancer diagnosis and prognosis by increasing the accuracy of identifying and delineating target structures and it has formed the foundation for three dimensional (3D)-based radiation treatment methods [1,2]. Besides the anatomical information, a whole array of methods has recently emerged and it is now available to provide biological information on metabolic, biochemical and physiological factors [3]. These have the potential of transforming the way radiation therapy is performed [4–6]. Thus, combining the detailed knowledge of tumor characteristics with recent advances in radiation treatment delivery has the potential to customize radiation therapy with very high precision and individualization by targeting specifically the adverse factors that might contribute to the failure of the treatment. The new imaging methods might also provide the necessary tools to monitor the response and the efficiency of the treatment used [5]. Among the imaging techniques, positron emission tomography (PET) has the advantage of being almost non-invasive since it uses tracers that are usually metabolic substitutes, versatile, as several tracers are already available for investigating various processes and

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quite sensitive since concentrations of tracers in the sub-micromolar range could be imaged [7].

The current practice in radiation therapy is however based on the physical optimization of dose distributions according to the anatomical information regarding the localization and the extent of the tumor and the normal tissues around it [1,3,8]. The routine planning for clinical radiation treatment does not take into account the particular radiation sensitivity of the tumor in individual patients, nor the heterogeneity, both spatial and temporal, of the tumor resistance. It is however thought that these aspects may be the cause for treatment failure for a considerable fraction of the non-respondent patients, as the conventional dose prescription might not ensure the curative doses needed to counteract the adverse factors in the tumor [9–12]. Among these adverse factors one has to count variations in cellular density in tumors and the distinct microenvironment characteristic to tumors [13,14]. The unique tumor microenvironment in particular is thought to influence strongly the response to both radiotherapy and chemotherapy as on one hand it is thought to determine a considerable increase of the radioresistance of the tumor cells and on the other it might interfere with the mechanisms of action of the various chemotherapeutic agents [13,15].

Few proposals to include molecular and functional imaging information into treatment planning have been made [16,17], most effort being put into counteracting the effects of tumor hypoxia, one of the most important components of the tumor microenvironment. A common approach in the literature is to delineate a supposedly radiation resistant subtarget associated to hypoxia in the tumor and prescribe an empirically escalated dose in the limits imposed by the tolerance of the normal tissues around the tumor [18,19]. The drawback of this approach is that the escalated dose might not be large enough to counteract the hypoxic radioresistance and therefore the probability of controlling the tumor might still be low although the tolerance of the normal tissues was pushed to its limit. Other approaches proposed the delivery of highly heterogeneous dose distributions based on a proportional increase of the dose according to the signal intensity in the PET or magnetic resonance (MR) image [20–22]. Another approach, more complex but also resulting in heterogeneous dose distributions, was based on dynamic PET information [23]. In order to preserve the average dose to the target, other studies have proposed the redistribution of the dose within the target, by increasing the dose levels to the hypoxic voxels while decreasing the prescribed dose to the remaining voxels in the tumor [24–26]. One of the problems associated with the prescription of highly heterogeneous dose distributions comes from the dynamics of tumor hypoxia. As the highly heterogeneous hypoxic regions change their spatial distribution during the course of radiotherapy, this could easily lead to mismatches between the resistant sub-regions and the planned hotspots in the distribution. Indeed, experimental and clinical studies have shown that tumor oxygenation is not static throughout the treatment. Thus tumor oxygenation changes on the microscopic scale due to variations of acute hypoxia [27]. This means that hypoxic cells could improve their oxygen supply through reoxygenation and vice versa following the opening and closure of the tumor blood vessels. Furthermore, other mechanisms, such as angiogenesis and proliferation, could change the chronic hypoxia pattern throughout the duration of the treatment as it has been observed in clinical studies [28–31]. These changes are present both on microscopic and on locoregional level and will affect considerably the hypoxic pattern in the tumor. Alternative methods for including molecular and functional imaging information into treatment planning propose treatment adaptation based on careful monitoring of the changes in the tumor appearance and hence repeated imaging sessions [5]. In spite of their limitations, these studies have shown that improvements in response could be achieved by incorporating information about the tumor microenvironment in all clinical phases starting from investigation with PET, to the choice of the treatment approach and to the verification and adaptation of the treatment.

