A theoretical framework for prescribing radiotherapy dose distributions using patient-specific biological and radio-biological information

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We present a formalism for using functional imaging both to derive patient-specific radiobiological properties and consequently to prescribe optimal non-uniform radiotherapy dose distributions. The ability to quantitatively assess the response to an initial course of radiotherapy would allow the derivation of radiobiological parameters for individual patients. Both an iterative optimization and an analytical approach to this problem were investigated and illustrated by application to the linear-quadratic model of cell killing using simulated parametric data for a modelled tumor. Potential gains in local control were assessed by comparing uniform dose distributions with optimized dose distributions of equal integral dose. The effect on local prescribed dose of variations in effective radiosensitivity, tumor burden and proliferation rate was investigated, with results suggesting that dose variations would be significant but clinically achievable. The sensitivity of derived parameters to image noise and the effect of varying the initial fractionation and imaging schedule were assessed. The analytical approach proved remarkably robust, with 10% image noise resulting in dose errors of approximately 1% for a clinically relevant set of parameters. Potential benefits were demonstrated by using this formalism to prescribe non-uniform dose distributions for model tumors using a range of literature-derived parameters. The redistribution of dose improved tumor control probability by factors between 1.03 and 4.27 for a range of model tumors.

I. INTRODUCTION

The primary aim of treatment planning for radical radiotherapy has traditionally been to deliver a uniform high dose to a tumor in order to eradicate all the tumor cells. This aim is formalized in guidance on radiotherapy planning from the International Commission on Radiation Units and Measurements (ICRU)^{1,2} and is supported both by years of clinical experience and by mathematical modelling of the radiobiology of tumors.³ This approach assumes tumors to be uniform, homogeneous entities, a perfectly sensible approximation in the absence of reliable techniques for determining the precise location and the anatomical and functional structure of the tumor, and for calculating and delivering complex dose distributions. However, emerging medical imaging techniques are giving us more information than ever before on structural, biological and chemical variations within tumors.⁴⁻⁸ At the same time, intensity-modulated radiotherapy (IMRT) techniques give us unprecedented control over the spatial deposition of dose within a patient.^{9,10} There has therefore been much recent discussion regarding how best to incorporate information on tumor inhomogeneities into the treatment planning process in order to produce a genuinely optimal non-uniform dose distribution.¹¹⁻²⁰

Most approaches to this problem begin with a mathematical model describing the response of the tumor to irradiation, and propose using imaging techniques to estimate spatial variations in the key parameters of this model (usually tumor burden and radiosensitivity). However, the values used are often baseline values of radiosensitivity parameters that come from *in-vitro* studies,²¹⁻²⁴ or at best clinical studies giving a population average.²⁵⁻²⁷ There are therefore large uncertainties in the values of these parameters for a given individual patient, causing errors in estimating the absolute effect of varying dose distributions. However, with the development of novel imaging agents and improvements in quantitative functional imaging, it may soon be possible to quantify tumour response by imaging before and after an initial course of treatment.^{8,28} Patient-specific radiobiological parameters could then be derived from this assessment and used to plan a further course of treatment. The aim of this work is to investigate possible strategies for using functional imaging both to derive patient-

specific radiobiological parameters and to design optimal dose distributions based on these parameters.

II. METHODS

II.A. Patient-Specific Optimization

We begin with a multi-parameter model describing the response of a tumor to treatment. In order to accurately predict the response of a particular tumor to a given course of treatment, we must have accurate knowledge of the value of each significant parameter. Some parameters, notably those relating to tumor burden and chemical environment, may be assessed by acquiring appropriate images of the tumor prior to treatment. However, parameters relating to the dynamic response of the tumor cannot be ascertained in this manner and a different approach is needed, the most common being to use the results of *in-vitro* studies or analyses of clinical outcome as an estimate. However, there is evidence that there may be significant variations in radiosensitivity within a population of otherwise similar tumors.^{29,30} In order for a model to produce useful predictions, it may therefore be necessary to determine patient-specific values for these parameters. We consider two approaches to this problem: the first is to acquire images of the tumor before and after a single phase of treatment, and numerically optimize the set of unknown parameters such that the response predicted by the model best matches the observed response; the second is to determine how much information is needed in order to derive the unique set of unknown parameters analytically and to design a sequence of treatment phases and image acquisitions to acquire this information. Here we apply both of these techniques to a specific radiobiological model and assess the feasibility, accuracy and robustness of each.

