A patient-specific computational model of hypoxia-modulated radiation resistance in glioblastoma using \( ^{18}\text{F}-\text{FMISO-PET} \)

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A patient-specific computational model of hypoxia-modulated radiation resistance in glioblastoma that has poor prognosis despite aggressive treatment. A hallmark of these tumours is diffuse invasion into the surrounding brain, necessitating a multi-modal treatment approach, including surgery, radiation and chemotherapy. We have previously demonstrated the ability of our model to predict radiographic response immediately following radiation therapy in individual GBM patients using a simplified geometry of the brain and theoretical radiation dose. Using only two pre-treatment magnetic resonance imaging scans, we calculate net rates of proliferation and invasion as well as radiation sensitivity for a patient’s disease. Here, we present the application of our clinically targeted modelling approach to a single glioblastoma patient as a demonstration of our method. We apply our model in the full three-dimensional architecture of the brain to quantify the effects of regional resistance to radiation owing to hypoxia \textit{in vivo} determined by \( ^{18}\text{F}-\text{fluoromisonidazole} \) positron emission tomography (FMISO-PET) and the patient-specific three-dimensional radiation treatment plan. Incorporation of hypoxia into our model with FMISO-PET increases the model–data agreement by an order of magnitude. This improvement was robust to our definition of hypoxia or the degree of radiation resistance quantified with the FMISO-PET image and our computational model, respectively. This work demonstrates a useful application of patient-specific modelling in personalized medicine and how mathematical modelling has the potential to unify multi-modality imaging and radiation treatment planning.

1. Introduction

Glioblastoma multiforme (GBM) is the most aggressive primary brain tumour and accounts for the majority of primary brain tumours [1]. Following diagnosis, GBM is often treated with surgical intervention followed by concurrent radiation and chemotherapy [2]. GBM is characterized by invasive tumour cells that can be found as far away as 4 cm from the tumour mass [3]. This tumour cell invasion is not revealed by magnetic resonance imaging (MRI), the principal means of monitoring GBM progression and response to therapy [4].
We study a single glioblastoma patient with two MRIs and an FMISO-PET study prior to RT to document our method and demonstrate an approach to quantifying hypoxia-mediated resistance to RT using patient-specific computational modelling.

2.5. Quantifying hypoxia in vivo with FMISO-PET
The co-registered FMISO-PET images were scaled to the average venous blood concentration of FMISO activity (see the electronic supplementary material for details) to produce a tumour/blood ratio (T/B) image seen in figure 1[24]. A T/B ratio greater than or equal to 1.2 (T/B ≥ 1.2) was associated with regions of hypoxia and used to determine the total hypoxic volume (HV; table 2)[24].
PET imaging is inherently noisy, and there can be isolated voxels of FMISO uptake scattered throughout the brain; defining HV as \( T/B \geq 1.2 \) and restricting the FMISO signal to the region of T2-weighted MRI abnormality largely excludes this noise and isolates the FMISO signal to the tumour area [25]. The HV is distributed within the tumour, from the bulk (T1Gd) to the periphery (T2+).

The target volumes are labelled as isodose curves of 61.2 and 54 Gy to the periphery (T2 region), to the invasive edge and tumour periphery, defined by the T2/FLAIR abnormality with a 2 cm margin. T2-T1Gd is the T2 abnormality with a uniform 2 cm margin. T2-T1Gd is the T2-defined abnormality with a 2.5 cm margin, which had a planned target dose of 54 Gy delivered in 30 daily fractions of 1.8 Gy per fraction. An additional dose was delivered to a smaller volume defined by the gadolinium-enhancing region plus a 2 cm margin of 7.2 Gy delivered in an additional four daily fractions of 1.8 Gy per fraction for a total of 61.2 Gy to this region. The target volumes are labelled as isodose curves of 61.2 and 54 Gy on the planning MRI in figure 1. Radiation was delivered with concurrent temozolomide (TMZ) 75 mg m\(^{-2}\) given daily during course of RT and continued adjuvantly for a total of 14 months [2].

