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ORIGINAL ARTICLE

LET-painting increases tumour control probability in hypoxic tumours

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Abstract

LET-painting was suggested as a method to overcome tumour hypoxia. In vitro experiments have demonstrated a well-established relationship between the oxygen enhancement ratio (OER) and linear energy transfer (LET), where OER approaches unity for high-LET values. However, high-LET radiation also increases the risk for side effects in normal tissue. LET-painting attempts to restrict high-LET radiation to compartments that are found to be hypoxic, while applying lower LET radiation to normoxic tissues. *Methods.* Carbon-12 and oxygen-16 ion treatment plans with four fields and with homogeneous dose in the target volume, are applied on an oropharyngeal cancer case with an identified hypoxic entity within the tumour. The target dose is optimised to achieve a tumour control probability (TCP) of 95% when assuming a fully normoxic tissue. Using the same primary particle energy fluence needed for this plan, TCP is recalculated for three cases assuming hypoxia: first, redistributing LET to match the hypoxic structure (LET-painting). Second, plans are recalculated for varying hypoxic tumour volume in order to investigate the threshold volume where TCP can be established. Finally, a slight dose boost (5–20%) is additionally allowed in the hypoxic subvolume to assess its impact on TCP. *Results.* LET-painting with carbon-12 ions can only achieve tumour control for hypoxic subvolumes smaller than 0.5 cm^3. Using oxygen-16 ions, tumour control can be achieved for tumours with hypoxic subvolumes of up to 1 or 2 cm^3. Tumour control can be achieved for tumours with even larger hypoxic subvolumes, if a slight dose boost is allowed in combination with LET-painting. *Conclusion.* Our findings clearly indicate that a substantial increase in tumour control can be achieved when applying the LET-painting concept using oxygen-16 ions on hypoxic tumours, ideally with a slight dose boost.

Tumour hypoxia is known to be a critical limiting factor for radiation therapy, as the response of cells to therapeutic ionising radiation is strongly dependent upon oxygenation level. In vitro experiments show that the radiation dose required to achieve the same response is up to three times higher in hypoxic cells than in cells with normal oxygen levels [1]. This factor is expressed by the oxygen enhancement ratio (OER). Oxygen deficient hypoxic cells in malignant tumour tissue have been shown to negatively influence prognosis both in terms of an effect on the response to therapy and by affecting malignant progression [2–4], especially in carcinomas of the uterine cervix and of the head and neck. It is estimated that around a third of all solid tumours are hypoxic [2,3].

Linear energy transfer (LET) is a parameter that describes the average amount of energy loss per

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track length of a given type of radiation. The higher LET of densely ionising radiation is commonly known to lead to a markedly increased efficiency of cell killing [5]. The concept of relative biological effectiveness (RBE), defined as the ratio of doses of a given LET and a reference radiation producing a same effect, account for this increased efficiency. High-LET irradiation induce clustered DNA damage which is much less dependent on the formation of reactive oxygen species for cell killing, so OER decreases with increasing LET [5]. The evidence that high-LET radiation is less dependent on oxygen status is derived from in vitro experiments [1], in which the cells are hit with well-defined monoenergetic ions with the same LET. Applying high-LET radiation to an entire tumour is unfavourable as risk for late effects in healthy tissues increase as well. For instance, half a century ago, several trials involving high-LET neutron beams were started in order to overcome hypoxia, and the results proved to be disappointing due to strong adverse effects [6].

Recently, the idea of adaptive treatment planning enabling specific hypoxia targeting combining photons and ions, or with ions of different LET [7–10], has started its development in the framework of the TRiP98 treatment planning system. The LET-painting idea [9] is to use recent functional imaging techniques to generate individual, patient-specific hypoxia maps, and restrict the high-LET radiation only to the radioresistant compartments within the tumour volume. This way, also the volume of normal tissues exposed to high-LET radiation is minimised, thereby reducing radiation-induced toxicity, and retaining repair capabilities of normal cells outside of the high-LET fields. While, as mentioned in [9], multimodal approaches are possible, we will here investigate redistribution of LET in the planning target volume (PTV) using a single ion species only. The key point is that the radiation quality of the applied ion beam can be used as a free parameter which can be utilised for treatment optimisation [8,9]. Redistributing LET in proton therapy in order to achieve better treatment outcome was also suggested later in [11], but this was solely motivated by the RBE and not by hypoxia.