II.B. Radiobiological Model

We follow the approach of Webb and Nahum³¹ by considering a tumor divided into n equal-sized voxels, each of volume v . If the radiation response is described by the linear-quadratic model, the surviving fraction of tumor cells following irradiation to dose D in f fractions is given by:

$$SF = \exp \left[-\alpha D - \left(\frac{\beta D^2}{f} \right) + \gamma \Delta t \right] \quad (1)$$

where α and β are the linear and quadratic parameters of cell kill, γ is the repopulation rate and Δt the overall treatment time. The tumor control probability (TCP) is found by assuming Poisson statistics and calculating the probability of there being no viable tumor cells remaining. The probability of killing all tumor cells within a single voxel i is given by:

$$TCP_i = \exp \left\{ -\rho_i v \cdot \exp \left[-\alpha_i D_i - \left(\frac{\beta_i D_i^2}{f} \right) + \gamma_i \Delta t \right] \right\} \quad (2)$$

Where ρ_i is the clonogenic cell density in voxel i and D_i the dose delivered to voxel i . The overall TCP for the whole tumor is then the product of the TCPs for all voxels:

$$TCP_{total} = \prod_{i=1}^n \exp \left\{ -\rho_i v \cdot \exp \left[-\alpha_i D_i - \left(\frac{\beta_i D_i^2}{f} \right) + \gamma_i \Delta t \right] \right\} \quad (3)$$

In order to choose the dose distribution (i.e. the set of D_i values for a chosen f and Δt) which will give the best overall TCP (subject to any dose delivery constraints), we need to know the spatial distribution of ρ , α , β and γ . At this point we will assume that the linear and quadratic parameters have some intrinsic value for a given patient, which is then modulated by spatial variations in chemical or biological properties within the tumor. The dominant modulating factor is likely to be oxygenation, since hypoxia is known to dramatically reduce radiosensitivity.³²⁻³⁴ We therefore require both a means of determining the intrinsic values of α , β and γ and techniques for quantitatively imaging the distribution of clonogenic cell density and of hypoxia. Recent advances in positron emission tomography (PET) and magnetic resonance imaging and spectroscopy, particularly the development of new techniques for imaging tumor cell metabolism^{35,36} and hypoxia,³⁷⁻⁴⁰ show progress towards fulfilling the imaging requirements. Here we present methods for quantifying the intrinsic radiobiological parameters for a specific patient.

II.C. Deriving Patient-Specific Radiobiological Parameters from Image Data

II.C.1. Method I: Numerical Optimization

Given images of the clonogen density distribution before a single initial treatment phase, a good estimate of spatial variations in oxygenation during treatment and knowledge of the delivered dose, an initial estimate of α , β and γ values can be used to generate a prediction of the post-treatment clonogen map. If a post-treatment clonogen density image is also acquired, the observed and predicted data can be compared and the parameter values iteratively adjusted to minimize the difference.

Within a given voxel i , phase 1 delivers total dose $D_i^{[1]}$ in $f^{[1]}$ fractions over a total time $\Delta t^{[1]}$. The effective linear and quadratic terms of radiosensitivity will be the intrinsic radiosensitivity terms multiplied by factors $A_i^{[1]}$ and $B_i^{[1]}$ respectively, such that

$$\begin{aligned}\alpha_{eff\ i}^{[1]} &= A_i^{[1]} \alpha \\ \beta_{eff\ i}^{[1]} &= B_i^{[1]} \beta\end{aligned}\tag{4}$$

where $A_i^{[1]}$ and $B_i^{[1]}$ are functions of the oxygenation. Note that we make no assumptions at this stage about the precise form of the relationship between oxygenation and radiosensitivity,^{41,42} we simply assume that $A_i^{[1]}$ and $B_i^{[1]}$ can be adequately estimated from the hypoxia images. If the number of clonogens present in the voxel prior to treatment is $N_i^{[0]}$, then following phase 1 the number of surviving clonogens is given by:

$$N_i^{[1]} = N_i^{[0]} \cdot \exp \left[-A_i^{[1]} \alpha D_i^{[1]} - \left(\frac{B_i^{[1]} \beta D_i^{[1]2}}{f^{[1]}} \right) + \gamma_i \Delta t^{[1]} \right]\tag{5}$$

A suitable objective function (OF) for the optimization process would then be given by:

$$OF = \sum_{i=1}^n \left(N_{i\ observed}^{[1]} - N_{i\ expected}^{[1]} \right)^2\tag{6}$$

where the sum is taken over all tumor voxels. Minimizing the value of this function should give the best estimate of α , β and γ .

II.C.2. Method II: Analytical Derivation

If ρ can be imaged directly, we will then require sufficient information to derive analytically the remaining independent parameters, in this case α , β and γ . If clonogen density is imaged before treatment, then again after each of three test phases of treatment, the linear-quadratic equations can be solved analytically to give effective values of α , β and γ within each tumor voxel. If spatial variations in oxygenation are also imaged for each treatment phase, these can be accounted for so that intrinsic radiosensitivity values can be derived. Fig. 1 shows the sequence of imaging sessions and treatment phases required for the analytical derivation of the radiobiological parameters in this case.