An intrinsic problem of all the above mentioned methods for incorporating PET information into treatment plans resides in the limited capacity of the PET technique to image the uptake at cellular level as shown by Busk et al. [32]. This also leads to difficulties in imaging the dynamics of hypoxia at cellular scale by repeated scans. To account for these limitations a mathematical algorithm for calculating the prescribed doses required by tumors to achieve a predefined level of control at the end of the treatment has been developed based on 3D maps of radiation sensitivities [33]. The method is based on the estimation of the variance of the distribution of radiation sensitivity or radiation resistance within the tumor from PET images taken with hypoxic tracers and takes into account changes in the radiation sensitivity at cellular level during the course of the treatment without the need for additional PET scans.

The present study aims to study the feasibility of using the mentioned algorithm for clinical dose prescription based on PET hypoxia images. The algorithm has been implemented into a system for advanced treatment planning studies that allows

the comparison of different dose prescription strategies and the calculation of the expected tumor response.

Material and methods

Patient data

Seven patients with locally advanced head and neck squamous cell carcinomas (HNSCC) have been investigated prospectively in this study. The primary tumor site was located on the larynx for three of the patients and on the oropharynx for the other four. The FMISO PET-computed tomography (CT) data were recorded for each patient before the start of the therapy. The median time interval between the PET scan and the start of the treatment was six days with a range of 1–14 days. Patient and tumor characteristics are summarized in Table I.

The PET investigations were performed on a Siemens PET/(CT) scanner (Erlangen, Germany). One static FMISO PET-CT scan was taken for each patient. The intrinsic resolution of the scanner was 4 mm in full width at half maximum. The PET images were acquired at 120–160 minutes after the intravenous injection of 370 MBq of 18F-fluoromisonidazole. The attenuation, scatter and random coincidences corrections as well as the image reconstruction were performed using the standard clinical FDG parameters as described in Dirix et al. [34].

Evaluation of the radiosensitivity distribution from the PET images

Tumor hypoxia imaging with nitroimidazole tracers like FMISO is based on the selective retention of the tracers according to the inhibition of the enzymatic reduction of the nitroaromatic in the presence of oxygen [35,36]. This results in a variation of the accumulated uptake of the tracer according to the local tissue oxygenation that will thus determine the resulting signal intensities in the tumor and normal tissues.

In this study FMISO PET images were used to determine the relative radiation resistance of the poorly oxygenated tumor regions compared to the well oxygenated ones. The correlation was based on a non-linear voxel scaling of the tracer uptake in the delineated targets (gross tumor volume or GTV and clinical target volume or CTV) relative to the average value in the patient outside the target. The average partial pressure of oxygen outside the target was assumed to be 60 mmHg, which correlates with the low background in the PET image [37,38]. This assumption allows the quasi-quantitative estimation of hypoxia at voxel level within the tumor.

The conversion of the intensities in the PET image into radiation sensitivities was done in two steps. First the conversion function from the PET intensities to oxygen partial pressures was obtained by fitting experimental data of the tracer uptake in oxic and hypoxic conditions with an equation describing the inhibition of chemical reactions (Equation 1).

$$Uptake = A - \frac{B \times pO_2}{C + pO_2} \tag{1}$$

where pO_2 is the local oxygen tension and A, B and C are reaction-specific parameters [39]. Experimental data on FMISO uptake has been obtained from Lewis et al. [40].

The fitted experimental data was then combined with the equation describing the modification of radioresistance according to the local oxygen tension (Equation 2) proposed by Alper and Howard-Flanders [41], in order to obtain a relationship between uptake values in images and the dose modification factors (f) needed to counteract the radioresistance of the cells:

$$f = \frac{OER_{max}(k + pO_2)}{k + OER_{max} \times pO_2} \tag{2}$$

where OER_{max} is the maximum effect that is achieved in the absence of oxygen, k is a reaction constant and pO_2 is the local oxygen tension. Biologically relevant values were used for the parameters in Equation 2 ($OER_{max} = 3$, $k = 2.5$ *mmHg*) [42,43].