### 2.7. A mathematical model of glioblastoma growth and response to radiation therapy

The proliferation–invasion radiation therapy (PIRT) model is a partial differential equation that quantifies the spatial and temporal rates of change of glioblastoma cell density and incorporates the delivery and effect of RT. The model describes tumour cell density, denoted \( c(x, t) \) at time \( t \) and location \( x = (x, y, z) \) in units cells per mm\(^3\), in terms of diffuse invasion and density-dependent logistic growth. Logistic growth relates the \( per \ capita \) growth rate to available space for the cells to grow, so that if there are few cells in a unit volume of tissue, the overall growth rate is higher than if there are many cells per unit volume. The maximum number of tumour cells that can fit in a cubic millimetre of tissue is known as the carrying capacity, denoted \( K \), and is computed to be \( 1.91 \times 10^6 \) cells mm\(^{-3}\) assuming a 10 \( \mu \)m diameter tumour cell. Once the tumour cell density reaches the carrying capacity \( (c = K) \) at a particular spatial location, the tumour cells are space-restricted and therefore do not proliferate. Because we do not incorporate the clearance of dead cells, when the tumour cell density reaches the tissue carrying capacity, we assume the tumour cells are dead or become quiescent in this region.

### Table 2. Hypoxic volume and maximum tumour-to-blood (T/B) pixel value within MRI-defined tumour regions for the patient. T2+ is defined to be the T2 MRI abnormality with a uniform 2 cm margin. T2-T1Gd is the T2 region less the contrast-enhancing T1-weighted tumour region, including regions of necrosis. HV is distributed throughout the tumour, from the bulk (T1Gd) to the periphery (T2+).

<table>
<thead>
<tr>
<th>region</th>
<th>HV (cm(^3))</th>
<th>T/B max</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2+</td>
<td>2.430</td>
<td>1.523</td>
</tr>
<tr>
<td>T2-T1Gd</td>
<td>0.646</td>
<td>1.454</td>
</tr>
<tr>
<td>T1Gd</td>
<td>0.698</td>
<td>1.523</td>
</tr>
</tbody>
</table>

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The PIRT model (equations (2.1) and (2.2)) quantifies glioblastoma growth in terms of two net rates: proliferation (\( P \), per year) and invasion (\( D(x) \), mm\(^2\) per year). The invasion of malignant tumour cells into the brain parenchyma is influenced by the anatomy of the brain, codified in equation (2.2): tumour cells preferentially migrate along the myelinated axons of neurons composing the white matter and move more randomly and slowly through the dense grey matter which composes the cortical surface and some internal structures of the brain \([26,27]\). The last term in equation (2.1) represents the loss of tumour cells owing to RT and is based on the linear-quadratic model and the clinical RT plan, discussed below and given in equations (2.3) and (2.4).

2.8. Differential motility

The invasive migration of tumour cells throughout the brain presents a challenge to understanding the true extent of the subclinical disease, as tumour dispersal speeds can vary up to 100-fold between pioneering cells in white matter compared with the more random motion in the core of the tumour and in grey matter \([7,27,28]\). To model this behaviour, the tumour cell invasion rate (equation (2.2)) is a function of the spatial variable \( x \), so that glioma cells migrate 100 times faster in the white matter than in the more dense grey matter, \( D_w = 100D_g \) \([29,30]\). The BrainWeb phantom was used for tissue classification, partitioning the brain into grey and white matter in addition to cerebrospinal fluid (CSF) on a 1 mm\(^3\) cubic grid. The phantom is used to define the invasion rate of tumour cells spatially in the brain \( D(x) \), figure 2 \([20,31]\). The simulated tumour is initiated as a single voxel of cells located at approximately the centre of mass of the T1Gd-defined tumour volume. The model equations are solved using a numerical approach, with time and spatial grids determined to meet stability requirements (see the electronic supplementary material) \([17]\).