Several modelling studies have demonstrated that for a given total radiation dose, improved tumour control can be accomplished by using a non-homogeneous dose distribution within the tumour (i.e. "dose-painting" [12,13]). A prerequisite for both dose- and LET-painting is the ability to identify hypoxic sub-compartments within the tumour entity, i.e. that reliable hypoxia maps showing the three-dimensional (3D) distribution of hypoxic foci at the time of treatment are available. Previous studies have shown that PET scans using the hypoxia tracer 18F-fluoroazomycin arabinoside (FAZA) provide quantitative images of the intratumoural distribution of hypoxic cells in vivo [14,15]. For this study we simply assume that functional imaging methods are or will be able to reliably image hypoxia, as the development of hypoxic imaging is out of scope of this work.

We want to test the central hypothesis raised in [9], whether LET-painting has the potential to improve tumour control probability (TCP) of a tumour that has an identified hypoxic compartment, opposed to treat this tumour with standard homogeneous fields where each field deposits a homogeneous dose within the PTV. We also attempt to give a first quantification on the maximum volume of hypoxic substructures within tumours which can be treated with LET-painting, even though several assumptions have to be made at this stage.

Material and methods

Patient case and tools used for LET-painting

This study is realised with a combination of several tools. Beam optimisation is performed with TRiP98 [16] on physical dose. The default beam kernels supplied with TRiP for carbon-12 ions are used. Carbon-12 ions may not achieve the desired reduction in OER for realistic tumours [9], which is why we include oxygen-16 as an additional ion for our studies. Oxygen-16 beam kernels and particle spectrum files for TRiP are prepared using the Monte Carlo particle transport code SHIELD-HIT12A (http://www.shieldhit.org) [17]. Treatment plans and scripts for treatment plan parameter studies are prepared and visualised using PyTRiP (https://svn.nfit.au.dk/trac/pytrip) which is specifically developed for this purpose. LET-volume histograms are used to check the quality of the realised plans.

An oropharyngeal cancer case from the DAHANCA 24 trial [15] is imaged with FAZA for hypoxia. A hypoxic target volume (HTV) region within the tumour, is identified and delineated along with PTV and gross target volume (GTV) as shown in Figure 1. The volumes are 3.2, 64.0 and 97.2 cm^3 for HTV, GTV and PTV, respectively.

Procedure

First, a regular homogeneous carbon-12 ion plan is prepared assuming normoxic tissue. Two pairs of opposing fields (i.e. four fields in total) are used which cover the PTV with a homogeneous physical dose. TRiP returns two voxel matrices with the dose distribution and the dose averaged LET which can be used for subsequent calculation of TCP. TCP is