From Eq. (5) it can be shown that if we consider only the first phase of treatment,

$$A_i^{[1]} D_i^{[1]} \alpha + \left(\frac{B_i^{[1]} D_i^{[1]2}}{f^{[1]}} \right) \beta - \Delta t^{[1]} \gamma = \ln \left(\frac{N_i^{[0]}}{N_i^{[1]}} \right) \quad (7)$$

Similar equations hold for phase 2 and phase 3, giving us the following set of relationships between α , β and γ and the surviving clonogen number following each phase:

$$\begin{pmatrix} A^{[1]} D^{[1]} & \frac{B^{[1]} D^{[1]2}}{f^{[1]}} & -\Delta t^{[1]} \\ A^{[2]} D^{[2]} & \frac{B^{[2]} D^{[2]2}}{f^{[2]}} & -\Delta t^{[2]} \\ A^{[3]} D^{[3]} & \frac{B^{[3]} D^{[3]2}}{f^{[3]}} & -\Delta t^{[3]} \end{pmatrix}_i \begin{pmatrix} \alpha \\ \beta \\ \gamma \end{pmatrix} = \begin{pmatrix} \ln \left(\frac{N^{[0]}}{N^{[1]}} \right) \\ \ln \left(\frac{N^{[1]}}{N^{[2]}} \right) \\ \ln \left(\frac{N^{[2]}}{N^{[3]}} \right) \end{pmatrix}_i \quad (8)$$

This set of equations can be solved voxel by voxel, provided the determinant of the 3×3 matrix is non-zero. In practice this means that no two treatment phases can have both the same dose per fraction and the same overall time per fraction. Note that if tumor repopulation is known to be negligible, γ can be set to zero and a two-phase treatment would then give sufficient information to solve for α and β .

II.D. Optimizing the Dose Distribution

Having derived patient-specific radiobiological parameters, the most recent set of clonogen density and oxygenation images can then be used to optimize the dose distribution

for a final phase of treatment. There are a number of possible approaches to the dose optimization problem, here we have used a method to maximize the overall TCP for a fixed integral dose, similar to that used by Yang and Xing.¹⁹ Details of the method are given in the Appendix.

II.E. Tumor Model

The technical feasibility of the methods described above is demonstrated by application to a model tumor. The tumor is spherical with a core of bulk disease of uniform clonogen density surrounded by a region of tumor spread in which clonogen density drops exponentially with distance from the core.⁴³ With a core clonogen density ρ_{max} , core radius R_C and overall tumor radius R_T , the clonogen density varies with radius r as shown in Eq. (9).

$$\begin{aligned} 0 \leq r \leq R_C &\Rightarrow \rho = \rho_{max} \\ R_C < r \leq R_T &\Rightarrow \rho = \rho_{max} \cdot \exp\left[-\ln(\rho_{max}) \cdot \left(\frac{r - R_C}{R_T - R_C}\right)\right] \\ r > R_T &\Rightarrow \rho = 0 \end{aligned} \quad (9)$$

Uniform intrinsic values of α , β and γ are specified for the whole tumor. The oxygen dependence takes the form suggested by Wouters and Brown,⁴¹ such that:

$$\begin{aligned} A_i &= \left(\frac{1}{OER_{\alpha_{max}}}\right) \cdot \left[\frac{(p_i \cdot OER_{\alpha_{max}}) + K_m}{p_i + K_m}\right] \\ B_i &= \left(\frac{1}{OER_{\beta_{max}}}\right)^2 \cdot \left[\frac{(p_i \cdot OER_{\beta_{max}}) + K_m}{p_i + K_m}\right]^2 \end{aligned} \quad (10)$$

where p_i is the partial pressure of oxygen in voxel i , $OER_{\alpha_{max}}$ and $OER_{\beta_{max}}$ are maximum oxygen enhancement ratios for α and β respectively, and K_m is the oxygen partial pressure at which half-maximum sensitization occurs. The partial pressure of oxygen takes a uniform value p_{max} outside the core, and drops exponentially to a minimum value p_{min} at the centre of the core:

$$\begin{aligned} r < R_C &\Rightarrow p = \exp\left[\ln(p_{max} - p_{min} + 1) \cdot \left(\frac{r}{R_C}\right)\right] + p_{min} - 1 \\ r \geq R_C &\Rightarrow p = p_{max} \end{aligned} \quad (11)$$

The resulting radial profiles for clonogen density and partial pressure of oxygen are shown in Fig. 2. Maximum and minimum oxygen pressures can be chosen independently for each imaging session and where temporal variations in oxygenation occur, it is assumed that the average of the pre- and post-treatment hypoxia images for each phase represents a good approximation to the effective oxygenation during that treatment phase. For simplicity, the proliferation rate has been chosen to be spatially invariant. However, spatial variations in γ as a function of oxygenation could easily be incorporated provided the form of the oxygen dependence was known, although the literature is somewhat inconsistent on this point.^{44,45} We have used the values of $OER_{\alpha_{\max}}$, $OER_{\beta_{\max}}$ and K_m proposed by Wouters and Brown⁴¹ throughout and results are presented for a range of literature-derived values for $\rho_{\max}$, α , β , γ , R_C , R_T , $p_{\max}$ and $p_{\min}$.