2.9. Modelling the effect of radiation therapy on glioblastoma multiforme tumour cell density

![Diagram of cerebrospinal fluid (CSF) with no migration, white matter with faster migration, and grey matter with slower migration](image)

Figure 2. The BrainWeb phantom provides a voxel-wise probability map used to define the invasion rate of the tumour in model simulations \([20]\). Each voxel is composed of grey matter, white matter and/or CSF in relative proportions such that the sum of all tissues in each voxel is unity. The voxels in the phantom are cubic with dimensions \( 1 \times 1 \times 1 \) mm\(^3\).

The radiation loss term in the PIRT model (equation (2.1)) is nonlinear and follows the same density-dependent logistic formalism as the tumour growth model, so that the rate of tumour cell death is related to the rate of killing and the density of tumour cells. The probability of cell death \((1 - S)\) from the linear-quadratic model (equation (2.3)) determines the rate of cell killing during each treatment fraction time (equation (2.4)). For low cell densities, the effect of RT is linearly related to the fraction of tumour cells killed. This assumption is consistent with the common understanding that cells actively undergoing mitosis are more susceptible to DNA damage and are found at the rim and periphery of the tumour more than the dense core \([11]\). However, when the cell density is close to the carrying capacity of the tissue \( K \), it is assumed that the effect saturates owing to increased interstitial pressure and decreased dose per cell. When the tumour cell density reaches carrying capacity \((c = K)\), there is no radiation effect. This situation corresponds to an unresponsive necrotic core, where we assume that there is no radiation-induced cell killing, because the cells are already dead. A necrotic core is a histologic and radiographic hallmark of glioblastoma that develops when the tumour growth exceeds the tissue carrying capacity.

2.10. Patient-specific radiation sensitivity

In order to quantify radiation sensitivity on a patient-specific basis, we use the linear-quadratic model with the ratio \( \alpha/\beta \) fixed. This allows us to regard \( \alpha \) as the single parameter to define radiation sensitivity. For each point in space and time, an effective dose and probability of cell survival can be calculated that corresponds uniquely to the individual patient’s treatment plan and the linear-quadratic dose–response model parameter \( \alpha \). Increasing \( \alpha \) decreases the probability of cell survival, \( S \), and therefore increases the probability of RT-induced cell death. Increasing values of \( \alpha \) correspond to increasing treatment effect and deviation from untreated growth. With the ratio \( \alpha/\beta \) fixed, the single parameter \( \alpha \) can be uniquely determined using either the T1Gd or T2 post-chemoradiation tumour size, using a bootstrap optimization technique, yielding a one-to-one relationship between \( \alpha \) and model prediction error, as described in Rockne et al. \([17]\). The first T2 MRI following chemoradiation was used to determine the radiation response parameter \( \alpha \) owing to the localization of FMISO-PET activity within the T2\( \supset \) region (table 2).
Table 3. Patient-specific tumour growth and response rates quantified with the patient-specific PIRT model.

<table>
<thead>
<tr>
<th></th>
<th>net invasion rate $D$ (mm$^2$ per year)</th>
<th>net proliferation rate $\rho$ (per year)</th>
<th>relative invasiveness $D/\rho$ (mm$^2$)</th>
<th>radio-sensitivity $\alpha$ (per Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12.84</td>
<td>13.82</td>
<td>0.93</td>
<td>0.055</td>
</tr>
</tbody>
</table>

2.11. Model of hypoxia-modulated radiation resistance
The ratio of the parameters $\alpha/\beta$ in the linear-quadratic model provides a measure of tissue response to radiation exposure. In our treatment simulations, the ratio $\alpha/\beta$ is held constant at 10 Gy, which is a reasonable assumption for tumour tissue and consistent with previous work [11,25,34–36]. The relative contribution of the ratio $\alpha/\beta$ to radiation response is modulated by the presence of hypoxia. We use the scaling oxygen enhancement ratio (OER), which determines relative resistance to RT in regions of low oxygen [37–39]. The implementation of the OER to the linear-quadratic model is to modify the radiobiological parameters $\alpha$ and $\beta$ to be spatially defined, so that the OER is applied in regions of hypoxia, as follows:

$$S = \exp\left(-\alpha(x)\left(\frac{\text{dose}}{\alpha/\beta(x)}\right)\right),$$