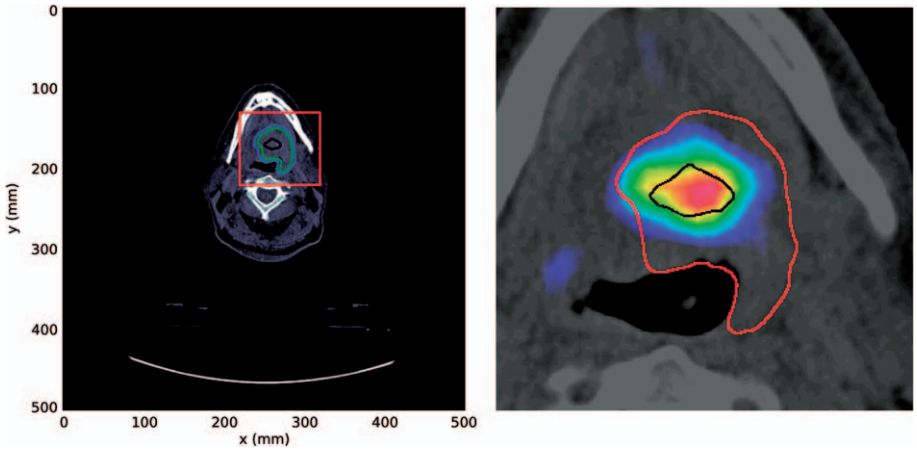

Figure 1. Patient CT scan used for this study. All subsequent images presented in the results section show the section marked by the (red) box in the left figure. Here, the PTV and GTV are outlined with blue and green lines, respectively. The black structure in the center marks the HTV. Right figure shows details of the FAZA scan and the delineated HTV (black line). The larger structure (red) again marks the GTV. GTV, gross target volume; HTV, hypoxic target volume; PTV, planning target volume.

calculated using the surviving fraction S_j , the cell density ϱ_j and voxel volume V_j:

$$TCP = \Pi_j \exp(-S_j \varrho_j V_j) \quad (1)$$

for each voxel j contained within the GTV. We assume a constant cell density of $\varrho = 10^4$ cells per mm^3 in all voxels, and V_j is constant at 3.0 mm^3. S_j is calculated using the repairable-conditionally repairable (RCR) model in the hypoxia-extended version as described in [18]. This model was benchmarked for a few cell lines, but only data for the V79 cell line are provided in this reference. Therefore we have exclusively used the V79 survival for all our calculations below. In the hypoxia-extended RCR model, a continuous function $\tilde{O}(LET)$ characterises experimental OER data at 10% survival. The $\tilde{O}$-LET relationship for the hypoxia-extended RCR model which we applied in our study is shown in Figure 2, and is identical with that published in [18].

The RCR model simply returns surviving fraction as a function of dose, LET and whether the tissue is hypoxic or not. Even if TRiP features the local effect model (LEM) it only very recently accounts for hypoxic structures [8]. Also, LEM is only available from within TRiP, as it needs the full particle spectrum in each voxel, which is why we for this first study implemented the RCR model.

Redistribution of LET is realised by applying opposing fields with dose ramps in the spread out Bragg peak (SOBP), a technique already presented in [19], but motivated for other reasons. We generate dose plans with either homogeneous or ramped (LET-painted) fields assuming both normoxic or presence of hypoxic tissues. Since the ramped fields needed for LET-painting changes the particle budget for the treatment plan, we have chosen to normalise (or "pin") the ramped plans to match the energy fluence needed to create the homogeneous plan which achieves 95% TCP in the normoxic case. This way we think we can reasonably compare the outcome of the homogenous and ramped plans.

The dose ramps are generated following the position and shape of the HTV. We add a 4 mm margin around the HTV, which we call the extended HTV (eHTV). The SOBP of each field which crosses the eHTV is reduced from 100% dose to 0% dose at the edges of the eHTV following their respective beam axes. The missing dose at the distal end of the eHTV is compensated by the 100% dose from the opposing field, thus we have two overlapping dose ramps which in total yields a homogeneous

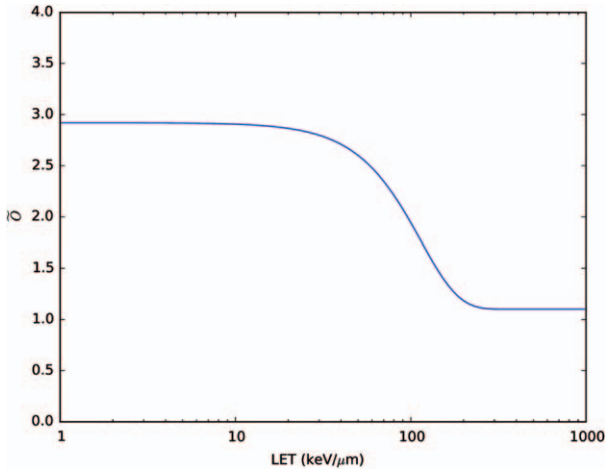

Figure 2. The O parameter from the hypoxia-extended RCR model [18] as a function of LET for the V79 cell line used in this study. $\tilde{O}$ is comparable with the OER at 10% survival. LET, linear energy transfer; OER, oxygen enhancement ratio; RCR, repairable-conditionally repairable.

dose along the eHTV. Outside the field of view of the eHTV the dose distribution remains homogeneous. Adding the 4 mm margin adds robustness and ensures that the HTV is well covered with high-LET radiation, as some dose and LET fluctuations may exist from the planning at the rim of the HTV, which could compromise TCP.