III. RESULTS

III.A. Importance of Radiobiological Parameters

For spatially varying dose prescriptions to be a viable proposition, the required level of dose inhomogeneity must be both clinically significant and clinically achievable. To investigate the sensitivity of prescribed voxel dose to variations in α , β , γ and ρ , a model tumor with a volume of 100cm^3 and with a set of literature-derived radiobiological parameters typical of prostate cancer²⁷ was considered. These parameters are listed in TABLE I. The voxel dose required to maximize total TCP subject to fixed integral dose was calculated in the case where the reference voxel (i.e. a voxel in which all parameters take the reference values) receives 78Gy, with the integral dose equal to that for a uniform irradiation to 78Gy in 39 fractions.

Fig. 3 shows the effect on voxel dose of varying each of α , β , γ and ρ over a clinically relevant range,⁴⁶ normalized to the reference voxel dose, with all other parameters fixed. It can be seen that the prescribed dose is relatively insensitive to variations in clonogen density, with wide variations in clonogen number resulting in modest alterations in voxel dose. Similarly, prescribed dose does not change dramatically with proliferation rate, except for

very rapidly proliferating tumors. However, changes in β and particularly α lead to significant changes in dose within a clinically realistic range. The importance of using patient-specific radiosensitivity can be seen by considering typical quoted values of population variance in α in the light of Fig. 3. Nahum *et al.*²⁷ quote a standard error of $\sigma_\alpha=0.06 \text{ Gy}^{-1}$ for prostate cancers. Variations in α of $\pm \sigma_\alpha$ would correspond to changes of prescribed dose of -13% or +17% respectively for this parameter set.

III.B. Method I: Numerical Optimization of Patient-Specific Radiobiological Parameters

The numerical optimization method was tested by using the model tumor described above to generate observed post-treatment clonogen density images based on an assigned set of radiobiological parameters. Expected clonogen maps based on an initial estimated set of parameters were generated in the same manner. The estimated values were then iteratively optimized to minimize the objective function described in Eq. (6). However, fundamental limitations of this method quickly became apparent, even when dealing with well-behaved modelled data.

If we consider only a single voxel within the modelled tumor, the objective function is given by:

$$OF = N^{[0]^2} \cdot \left\{ \exp \left[-A^{[1]} \alpha D^{[1]} - \left(\frac{B^{[1]} \beta D^{[1]^2}}{f^{[1]}} \right) + \gamma \Delta t^{[1]} \right] - \exp \left[-A^{[1]} \alpha_{est} D^{[1]} - \left(\frac{B^{[1]} \beta_{est} D^{[1]^2}}{f^{[1]}} \right) + \gamma_{est} \Delta t^{[1]} \right] \right\}^2 \quad (12)$$

where α , β and γ are actual values and α_{est} , β_{est} and γ_{est} are estimated values.

This function becomes zero when

$$A^{[1]} \alpha_{est} D^{[1]} + \left(\frac{B^{[1]} \beta_{est} D^{[1]^2}}{f^{[1]}} \right) - \gamma_{est} \Delta t^{[1]} = A^{[1]} \alpha D^{[1]} + \left(\frac{B^{[1]} \beta D^{[1]^2}}{f^{[1]}} \right) - \gamma \Delta t^{[1]} \quad (13)$$

This condition can be satisfied by numerous combinations of α_{est} , β_{est} and γ_{est} , so in this case the problem is degenerate. Now consider the whole tumor for a case in which phase 1 consists of a uniform irradiation of a tumor with uniform oxygenation. Each voxel contributes a term of the form given in Eq. (12) to the objective function, with each term simply scaled by the

initial clonogen number in that voxel. If the condition in Eq. (13) is met, then each term will be zero, so the problem remains degenerate.

If the phase 1 dose is non-uniform, each voxel has a different value of $D^{[1]}$, so Eq. (13) now represents a set of conditions, each of which must be satisfied in order to find the optimal α , β and γ . This breaks the degeneracy of the problem and results in a single global minimum of the OF, but a large number of local minima remain and the global minimum is extremely narrow, as illustrated in Fig. 4. The optimization process will therefore either be extremely time-consuming or prone to significant errors, even when considering perfect data.

If random noise is introduced into the modelled image data, the depth of the global minimum in the OF is reduced to a much greater extent than that of the local minima. This effect becomes more prominent as the signal-to-noise ratio (SNR) is reduced and by the time random noise represents just a few percent of the image signal the global minimum is indistinguishable from the local minima. In practice, for any realistic set of clinical images, the problem will once more become effectively degenerate and the optimization process is unlikely to yield reliable, clinically relevant results. We therefore turn our attention to the analytical approach to deriving α , β and γ .