Dose prescription

The prescribed dose to the tumor taking into account the heterogeneity in radiosensitivity was calculated using the method described in Toma-Dasu et al. [33]. The calculation is based on the estimation of the local radiation sensitivity expressed by the $\alpha(\mathbf{r})$ and $\beta(\mathbf{r})$ parameters of the LQ model [44–46] which depend on the local oxygen tension according to Equations 3 and 4, where f is given by Equation 2 [47].

Table I. Details of the patient data used for this study.

Patient no.	Primary tumour site	Age	Gender	Clinical T classification	Clinical N classification
1	Larynx	48	M	3	0
2	Larynx	60	M	4a	2c
3	Larynx	61	M	1	2c
4	Oropharynx	57	M	3	2b
5	Oropharynx	60	M	2	2c
6	Oropharynx	48	M	4a	1
7	Oropharynx	55	M	4a	1

$$\alpha(\mathbf{r}) = \frac{\alpha_{oxic}}{f(\mathbf{r})} \tag{3}$$

$$\beta(\mathbf{r}) = \frac{\beta_{oxic}}{\left[f(\mathbf{r})\right]^2} \tag{4}$$

The resulting heterogeneous dose distribution $D(\mathbf{r})$ accounts for the local oxygenation of the cells but does not take into account the temporal variation in local radiosensitivity associated with reoxygenation. One way to prevent the potential mismatches between the voxels containing cells lacking oxygen and the corresponding high doses needed to eradicate them during the course of fractionated radiotherapy is to deliver a uniform high dose to the whole tumor that accounts for the maximum hypoxic protection that may be encountered, which might not be practical.

As an alternative to this approach, Toma-Dasu et al. [33] proposed to segment the target in several regions and to prescribe a uniform dose, D_P, to each segment in the target which could counteract the effects of dose and radioresistance heterogeneity ensuring a level of tumor control probability P as given by Equation 5:

$$D_P = \frac{\bar{D}}{\left[1 - \frac{\gamma}{2P(\bar{D})}\left(\frac{\sigma_D}{\bar{D}}\right)^2\right]} \tag{5}$$

where $\bar{D}$ and σ_D are respectively the average and standard deviation of the corresponding segments from the heterogeneous dose distribution $D(\mathbf{r})$ and γ is the slope of the dose response curve [33].

This dose prescription method has been compared to prescription methods recommending a uniform dose to the target volume that could account for the effects of mixed radiosensitivities in the whole tumor. Two different cases have been considered for comparison purposes: one assuming that the oxygenation of the whole target volume is the same throughout the treatment ('static oxygenation') and the other assuming that the overall oxygen distribution of the target is the same, while the oxygenation of the individual voxels could change between the fractions according to the initial distribution ('dynamic oxygenation'). These two cases bracket the clinical observations of repeated investigations of tumor oxygenations.

Advanced treatment planning system

The algorithm for calculating the prescribed doses has been implemented into the ORBIT Workstation, an advanced system for treatment planning developed by RaySearch Laboratories AB. The system is built up as a clinical treatment planning system in which the user could define the clinical targets (GTV, CTV and PTV), organs at risk and other regions of interest. The system also allows the simultaneous display of the uptake in the PET image superimposed on the CT images. In order to devise a plan according to the proposed algorithm, the user also has to define the hypoxic compartments within the GTV/CTV based on the uptake levels calculated relative to a well-oxygenated region in the patient. In the present study hypoxic regions were defined with a threshold corresponding to an oxygen tension of 10 mmHg, but alternative methods could easily be included in the system. The parameters of the conversion function relating PET tracer uptake to oxygen partial pressure are given as input parameters, so that the algorithm could be adapted to the features of various hypoxic tracers. Based on this information, the system transforms the PET image into an oxygenation map, which is delivered to the response prediction module. The distribution of dose modifying factors, f, calculated from the oxygenation map is then used for defining physical dose objectives according to Equation 5 for the subregions of the clinical target volume. These objectives are then delivered to the treatment planning module, where the user may add additional objectives and constraints regarding target and organs at risk which will all be subsequently used to devise a treatment plan (Table II). Differences in resolution between the PET or radiosensitivity matrix and the dose grid were resolved with a method based on the weighted average given by the distances between voxel centres. The resulting doses from the prescription algorithm described in the sections above are compared to the dose levels required for the uniform target dose approach to reach the same tumor control probability under the assumption of static or uniform tumor oxygenation as mentioned above. For TCP calculations, the algorithm uses biologically-relevant parameters derived from clinical studies [48,49].