Since the RCR model accepts only a binary parameter regarding the oxic status of the tissue, there is some room for interpretation at what oxygenation level one might consider the tissue as hypoxic, and how to delineate the HTV which will be targeted for LET-painting. To address this issue, we have carried out a parametric study using the volume of the hypoxic area as a free parameter. To get a feeling for how TCP varies as a function of the size of the HTV, a spherical structure is centered at the hypoxic area. By using a spherical HTV, we can vary the HTV from 0 cm^3 and up to 10 cm^3 by increasing the radius in small steps. This parametric study is done for both carbon-12 and oxygen-16 ions. Additionally, a parameter study is carried out with oxygen-16 ions where an additional 5–20% dose boost is applied to the eHTV, still retaining the total energy fluence.

We are aware of the fact that radiobiological effect in the surrounding healthy tissue does not scale linearly with the total energy fluence, i.e. two different types of particle giving the same dose may have different RBE and produce different surviving fractions. In order to have a rough feeling for how large this possible error may be, we have also calculated number of surviving cells in the normal tissues surrounding the PTV using the same radiobiology model.

Results

Main findings show that LET-painting is possible and yields an improved TCP as opposed to using a conventional homogeneous dose distribution. Upper and middle row in Figure 3 show resulting plans for carbon ions, for homogeneous (upper row) and ramped (LET-painted, middle row) plans using an actual HTV, delineated from a FAZA scan. This clearly demonstrates that the LET-painting technique using opposing ramped fields can cover irregular areas within the tumour.

However, even when applying LET-painting, the ramped carbon-12 ion plan with the hypoxic substructure yield a TCP of only 5% since the LET is too low to reduce the OER sufficiently. The ramped plan assuming purely normoxic tumour also has a reduced TCP of 86% compared to the homogeneous plan (which is pinned to 95%). Ramped fields for oxygen-16 ions are shown in the last row in Figure 3, and here the TCP is 71% assuming hypoxia. The maximum LET colour scale shown in the LET maps is set to 120 keV/um as beyond this point the OER is close to 1 and the exact keV/um value becomes irrelevant. The average physical dose is 16.7 Gy in the homogeneous oxygen-16 plan and 19.6 Gy in the homogeneous carbon-12 plan.

Figure 4 shows TCP as a function of an assumed spherical HTV for ramped plans using either carbon-12 or oxygen-16 ions. Oxygen-16 ions obtain tumour control in 1 cm^3 larger HTV structures than carbon-12 ions can. Oxygen-16 ions and various degrees of dose boosts ranging from 0% to 20% (still retaining the energy fluence budget), improve the TCP further. With a dose boost of 5% a 2 cm^3 large HTV can be controlled at 50% TCP. For larger boosts this enhancement is less pronounced, since the energy fluence is pinned and less dose is deposited in the PTV outside of the HTV.

Integral dose and cell survival for non-PTV tissues are found to be equal for the homogeneous and ramped plans.

Discussion

If hypoxic tissue is present within the tumour, then TCP drops to zero as expected when applying homogeneous fields of carbon-12 ions. Performing LET-painting on the hypoxic structure increases TCP considerably only if the hypoxic volume is below 0.5 cm^3. Assuming a fully normoxic case, the ramped plan gives inferior TCP than that acquired by the homogeneous plan. This is no surprise, as ramped plans shift more dose from the PTV into the entry channel in order to create the ramped SOBP with the highest dose at the proximal end of the SOBP. Thus for the same energy fluence budget, a reduced PTV dose (Figure 3 left subfigure, middle row) can be observed, leading to inferior TCP than in a homogeneous normoxic plan.