(2.5)

$$\alpha(x) = \begin{cases} \frac{\alpha}{\text{OER}} & \text{if } x \in \text{ hypoxic region} \\ \frac{\alpha}{\beta} & \text{if } x \notin \text{ hypoxic region} \end{cases}$$

(2.6)

and

$$\frac{\alpha}{\beta}(x) = \begin{cases} \frac{\alpha}{\text{OER}} & \text{if } x \in \text{ hypoxic region} \\ \frac{\alpha}{\beta} & \text{if } x \notin \text{ hypoxic region} \end{cases}$$

(2.7)

The OER assumes values between one and three [40], corresponding to no hypoxic effects and maximum effect, respectively. Although the OER is often considered a function of oxygen tension measured in units of mm Hg, we associate the T/B FMISO-PET image with a volume fraction of hypoxia and implement the OER in a binary, voxel-wise manner as shown in equations (2.5)–(2.7).

2.12. Quantifying hypoxia-mediated radiation resistance with the proliferation – invasion radiation therapy model
The PIRT model is used to investigate the role of FMISO-PET-defined hypoxia in determining model-predicted radiation response and to test the sensitivity of our definition of hypoxia in influencing radiographic response to RT. Each simulation was run using an anatomically accurate three-dimensional brain phantom [20] and the patient’s three-dimensional conformal radiation dose prescription extracted from the treatment planning system (Philips Pinnacle). The following treatment scenarios are considered:

1. Clinical radiation dose delivered with spatially uniform treatment response. This corresponds to a value for the OER equal to one (OER = 1) at all locations in the brain, and assumes that all tumour cells are equally susceptible to RT damage.
2. Clinical radiation dose with localized radio-resistance owing to hypoxia via a binary relationship. This quantifies focal radio-resistance defined by the patient’s FMISO-PET scan, where the tissue to blood value is greater than or equal to 1.2 [24], defines the HV where the OER is modified. Four simulations were performed with the OER equal to 1.5, 2.0, 2.5 and 3.0 to characterize a range of hypoxia-mediated responses. The spatially defined OER is given by

$$\text{OER}(x) = \begin{cases} 1.0 & \text{if } \frac{T}{B}(x) < 1.2 \\ 1.5, 2.0, 2.5 \text{ or } 3.0 & \text{if } \frac{T}{B}(x) \geq 1.2. \end{cases}$$

(2.8)

2.13. A patient-specific proliferation – invasion radiotherapy model
To establish a histopathological correlation of cellular density to imaging, we associate enhancing features on T1Gd and T2-weighted MRIs with high and low tumour cell densities, respectively [41,42]. One corollary of this estimate is the modeling of a diffuse gradient of tumour cells invisible to imaging. The relative proportion of occult disease is characterized by an invisibility index (the ratio of the model parameters $D/\rho$ [43]) which has been inversely related to the volume of hypoxia within the tumour measured on FMISO-PET relative to the overall tumour mass on MRI, so that more nodular tumours (small ratio $D/\rho$) are more hypoxic than diffuse tumours (large ratio $D/\rho$) [9]. This can be interpreted as the difference between vascular cooption and tumour-driven angiogenesis in diffuse versus nodular neoplasms, respectively.

The PIRT model (equation (2.1)) predicts a nearly linear radial growth of the abnormality seen on imaging, which approaches a constant velocity defined by Fisher’s approximation $v = 2\sqrt{D\beta}$ [44,45]. A constant velocity of imageable growth on MRI has been demonstrated for 27 untreated low-grade gliomas [46] computed from serial MRI observations. The invisibility index and velocity of growth are computed from gross tumour volumes and combined to calculate patient-specific net rates of diffusion ($D$) and proliferation ($\rho$) [17,42].

2.14. Patient-specific model parameters
Patient-specific model parameters $D$ and $\rho$ were calculated based on baseline tumour growth kinetics using pre-biopsy MRI. Specifically, within the spectrum of dynamics observed in glioblastoma, the patient’s net rates of invasion and proliferation that characterize the tumour growth lie within 1 standard deviation of the population mean observed in 63 patients [16]. Similarly for the patient-specific radio-sensitivity parameter $\alpha$, the calculated value of $\alpha = 0.055$ (per Gy) reflects neither an exceptionally resistant nor sensitive response (table 3). The relative invasiveness or ‘invisibility index’ ($D/\rho = 0.93$ mm$^2$) reflects a tumour growth pattern which is balanced between cooptive and angiogenic vascularity and therefore predicts a modest hypoxic burden.