III.C. Method II: Analytical Derivation of Patient-Specific Radiobiological Parameters

III.C.1. Sensitivity to Image Noise

When applied to noise-free modelled data in which clonogen density images perfectly represent a tumor for which the linear-quadratic model is an exact fit, this method returns the correct values of α , β and γ for each voxel. In order to assess the sensitivity of the solutions to image noise, random fluctuations were introduced into the modelled image sets and the errors in calculated parameters assessed. In each case a maximum noise amplitude a_N was set as a percentage of voxel signal, and the true voxel value multiplied by a factor $1 + v_N$ where v_N was randomly selected with uniform probability in the range $-a_N$ to $+a_N$ for each voxel. Noise was randomly introduced in this way to each of the 4 clonogen density maps. The tumor model incorporated a standard set of parameter values representative of prostate cancer²⁷ and a fixed

treatment regime for phases 1 to 3 was used, as shown in TABLE I. The model tumor was fully oxygenated throughout. The noise amplitude was varied between 0% and 100%, the simulation was run 10 times for each noise level and both the mean value and the standard deviation (SD) over the tumor for each parameter (α , β and γ) was recorded on each occasion. Fig. 5 shows the root mean square (RMS) of the error in the mean value and the average SD for each noise level for α , β and γ . The RMS error indicates the accuracy with which the mean voxel value represents the true value of a parameter, whilst the SD of the voxel values is representative of the stability of calculation results for individual voxels, given that the tumor model has uniform intrinsic radiosensitivity and proliferation. It is clear that for α and β , the mean value is much more stable than the individual voxel values with increasing noise, suggesting that for a realistic signal-to-noise ratio (SNR) it may be necessary to average the radiosensitivity values over the target. For a noise level of 10%, the RMS errors of mean values of α , β and γ are 1.1%, 3.1% and 9.2% respectively. When applied to the model outlined in the previous section, these errors combine to give an uncertainty in voxel dose of approximately 1%.

III.C.2. Effect of Treatment Parameters

It should be noted that the sensitivity to noise of the parameter calculation will vary depending on the treatment parameters (D , f and Δt) chosen for the initial treatment phases. For perfect modelled data, the determinant of the 3×3 matrix in Eq. (8) need only be non-zero. In general however, increasing the magnitude of the determinant will reduce the effect of noise on the calculation so it would be desirable to maximize the determinant subject to practical or clinical constraints.

To illustrate the effect of the various parameters on the determinant and consequently on the errors in calculated radiosensitivity and proliferation rate, we consider two specific scenarios. First, consider a situation in which phase 1 and phase 2 are both delivered at 2Gy per fraction. Phase 1 consists of 10 fractions delivered over 12 days (e.g. daily on weekdays only), whilst phase 2 consists of 5 fractions delivered over 5 days. Supposing we then wish to

deliver phase 3 in a single fraction, Fig. 6(a) illustrates the dependence of the determinant upon the size of this fraction. The noise sensitivity analysis described in the previous section was repeated using a 10% noise level and standard tumor model as outlined in TABLE I for a range of determinant values attained by adjusting the phase 3 fraction size, with the results presented in Fig. 6(b). It can be seen that for large values of the determinant, errors in the mean calculated α and β approach approximately 0.3%, and that errors of both parameters are stable and below 1% when the magnitude of the determinant is greater than 100, corresponding to a phase 3 dose of approximately 3.5Gy. It should be noted, however, that if $D^{[3]}$ is fixed then the determinant increases linearly with $f^{[3]}$, so a determinant of -100 could equally be achieved if phase 3 consisted of 4 fractions each of 2.5Gy. Fig. 6(b) also shows that errors in calculated γ are unaffected when the determinant is increased in this way, since the overall treatment time is not being changed so the ability to distinguish between different proliferation rates is not improved despite the increase in the determinant.

Secondly, we consider the effect of varying the overall treatment time for phase 1, with all other parameters fixed. In this case we have chosen phase 3 to consist of 3 fractions each of 2.5Gy delivered over 3 days, with all other parameters as in the previous example. The dependence of the determinant on $\Delta t^{[1]}$ and the consequent errors in computed parameters are shown in Fig. 6(c) and 6(d). In this case it can be seen that increasing the determinant in this way reduces errors in α , β and γ . It is therefore clear that uncertainties in α , β and γ depend not only on the magnitude of the determinant, but also on the means of increasing the determinant, so the relative importance of errors in these 3 parameters must be considered when designing the initial treatment phases.