Table II. OAR constraints used for planning optimization for all seven patients included in the study.

OAR constraints				
Spinal cord	Mandibula	Left parotid gland	Right parotid gland	Non-specific normal tissue
Maximum dose 38 Gy	Maximum DVH 30 Gy to 1% volume	Maximum DVH 38 Gy to 5% volume	Maximum DVH 38 Gy to 5% volume	Maximum DVH 50 Gy to 1.5% volume

Results

Figure 1 shows the fitting of experimental data on tracer uptake leading to conversion curves used for decoding the hypoxia information in the PET images. Experimental data on tracer uptake variation with oxygen tension had been fitted with an equation describing the inhibition of chemical reactions leading to $A = 10.9$, $B = 10.7$, $C = 2.5$ mmHg for the parameters of Equation 1. Combining the result with the curve giving the cellular radiosensitivity as a function of oxygen tension leads to a non-linear dependence of the three parameters as illustrated in Figure 1. The conversion curve relating directly the relative uptake and the dose modifying factors could be obtained by projecting the curve onto the corresponding plane of parameters. This has subsequently been used for PET image conversion in the advanced treatment planning system.

Table III shows the result of the automatic dose prescription algorithm based on the clinical FMISO PET data for all the seven patients included in the study. The prescribed doses for the clinical targets were calculated with the advanced treatment planning system assuming a target control probability of 95% and accounting for the individual tumor oxygenations. The results show that for those patients with generally low and rather homogeneous PET tracer uptakes in the tumors (illustrated by patients 2–7 in Table III), indicating tumors that were only mildly hypoxic, there were small differences between the predicted doses for the three investigated approaches. This contrasted to the prescriptions for patient 1 that had a pronounced FMISO uptake (left panel in Figure 2) indicating a rather hypoxic tumor, for which the different prescription approaches led

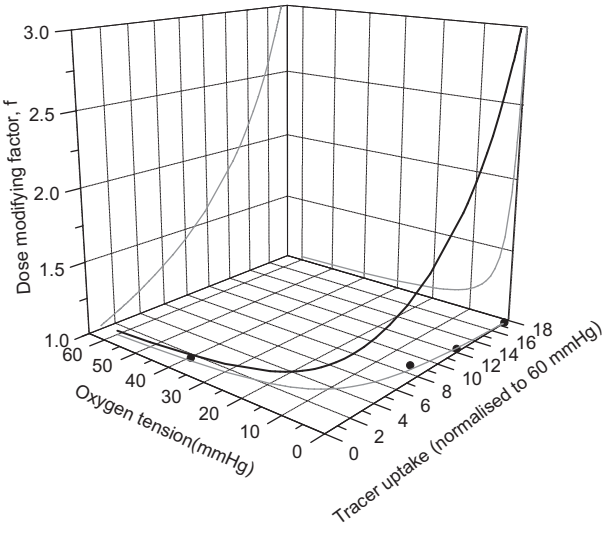

Figure 1. Conversion of tracer uptake into relative radiation sensitivity curves used in the study.

Table III. Prescribed doses for 95% TCP for several targets under various assumptions regarding the oxygenation of the tumor.

	Calculated dose (Gy)				
	Static oxygenation	Dynamic oxygenation	Segmented method		
Patient no.	Clinical target	Clinical target	CTV	GTV	HTV
1	121	77	66	73	98
2	70	70	66	70	72
3	71	68	65	70	73
4	69	67	64	69	71
5	68	66	64	67	70
6	67	65	64	66	70
7	76	75	72	76	78