It should be mentioned that the observations hold as long as we only consider the surviving fraction in the GTV. When including the normal tissues or nearby organs at risk there may be other reasons to move the high-LET areas out of the normal tissue found at the rim of the GTV or PTV, but this was not subject for investigations here.

From Figure 4, it seems unlikely that carbon-12 ions can be used to overcome hypoxia when these structures are larger than 0.5 cm^3. This is close to the achievable precision in carbon therapy, and for the sake of robustness of these plans it is very unlikely of being successful. Applying oxygen-16 ions instead of carbon-12, larger hypoxic structures up to 1 cm^3 can be targeted. In the same figure we observe a dip around 1.2 cm^3 HTV volume, which is attributed to an artifact in the optimisation process. As the HTV

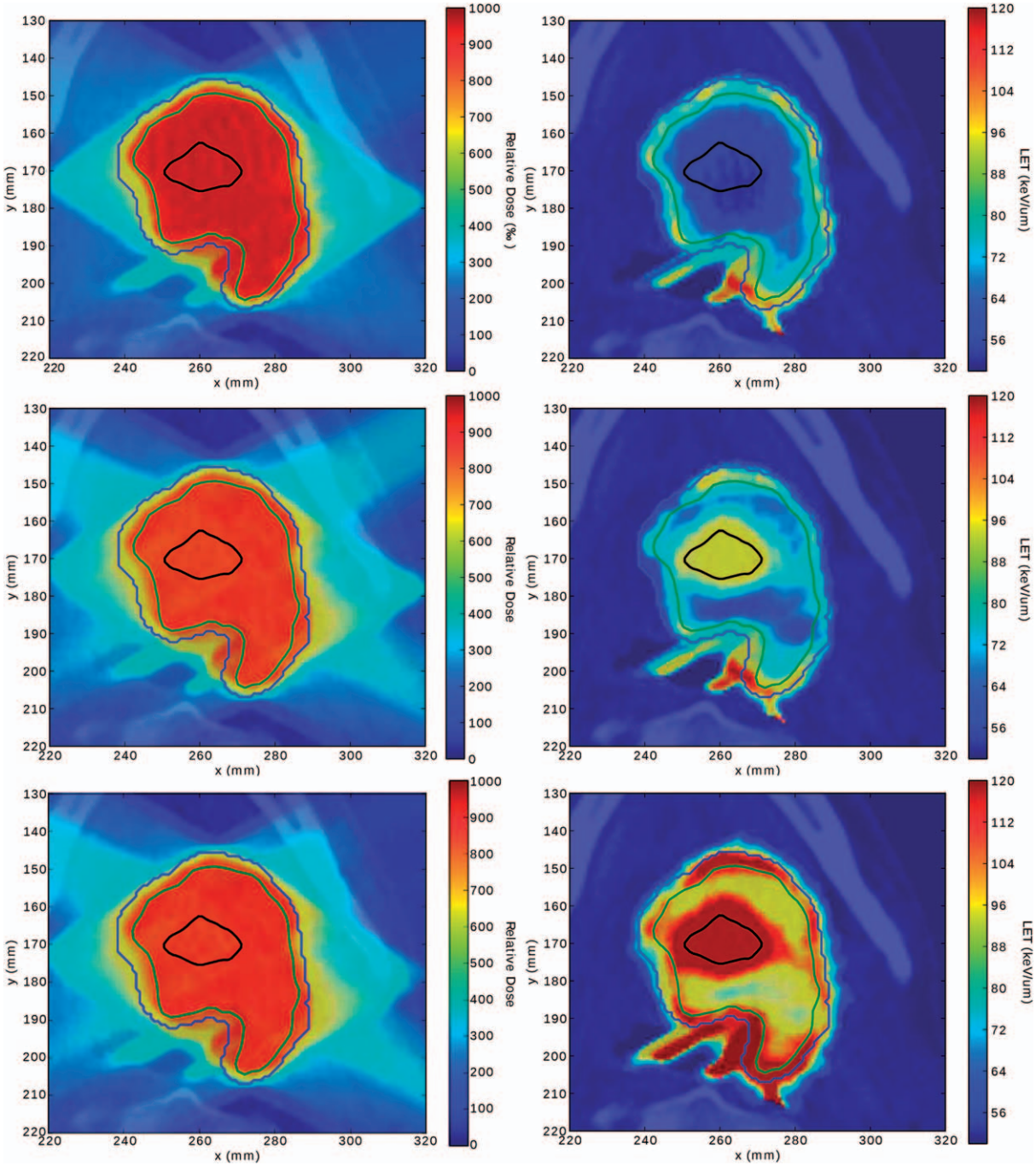

Figure 3. Dose and dose-averaged LET profiles shown in left and right column, respectively. First row is a carbon-12 ion plan using four conventional fields with homogeneous dose. The highest LET is then found at the rim of the SOBPs as seen in the upper right figure. LET-painting, as shown in the middle row, allows for redistributing LET to cover the assumed hypoxic structure, depicted as the black entity, with increased LET. The energy fluence budget for the amount of particles used is the same for both plans in the upper two rows. The last row shows LET-painting again, but now with oxygen-16 ions, resulting in a pronounced increase of LET in the HTV. HTV, hypoxic target volume; LET, linear energy transfer; SOBP, spread out Bragg peak.

increases in size, a bone structure comes into view in one of the fields. This occasionally interferes with the discrete nature of the raster scan pattern, leading to sporadic inferior optimisation patterns.