III.D. Optimization of Final Phase Dose Distribution

Clonogen density and hypoxia data was generated for 4 different model tumors (without added noise), and in each case the radiobiological parameters were derived and the dose distribution giving the maximum TCP was generated. Models T1 and T2 use radiobiological parameters typical of a prostate tumor, whilst T3 and T4 represent a

glioblastoma or high-grade astrocytoma.²² T1 is well oxygenated, whilst T2 has reduced oxygenation in the core throughout the course of treatment. Similarly, T3 contains a core which remains mildly hypoxic throughout treatment, whilst the core of T4 is initially hypoxic, but is allowed to reoxygenate during the course of treatment. Details of the parameters used for each model are given in TABLE II, which also includes both the TCP values for uniform irradiation and the maximum achievable TCP for the same integral dose. In each case the correct α , β and γ values were derived. Fig. 7 shows the initial clonogen density and hypoxia maps, and the optimized final phase dose distribution through the centre of the tumor for each model.

The results for T1 indicate that for a well oxygenated prostate tumor, uniform irradiation gives a high probability of local control and there is relatively little benefit from redistributing dose purely to account for variations in clonogen density. However, when a persistently hypoxic region is introduced in T2, the TCP for the conventional treatment drops dramatically, indicating a probable failure of local control, whilst the redistribution of dose allows a TCP close to 1 to be achieved. The maximum final phase voxel dose for T2 was 106.2Gy, representing an increase by a factor of nearly 2.7 compared with the uniform final phase dose of 40Gy, whilst for T1 the maximum voxel dose was 62.7Gy.

T3 also suggests that hypoxia can limit the TCP for a conventional treatment, and that redistribution of dose could lead to significant increases in TCP. The maximum voxel dose of 68Gy represents an increase by a factor of 2.1 compared with the uniform final phase dose of 32Gy. T4 highlights the importance of imaging hypoxia more than once during the course of treatment. Initially, this tumor appears to have a poorer prognosis than T3, since it contains more clonogens and has a larger hypoxic region with lower relative oxygenation. However, the hypoxia in this case does not persist through the course of treatment, and consequently the TCP for the conventional uniform dose treatment is higher than for T3 and the gain in TCP due to redistribution of dose is more modest, as is the increase in maximum voxel dose to 54.9Gy.

IV. DISCUSSION

We have presented a theoretical framework for optimizing radiotherapy based on patient-specific radiobiological parameters derived from a series of functional images. This method has been illustrated by application to a specific radiobiological model and different strategies for acquiring the necessary parameters have been investigated. The basic approach, however, is independent of the precise form of the chosen model and could be used to assess the validity of a range of models in a clinical setting.

Of the two approaches discussed for deriving the radiosensitivity parameters, the optimization of the parameter set based on a minimal set of radiation response information is logistically the more attractive, for a number of reasons. Firstly, it would require only two imaging sessions, and secondly only a single phase of treatment would be needed to derive the parameters, and this phase may form part of a conventionally prescribed treatment using a standard fractionation. However, in the case of the linear-quadratic model the optimization problem becomes effectively degenerate in the presence of image noise, and this technique is unlikely to prove practicable in a clinical setting. The analytical derivation based on multiple test phases may be logistically more difficult to implement as it requires numerous imaging sessions, relies on the careful co-ordination of treatment and imaging schedules, and necessitates deviations from conventional fractionations in order to produce the necessary information. However, this approach proves to be surprisingly robust to image noise, and the required variations in fractionation appear to be relatively modest. It also appears that adequate variations in overall treatment time between test phases may be achievable simply through judicious scheduling to make use of natural breaks in treatment (e.g. weekends). Overall, the analysis we have presented suggests that the application of this technique may be feasible using a clinically acceptable schedule of test treatments.

In general, the number of imaging sessions required will depend on the complexity of the radiobiological model and will increase linearly with the number of independent parameters in the model. The basic methodology is sufficiently flexible to allow changes in the fundamental form of the model, or simply the extension of the model to include additional

factors or phenomena: the model could be extended such that hypoxic regions contain a mixture of active, quiescent and necrotic cells, with quiescent cells becoming active with reoxygenation; the bystander effect could be modelled so that the TCP in one voxel depends on the dose in neighbouring voxels; temporal variations in proliferation rate, if sufficiently well understood, could be incorporated into the model. Conversely, if any of the parameters can be reliably determined prior to treatment (e.g. estimating proliferation rate using magnetic resonance spectroscopy, or *a priori* knowledge that the proliferation rate is negligible), fewer images will be needed to solve for the remaining free parameters.