to quite different dose levels. In this particular case, the hypoxic core of the tumor is reflected in the map of dose modifying factors accounting for tumor hypoxia (middle panel of Figure 2). Assuming that the tumor oxygenation remains the same for the whole duration of the treatment, a dose of 121 Gy would be required for the clinical target volume to achieve the target tumor control probability of 95%. While not very realistic, the assumption of a static oxygenation could be regarded as a conservative approach since it does not take into consideration the reoxygenation of the tumor leading to a gradual increase in radiation sensitivity as the treatment progresses. Delivering such a high dose is practically impossible with most of the existing techniques, given the tolerance levels of the organs at risk near the tumor. This also indicates that doses in the current clinical curative range cannot sterilize tumors with static radioresistant regions. In contrast, when taking into consideration that individual voxels have acutely varying oxygenations throughout the treatment, while the overall regional oxygenation of the tumor remains the same, by determining the distribution of tracer uptake in the various delineated volumes and keeping it the same between fractions but varying the actual values in individual voxels, the corresponding dose for patient 1 is 77 Gy. This value is closer to those used rather successfully in current clinical practice than the one calculated assuming a static pattern of oxygenation, thus confirming that reoxygenation has to occur in tumors in order to control them with doses in the clinical range.

The dose prescription levels in Table III were subsequently used as objectives for the optimization of treatment plans aimed at delivering segmented dose distributions adapted to the oxygenation in the clinically-defined targets as proposed by Toma-Dasu et al. [33]. The target objectives for the patients with non-hypoxic tumors are within 10% of each other (e.g. 64–70 Gy, 72–78 Gy) and in fact quite similar

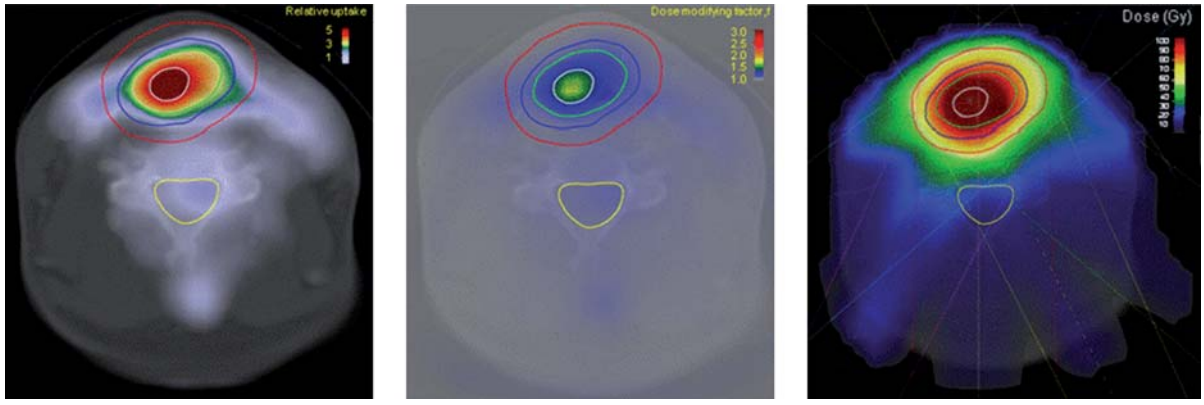

Figure 2. Clinical tracer uptake (left panel) and corresponding patient-specific dose modifying factors (middle panel) calculated with the algorithm proposed in the study for patient 1. The resulting dose distribution (right panel) calculated by the treatment planning system based on the segmented objectives for patient 1. The clinically-defined GTV, CTV and PTV are indicated respectively by the green, blue and red contours. Inside the GTV, the hypoxic segment is delineated in white.

to the dose levels used in current clinical practice. This indicates that treatments for these patients may easily be devised with a uniform dose planning approach. In fact, such an approach would be preferred from the point of view of Occam's principle as it would save the resources of the radiation therapy department, while leading to essentially the same result. Conversely, hypoxia-targeting approaches for these patients might fail to provide significant improvement of the outcome.