2.15. Spatial metrics of model accuracy
In order to assess the accuracy of model predictions, we compare the simulated and actual tumour regions on T1Gd and T2-weighted MRI using spatially defined similarity metrics. Each metric returns a value indicating the quality of agreement between model and observed tumour growth. This analysis was performed on the two MRIs prior to RT and on the first MRI following RT on both the T1Gd and T2 tumour volumes. Model-predicted RT response is defined with the first MRI performed post-RT [17]. Because we do not explicitly model chemotherapy, we cannot confidently apply this model or analysis...
to MRI observations beyond the first two post-radiation scans, when adjuvant chemotherapy is often administered. Similarity metrics using algebraic combinations of true-positive (TP), false-positive (FP), false-negative (FN) and true-negative (TN) are computed on a voxel-wise basis and include the positive predictive value $\frac{TP}{TP + FP}$, sensitivity $\frac{TP}{TP + FN}$, specificity $\frac{TN}{FP + TN}$, Jaccard index $\frac{TP}{FN + TP + FP}$ and volume similarity $1 - \frac{\text{Vol}(FP - FN)}{\text{Vol}(2TP + FN)}$. These metrics take values from 0 to 1, with one indicating exact agreement. Model-predicted and observed tumour radii were also compared.

In addition to voxel-wise metrics of concordance, we quantified morphological similarity by computing the distance between the predicted and observed tumour surfaces in three dimensions. This measure returns a distribution of distances, so that a value of zero in this distribution indicates intersection of the simulated and actual tumour surfaces. We report the median and standard deviation of this distribution—the closer to zero and smaller the variance, the better the model prediction. Reporting the median and standard deviation allows us to evaluate both variance and bias in our model predictions and avoid a cancelling effect of including both positive and negative distances that would be reflected in the mean of the distribution.

3. Results

Using our patient-specific model for glioma growth and response to RT, we find the incorporation of hypoxia-mediated radiation resistance defined with FMISO-PET leads to an order of magnitude decrease in relative volumetric error, from 14.6% to 1.1% (table 4). Incorporation of hypoxia-mediated resistance provided better qualitative and quantitative predictive value to the model in regions of high cellular density where the hypoxia was localized, despite the relatively small volume of hypoxia within the tumour region, representing only 13% of the bulk tumour mass. Relative error on the T2-weighted MRI-based tumour size was improved more modestly, from 0.5% to 0.2%. Absolute differences between volume-based tumour radius ranged from 0.04 to 2.63 mm. Interobserver error in gross tumour radius has been estimated as $\pm 1$ mm [47], indicating that simulation predictions are comparable to estimated uncertainty in measurable tumour size, summarized in table 4 and illustrated in figure 3. Additionally, when comparing the PIRT model simulation with and without incorporating the OER, 238% more tumour cells survived owing to local hypoxia resistance effects and 24% of the model-predicted
estimation, with zero distance indicating intersection of the surfaces. (Online version in colour.)


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between 2.0 and 3.0 yielded relative volumetric errors at or
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OER using T1Gd size such that the minimum model–data
parabolic relationship between relative volumetric error and
hypoxic regions and parameter selection, we considered a range
To investigate the sensitivity of our predictions to definitions of
3.1. Sensitivity analysis
To investigate the sensitivity of our predictions to definitions of
hypoxic regions and parameter selection, we considered a range
of OER values in the HV ranging from 1.5 to 3.0. This produced a
parabolic relationship between relative volumetric error and
OER using T1Gd size such that the minimum model–data
error occurred at approximately OER = 2.5. OER values
between 2.0 and 3.0 yielded relative volumetric errors at or
below approximately 1%, and all resulted in an order of magni-
tude improvement to the model prediction. This analysis
demonstrates the robustness of the model predictions to
variations in OER, and by extension, the volume fraction of
hypoxic cells the T/B FMISO-PET image represents.