Parametric sensitivity analysis and the application of the tuned radiobiological model to a number of modelled test cases showed that the dominant factor necessitating the redistribution of dose within a tumor was the reduction of radiosensitivity due to local hypoxia. The examples chosen indicate that where significant hypoxia exists, redistributing dose can lead to a substantial increase in TCP, and suggest that hypoxia may be the most significant factor in limiting local control rates for conventional treatments. This is in good agreement with other similar work.^{19,20,42} Even in the absence of hypoxia, if a relatively large volume of the target contains a low density of clonogens the redistribution of dose may allow a small but worthwhile increase in TCP and may also benefit organs at risk peripheral to the target. It should be noted that the optimized dose distributions presented here represent an ideal prescribed dose distribution over the tumor and take no account of organs at risk, or the clinical acceptability of the changes in fractionation due to dose redistribution. In practice, a final treatment plan would need to be optimized considering normal tissue dose constraints and limitations in the physical delivery of treatment in addition to the ideal prescribed distribution, and in many cases the ideal distribution may not prove clinically deliverable. However, the magnitude of the potential increases in TCP shown for hypoxic tumors suggests that even in cases where only a limited redistribution of dose was possible, substantial increases in TCP may be achievable within sensible clinical constraints.

Potentially the most serious limitation of our current model is the implicit assumption that cell death occurs effectively instantaneously following irradiation. This is clearly not the

case, and there are two obvious approaches to solving this problem. The first would be to adapt the schedules to allow several cell cycles between each treatment phase and the subsequent imaging session, allowing the majority of cell damage to be fully expressed. This would be less than ideal for rapidly proliferating tumors as it would result in prolonging the overall treatment. The second alternative would be to incorporate the time-dependence of the progression from cell damage to cell death into the radiobiological model, requiring a more thorough understanding of this process than is currently available in the literature. However, recent work by Yang *et al.*⁴⁷ suggests that early evaluation of the response of tumors to irradiation may be possible by developing markers to image early changes in cellular behaviour, such as proliferation, which correlate well with eventual cell survival.

The model we have presented is limited by the availability of suitable imaging, radiobiological assumptions and clinical practicality, and the development and assessment of suitable parametric imaging techniques remains paramount. However, even given sizeable uncertainties in parametric data we have demonstrated significant potential gains, showing how this kind of technique could unlock the true potential of IMRT and functional imaging. It should also be noted that it would not be necessary to use clinically derived radiobiological parameters immediately to prescribe non-uniform dose distributions: in the first instance the technique could be used to simply calculate radiosensitivity and use the calculated parameters to predict TCP for a conventional final phase of treatment. From Eq. (8) it is clear that the calculation of α , β and γ does not depend on absolute clonogen densities, but only on the ratios of pre- and post-treatment clonogen numbers. In order to simply calculate the model parameters we do not therefore need to be able to absolutely quantify clonogenic cell density, we simply need images from which relative tumor burden can be derived. Using the method in this manner would provide a means of testing the predictions of a radiobiological model in a clinical setting prior to the application of the model for dose prescription.

V. CONCLUSION

We have considered the question of how emerging functional imaging techniques may be used to inform the planning of radiotherapy treatments and proposed a formalism for

using functional imaging both to determine patient-specific radiobiological properties and to prescribe an optimal non-uniform dose distribution based on these parameters. The feasibility of this approach has been demonstrated by application to a specific radiobiological model. The development and validation of techniques for quantitative imaging of both tumor burden and hypoxia would pave the way for clinical trials to assess the validity of current models for predicting tumor response. This in turn would allow the technique to be used to prescribe optimal dose distributions for individual patients. Results show potential for significant improvements in tumor control over a range of realistic parameters and assumptions.

TABLE I. Standard parameter set.

Radiobiological Parameters		Treatment Parameters	
α [Gy ⁻¹]	0.26	Phase 1	
β [Gy ⁻²]	0.0312	$D^{[1]}$ [Gy]	20
γ [day ⁻¹]	0.0173	$f^{[1]}$ [#]	10
ρ_{max} [cells cm ⁻³]	10 ⁷	$\Delta t^{[1]}$ [days]	12
$OER_{\alpha_{max}}$	2.5	Phase 2	
$OER_{\beta_{max}}$	3.0	$D^{[2]}$ [Gy]	10
K_m [mm Hg]	3.28	$f^{[2]}$ [#]	5
		$\Delta t^{[2]}$ [days]	5
		Phase 3	
		$D^{[3]}$ [Gy]	7.5
		$f^{[3]}$ [#]	3
		$\Delta t^{[3]}$ [days]	3

TABLE II. Parameters for tumor models T1-T4.