Adding a small boost in HTV of 15% of the PTV increases the volume of hypoxia treatable with up to 2–3 times. Being able to target larger volumes with high-LET radiation also may make plans more robust as an additional margin can be introduced to cover the hypoxic structure. It is also clear that the effect of a dose boost to the HTV has a more pronounced impact on the TCP if LET is increased first, which

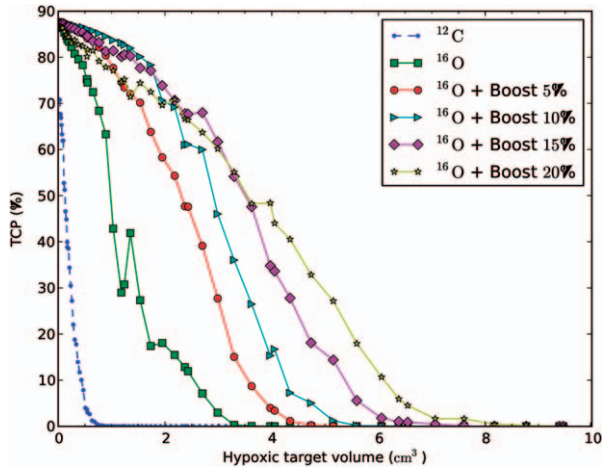

Figure 4. TCP calculated for the patient case, as a function of varying spherical HTV using carbon-12 ions, oxygen-16 ions and oxygen-16 ions with an additional dose boost to the HTV. The energy fluence is normalised for all plans to result in 95% TCP for their corresponding homogeneous normoxic cases. HTV, hypoxic target volume; TCP, tumour control probability.

may lend credit to the idea of combining LET-painting with dose-painting.

The strategy presented here can easily be realised utilising scanned ion beams for generating the ramped fields, as described in [19]. Passive or semi-passive beam delivery systems, such as those applied at most heavy ion facilities in Japan, cannot utilise the technique presented here, however LET-painting could instead be realised by adding a smaller high-LET boost on top of a low-LET plan, as suggested in [9].

Using ramped opposing fields may add robustness to the plans, as effects from range uncertainties are reduced. This was also motivating the study which first suggested the idea of ramped fields [19] in order to avoid patched fields with steep dose gradients. Normally the profile of the biological dose is substantially deviating from the physical dose in a non-constant way along the extended irradiated target. However, it has recently been shown that these differences are substantially reduced when applying more than one field [20]. This implies a larger confidence on robustness of the overall target response.