To further investigate the role of spatial localization of
radiation resistance, simulations were also performed in
isotropic three-dimensional spherical symmetry without
anatomical complexity, using the T1Gd isodensity as a
lower bound threshold to determine the hypoxic region.
In these simulations, we observed a similar outcome, that
is, that model–data agreement is substantially improved
with the inclusion of hypoxia-mediated radiation resistance,
where HV is within the bulk tumour region. However, the
model predictions were not as accurate with this simplifica-
tion. This suggests that the contrast-enhancing region is not
a suitable surrogate for hypoxic tumour, and that a more
specific indicator such as FMISO-PET in three dimensions
not only improves the model prediction, but is also needed
in a spatially heterogeneous tumour such as GBM. Sensitivity
of model-predicted tumour burden following RT based on
variability in the tumour growth (D, ρ) or response rates (α,
α/β) is discussed in detail in the supplement to Rockne
et al. [17] and is not sufficient to account for the improvement
in model–data agreement.

3.2. Limitations and considerations
This study focuses on one patient to document our method and
demonstrate an approach to quantifying hypoxia-mediated
resistance to RT using patient-specific computational model-
ling. More patients must be studied in order to support our
findings that incorporation of FMISO-PET-defined hypoxia
improves the predictions of the computational model.

As in our previous work [17], we assume the delivery and
effect of RT to be an instantaneous, deterministic event using
the linear-quadratic equation and its corresponding prob-
ability of cell survival/death. Concurrent chemotherpay
is assumed to be included in the net effect of RT and is not
modelled explicitly. The survival benefit of adding TMZ
chemotherapy to radiation treatment was demonstrated in the
landmark study by Stupp et al. [2] and established a ubiqui-
tous standard of care for newly diagnosed glioblastoma.
However, it remains an open question of how best to translate
the additive therapeutic benefit of TMZ into a mathematical model. The assumption that the effect of TMZ is included in the response rate parameter $a$ does restrict the interpretation of the model predictions for this study.

To further study the additive effect of TMZ to radiation response, one could identify patient cohorts that received RT alone and compare the radiation sensitivity parameters in that cohort with those who received both RT and TMZ. A paired analysis could be performed to control for variations in the tumour growth rates $D$ and $p_r$ as is done in the recent study by Adair et al. [48]. For intravenously delivered therapy such as TMZ, the blood–brain barrier will result in heterogeneous drug delivery spatially within the tumour. Advanced imaging such as dynamic contrast enhanced or perfusion MRI could be used to infer a drug concentration gradient within the tumour, and a similar mathematical formalism for the loss of tumour cells owing to RT could be used to model the effects of TMZ. A study of this kind would aid in the development of a TMZ model that could be used to study the effects of TMZ that is administered alone following chemoradiation.

The patient’s stereotactic needle biopsy was not modelled, as the volume of tissue removed was at the core of the tumour and not a significant portion of the overall tumour mass. The inflammatory response of the tumour and normal appearing surrounding brain owing to surgery may impact MRI abnormalities, particularly on T2/FLAIR. We assume any such effects arising from only a needle biopsy did not impact response to RT, presentation of disease on follow-up imaging or tumour progression. Most glioblastoma patients receive extensive surgical removal of their lesion, which can be modelled by setting that portion of the computational domain and tumour model to zero.

This study assumes no changes to hypoxia through the course of radiotherapy, which does not include the effects of re-oxygenation that could change the distribution of hypoxia within the tumour [49]. The linear-quadratic model does not reflect myriad repair processes and micro-environmental changes induced by radiotherapy [50], although extensions to the L–Q model exist to approximate the effects of re-oxygenation and hypoxia [51]. Hypoxia dynamics can be studied with kinetic FMISO-PET imaging [52]; however, this approach remains relegated to the imaging time point. Moreover, we consider hypoxia a binary variable, which does not account for intravoxel heterogeneity. A more detailed mathematical model of the angiogenic process as it relates to hypoxia could be implemented to explore this heterogeneity, as proposed in [53,54].