The situation is however quite different for patients with hypoxic tumors, like patient 1, for which it was calculated that the dose to the hypoxic target for the preset TCP level of 95% has to be 98 Gy, the dose to the surrounding GTV 73 Gy and the dose to the better oxygenated periphery of the clinical target volume only 66 Gy. Table IV summarizes the specific dose prescription objectives used together with the more general constraints in Table II to devising clinically relevant treatments with the three approaches described above. The target coverage from the resulting plans (Table V) indicates that a segmented dose distribution could be achieved in practice with an IMRT technique with seven beams as illustrated in the right panel of Figure 2. Such a plan has the advantage that it better spares the normal tissues surrounding the target since the high dose is focused to the hypoxic target, centrally-located within the tumor, while the periphery requires approximately 10 Gy less than in the case of homogeneous dose delivery and thus reducing the dose burden of the adjacent normal tissues. Indeed, the normal tissues constraints prevented a satisfactory coverage of the CTV for the planning approach assuming a uniform dose to the target.

Discussion

At present, the scientific community is engaged in a debate on the value added by quantitative functional PET imaging for predictive or prognostic purposes that would probably be settled only after the results of large and very thoroughly designed clinical trials will be reported. Theoretical modelling has an important role in this debate as it could be used to investigate the gain that could be brought by PET based hypoxia targeting and to identify the relevant issues that should be investigated in clinical trials. This paper explores theoretically the potential of targeting hypoxia in order to identify the relevant issues that should be investigated in clinical trials. The present study has therefore investigated the clinical feasibility for patient treatment planning of a new method for targeting the hypoxic regions in tumors imaged with

Table IV. Function parameters used for planning optimization for three different treatment planning approaches for patient 1.

Optimization function definitions	Target physical objectives			
	PTV	CTV	GTV	HTV
Plan 1. Segmented dose distribution	Minimum dose 60 Gy	Minimum dose 66 Gy	Minimum dose 73 Gy	Minimum dose 98 Gy
Plan 2. Dynamic oxygenation	Minimum dose 60 Gy	Minimum dose 77 Gy	Minimum dose 77 Gy	Minimum dose 77 Gy
Plan 3. Static oxygenation	Minimum dose 60 Gy	Minimum dose 121 Gy	Minimum dose 121 Gy	Minimum dose 121 Gy

Table V. Target coverage obtained from three different planning approaches for patient 1.

	Volume receiving 100% of the prescribed dose			
	PTV	CTV	GTV	HTV
Plan 1. Segmented dose distribution	86%	100%	100%	100%
Plan 2. Dynamic oxygenation	86%	90%	100%	100%
Plan 3. Static oxygenation	86%	35%	66%	98%

PET tracers. The results indicate the potential for dose sparing that could be obtained clinically by focusing the dose to the radioresistant regions. They also showed the importance for any targeting approach to take into consideration the dynamic aspect of hypoxia as well as its combined effect with the spatial heterogeneity of the radioresistant regions. The algorithm described in this study takes these aspects into consideration and could therefore be considered an important step towards the individualization of radiation therapy that aims to take into consideration the particular features of the patient.

The investigated dose prescription approach is based on the non-linear conversion of the intensities in PET images into modifying factors of the cellular radiation sensitivity and the segmentation of the target according to the predicted radiation resistance. The dose prescription method is based on a simultaneous boosting of the hypoxic areas while avoiding an active reduction of the dose in the potentially non-hypoxic areas in the tumor. Indeed, as the specificity of the imaging methods is lower than unity, an active reduction of the dose in the areas with false negative signals would be equivalent to an effective underdosing that leads to a reduction in the probability of local control. Using clinically-derived radiobiological parameters, the proposed method keeps the dose to the probably non-hypoxic areas to a realistic minimum level that would anyhow be used according to current routine dose prescription approaches, i.e. those that do not take actively into consideration the imaging information, thus resulting in a robust and safe dose prescription approach. This way, the method ensures that the current outcome levels are reached without risking the underdosage of targets. Furthermore, being based on the uptake properties of the tracer, the method is expected to lead to a better interpretation of the images used as input that avoids dangerous underestimating or overestimating of the cellular radiosensitivities in the target that may result from empirical approaches. From this point of view, the proposed method of dose prescription is expected to lead to improved outcome levels compared to empirical or suboptimal dose prescription approaches. It should be mentioned however that the accuracy in determining the dose that should be prescribed relies on several aspects including the relationship between the uptake of the tracer and the oxygenation of the cells. The influence of the conversion function from uptake to prescribed doses has been previously investigated and discussed [39,50]. There is therefore a need for more information in this area to supplement the few experimental data that currently exist. Experimental studies are also needed to identify possible variations that may be encountered for different tracers in various cells with different metabolic properties. This would offer valuable information on the possible variations that could be encountered for different tumor sites or types.