In the present paper, we focus on a simple approach dealing with a binary parameter for the oxygen concentration. We do not attempt to validate the RCR model, and strictly speaking we extrapolate it to high doses, exceeding those of the available experimental data set. However, since we aim at relative gains between treatment plans with and without LET-painting, potential shortcomings of the radiobiological model should be of second order. We only assume a single fractionation scheme, although that it is clear that reoxygenation plays an important role in fractionated therapy. However, we do not see that this can alter our conclusions in general. Here, we merely show that LET-painting is possible for arbitrary structures and that this may lead to an increased TCP for tumours with hypoxic entities.

Very recently, TRiP98 was extended to account for hypoxia [8]. The biological effect calculation was extended beyond the RBE-weighted dose, aiming at iso-survival profiles, including an OER term derived at any voxel, for any oxygenation level and dose-average LET, according to a semiempirical model, and the results were validated experimentally. In the same reference, the possible use of oxygen ion beams for irradiation of hypoxic compartments was studied, and the ability of such ions to target hypoxia was demonstrated. We plan to investigate realistic situations of different oxygen levels using the latter method in a forthcoming work.

Clinical experience with heavy ions today is mainly limited to carbon-12 ions, and only few investigated hypoxia. A single specific clinical trial was performed at Chiba (Japan) for irradiation of hypoxic uterine cervix cancer with carbon ions [21], but no specific targeting strategy was applied here. A much reduced dependence of ion radiotherapy outcome on oxygenation level was reported. The same reference reports local control rates which are independent on oxygenation status when irradiating with carbon-12 ions, however no dose-average LET is reported. Also, local control rates decreased when switching from photons to carbon ions in normoxic tissues, therefore there may be some misgivings that the reported oxygenation independence can be attributed to carbon-12 irradiation.

High-LET carbon ion therapy was applied for chordoma, chondrosarcoma and adenoid cystic carcinoma in a pilot study at the GSI Helmholtzzentrum für Schwerionenforschung in Darmstadt, Germany, where a biological optimised dose was given to the entire tumour volume [22]. At GSI also some initial work on multimodal therapy was initiated by using intensity-modulated radiation therapy (i.e. photons) along with a boost of carbon ions to the entire tumour volume [23]. Both studies were motivated by steeper lateral dose gradients of carbon ions and a favourable distribution of RBE along the beam, and were not considering the possible presence of hypoxia.

Since it is known that carbon ions cannot be considered as really high-LET particles, it was expected that it may be worthwhile to investigate heavier ions in the future. Consequently, the layout of the Heidelberg Ion Therapy (HIT) facility in Germany was adapted to provide also oxygen-16 ions with the full clinically needed range. In principle also heavier ions can be provided, but with reduced range in tissue. In the meantime scanned

oxygen beams have been technically commissioned at HIT and have already been used for radiobiology experiments [24]. However, clinical application of oxygen-16 ions will require additional clarification of regulatory issues.

We do not claim that our described approach is the optimum way to cope with the problem of hypoxic tumours, but merely show general trends. It is very desirable to back up the model predictions with in vivo experiments. In vitro data are needed to find good estimates on transcription functions that correlate oxygenation level with required LET and dose. This supports the call for irradiation facilities where ample amounts of beam time is available for in vitro and in vivo studies with well-defined protocols such as those at GSI or recently proposed at CERN [25]. Finally, it should be mentioned that this method is not limited to hypoxic structures, but could be applied to any radioresistant substructures in tumours that respond to high-LET radiation.

Conclusion

Hypoxia in tumours is a well-known factor contributing to radiation resistance, which may in turn lead to treatment failure. Within the limits of our approach, we demonstrate that LET-painting is a promising method to achieve better TCP if the presence of hypoxic entities within the tumour otherwise would lead to reduced outcome. However, ions heavier than carbon-12 ions may be necessary in order to reduce the OER to sufficient levels. Oxygen-16 ions along with a slight dose boost could be a promising candidate when targeting hypoxic structures of 1–4 cm^3 in size. LET-painting is feasible today from a technological point of view. Next steps involve in vitro and in vivo radiobiologic experiments, which eventually will lead to clinical trials necessary to validate the true potential of LET-painting.

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