Finally, this approach is driven by imaging modalities and does not account for molecular or genetic heterogeneity that is known to exist within glioblastoma, based upon data generated by the TCGA Research Network: http://cancer genome.nih.gov/ [55]. It has been shown that the molecular subtypes defined by the TCGA vary spatially within a single patient’s tumour [56], suggesting that a single molecular subtype may not be sufficient to characterize a patient’s disease. This emphasizes the need for targeted and image-localized biopsies within various regions of the tumour, as shown by Gill et al. [57]. To account for genetic and molecular heterogeneity influence in imageable response to treatment, one would need a multi-scale, patient-specific model framework. Such an undertaking is not attempted here, although the authors recognize that molecular alterations likely play an important role in determining tumour evolution and response to treatment.

4. Discussion

We have investigated a computational model of human glioblastoma growth that incorporates hypoxia-mediated resistance to RT based on FMISO-PET in the complex architecture of the brain on a patient-specific basis. Incorporation of focal radiation resistance improves model–data agreement, measured with a variety of metrics, despite the small hypoxic burden (13%) of the tumour. The model predictions are improved by the incorporation of an OER to approximate the degree of radio-resistance created by hypoxic conditions within the tumour. The large improvements in model–data agreement attributable to a modest volume of hypoxia-mediated resistance to radiation effect underscores the significance of spatial heterogeneity in delivery and response to RT in glioblastoma and the complexity of a three-dimensional model.

Without the incorporation of OER and localized radiation resistance, the model is unable to fully capture post-RT tumour size in regions of high cellular density, motivating the addition of the OER parameter derived from in vivo clinical data. Ideally, a more patient-specific, biologically driven model of the process of angiogenesis, hypoxia and necrosis using a modelling approach which integrates multi-modality imaging is desired [53,54]. In conjunction, prospective interventional imaging studies which capture changes in intratumoural hypoxia throughout the course of therapy are needed in order to improve models of hypoxia-driven resistance to RT to account for changes in the hypoxic state of the tumour. Moreover, daily fraction radiotherapy likely introduces phenotypic and genotypic selection pressures which eliminate the sensitive tumour cells and leave the most aggressive, resistant clones to repopulate following therapy completion [58].

The goal of modelling biological response to therapy has been long sought after, but there have been no demonstrable successes with the potential for impacting individual treatment planning [59]. Other efforts to incorporate biological effect into radiation treatment plans have either relied on static features of the tumour [60] or are not capable of being truly patient-specific because of the large number of parameters to be estimated [61–65]. We have developed a technique to incorporate proliferation, invasion and response to RT of the tumour over the time course of treatment within the three-dimensional anatomy of the brain. Granting all the assumptions and limitations of the simple proliferation–invasion tumour growth model, this framework has provided a methodology to investigate the role of FMISO-PET-defined hypoxia in modulating radiation response in vivo quantitatively. By providing quantitative metrics of a patient’s response to radiotherapy, our model has the potential to unify multi-modality imaging and treatment planning and establish a useful application of patient-specific modelling in personalized medicine.

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Addendum to ‘A patient-specific computational model of hypoxia-modulated radiation resistance in glioblastoma using $^{18}$F-FMISO-PET’

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The reader should take note that the radiation loss term in the PIRT model (equations (2.4) and (2.1) in [1]) determines the rate of cell death due to radiation by interpreting the surviving fraction of cells ($1 - S$) from the linear-quadratic model (equation (2.3)) as the probability of cell death per treatment fraction. For this interpretation to make sense in the PIRT model, the unitless probability ($1 - S$) is interpreted as a rate because it is the instantaneous rate of cell death per treatment fraction. As fractionation was daily, this translates the units of this term to 1/day so that the net rate constant during therapy simulation ($\rho - (1 - S)$) is well defined. The net proliferation rate ($\rho$) is presented in the text in units per year (1/year) as a matter of convenience, as tumour growth on the scale of year(s) is more easily understood on an intuitive level than growth per day (1/day).

Reference