The dose prescription approach used in this study is based on the information in an initial PET image and therefore there could be the risk that the planning image does not reflect the distribution of hypoxia at a later time during the treatment. It should be mentioned however that the dose prescription method used in this study that uses dose levels calculated according to Equation 5 has been designed to account for variations of hypoxia on the microscopic level. Furthermore, theoretical investigations have shown that the method is also quite robust to macroscopic variations [33]. By ensuring that the minimum prescribed dose level corresponds to current clinical practice, the risk of biological misses in individual patients is therefore reduced. Furthermore, in accordance to the conclusion of the recently published review by Thorwarth and Alber [17], the results of this study highlight the need of including information regarding the changes in hypoxia in treatment planning.

Of course, further improvement of the expected results could be obtained when the dose prescription is adapted to the variation of local radiosensitivity during treatment according to repeated imaging of the target. Such an adaptive method however is expected to lose its effectiveness after a few weeks into the treatment when the tumor cell density decreases as the result of the treatment and the functional imaging of the target will be dominated by non-tumor cells [5].

The results also showed another benefit for the treated patients from the inclusion of such an algorithm into clinical treatment planning systems. Thus, it could allow an easy identification of the patients with better oxygenated tumors which could be treated with standard methods as they do not require advanced customization of the treatment. This is illustrated by the results of patients 2–7 in Table III for which the advanced dose prescription method recommended only moderate dose escalation, this being in agreement to the findings of the meta-analysis reported by Overgaard [51] that antihypoxic strategies applied indiscriminately would lead to

small improvements in all the patients, but higher effects are expected in those with hypoxic tumors and therefore in need for such strategies. Such patients could therefore be successfully treated according to conventional prescription approaches without retorting to advanced methods that might be more demanding in terms of planning, verification and delivery. This would allow a judicious use of the resources of the radiotherapy departments that could ultimately be translated into a direct benefit for their economy.

The limited size of the patient population included in this study does not allow a generalization with respect to the fraction of patients that might benefit from the proposed dose prescription approach. The results indicate however that the predicted benefits are greater for patients with hypoxic tumors. The algorithm used in this study proposes both a method to calculate the required doses for each such tumor and a measure of the expected effects for clinically realistic treatment plans. It could thus directly identify the clinical cases that could benefit from dose escalation, as well as the dose levels needed for the success of such an approach. For clinical patients with centrally located hypoxic regions, the method had shown potential for limiting the dose burden of the normal tissues around the target and hence the complications following radiation treatment. This has a direct impact upon the quality of life of the patients after the treatment.

The method could provide valuable benefits for the other patients as well. Thus, it could identify the difficult cases that require very high doses to the hypoxic regions or cases where the hypoxic regions might be located close to organs at risk and could thus not be irradiated without producing unacceptable damage to the normal tissues nearby. This is an indirect benefit that could not be obtained from empirical dose-escalation methods. Indeed, the proposed method identifies in the planning stage the patients from which suboptimal results could be obtained from radiation therapy with current methods. These patients could therefore be directed rather early to alternative methods than low LET irradiation, such as light ion therapy, the use of radiosensitizers or other practical methods to overcome tumor hypoxia than dose escalation. This would result in increased benefit for both the patients that could thus receive an optimal treatment from the very beginning and for the oncology departments as they could directly use their resources for the most efficient treatment method.

Conclusions

The present study investigated the feasibility of clinical implementation of a new algorithm for clinical dose prescription based on PET hypoxia images. The algorithm provides an objective method to prescribe minimum dose levels required to counteract the hypoxic radioresistance in individual tumors. The proposed approach is expected to lead to improved local control and reduced complication levels as it takes into consideration the heterogeneity and the dynamics of the hypoxic regions. It also provides early identification of the clinical cases that might benefit from dose escalation as well as the cases that could benefit from other counter-hypoxic measures.

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