Parameter	T1			T2			T3			T4		
ρ_{max} [cells cm ⁻³]	5x10 ⁶			5x10 ⁶			1x10 ⁷			1x10 ⁷		
α [Gy ⁻¹]	0.26			0.26			0.31			0.31		
β [Gy ⁻²]	0.0312			0.0312			0.06			0.06		
γ [day ⁻¹]	0.0173			0.0173			0.1155			0.1155		
Core radius [cm]	2.0			2.0			0.8			1.2		
Tumor radius [cm]	4.0			4.0			4.0			4.8		
Total clonogens	2.1 x 10 ⁸			2.1 x 10 ⁸			5.5 x 10 ⁷			1.5 x 10 ⁸		
Initial Min pO ₂	20			2			5			1		
[mm Hg]												
Initial Max pO ₂	50			50			50			50		
[mm Hg]												
Phase:	[1]	[2]	[3]	[1]	[2]	[3]	[1]	[2]	[3]	[1]	[2]	[3]
D [Gy]	20	10	7.5	20	10	7.5	10	10	7.5	10	10	7.5
f [#]	10	5	3	10	5	3	5	5	3	5	5	3
Δt [days]	12	5	3	12	5	3	7	5	3	7	5	3
Min pO ₂ [mm Hg]	20	20	20	2	2	2	5	5	5	5	10	20
Max pO ₂ [mm Hg]	50	50	50	50	50	50	50	50	50	50	50	50
$D^{[4]}$ [Gy]	40			40			32			32		
$F^{[4]}$ [#]	20			20			16			16		
$\Delta t^{[4]}$ [days]	26			26			22			22		
D_{total} [Gy]	78			78			60			60		
(2Gy/# equiv.)												
Unif. Dose TCP	0.9698			0.2340			0.3691			0.5832		
Max TCP	0.9999			0.9998			0.9996			0.9991		

FIG. 1. Sequence of imaging sessions and treatment phases for the analytical derivation of radiobiological parameters.

FIG. 2. Radial profile of clonogen density and partial pressure of oxygen within the spherical model tumor.

FIG. 3. Sensitivity of the dose prescription for a particular voxel to variations in the value of (a) effective α ; (b) effective β ; (c) proliferation rate γ (potential doubling times of 1, 10, 100 and 1000 days are labelled); (d) clonogen density ρ . Doses are normalized to a reference voxel with the parameter values given in TABLE I.

FIG. 4. Local and global minima of the objective function (OF) in the α - β optimization plane.

FIG. 5. Effect of increasing image noise on derived radiobiological parameters. Solid lines show the RMS error in the mean computed value, dashed lines indicate the standard deviation of individual voxel values.

FIG. 6. (a) The effect on the matrix determinant of varying the phase 3 fraction size; (b) shows how uncertainties in calculating α , β and γ vary as the determinant is varied in this manner; (c) shows how the matrix determinant varies with phase 1 treatment time; (d) shows the subsequent effect on uncertainties in calculated parameters. (For (b) and (d), solid lines show the RMS error in the mean computed value, dashed lines indicate the standard deviation of individual voxel values).

FIG. 7. Initial parametric maps and final dose distributions for 4 tumor models. The parameters assigned to each model are given in TABLE II.

APPENDIX

The Lagrange multiplier method can be used to maximize TCP as follows:

For fixed integral target dose E_t ,

$$\sum_i m_i D_i = E_t \quad (\text{A.1})$$

where m_i is the mass of the i th voxel.

Let

$$L(TCP_1 \dots TCP_i \dots TCP_N) = \prod_i TCP_i + \lambda \left(\sum_i m_i D_i - E_t \right) \quad (\text{A.2})$$

For maximum total TCP,

$$\frac{\partial L}{\partial TCP_i} = 0 \quad (\text{A.3})$$

so

$$\lambda TCP_i \frac{\partial(m_i D_i)}{\partial TCP_i} = \lambda TCP_{ref} \frac{\partial(m_{ref} D_{ref})}{\partial TCP_{ref}} = -TCP \quad (\text{A.4})$$

where D_{ref} is the reference dose to a voxel with reference values of the radiobiological parameters (ρ_{ref} , α_{ref} , β_{ref} and γ_{ref}) resulting in a TCP of TCP_{ref} within this voxel.

If we assume all voxels have equal mass, then for $\lambda \neq 0$

$$TCP_i \frac{\partial D_i}{\partial TCP_i} = TCP_{ref} \frac{\partial D_{ref}}{\partial TCP_{ref}} \quad (\text{A.5})$$

and

$$TCP_i = \exp \left\{ \rho_i v_i \left[\alpha_i \left(1 + \frac{d_i}{\left(\frac{\alpha_i}{\beta_i} \right)} \right) D_i \right] - \gamma_i \Delta t \right\} \quad (\text{A.6})$$

It can then be shown that

$$D_i = - \left(\frac{f \alpha_i}{2 \beta_i} \right) + \left\{ \left(\frac{f \alpha_i}{2 \beta_i} \right)^2 + \left(\frac{f}{\beta_i} \right) \left[- \ln \left(- \frac{1}{\rho_i v_i} \ln TCP_i \right) + \gamma_i \Delta t \right] \right\}^{\frac{1}{2}} \quad (\text{A.7})$$

and

$$\frac{\partial D_i}{\partial TCP_i} = - \left[\frac{1}{2\rho_i v_i TCP_i} \right] \left[\frac{f\rho_i v_i}{\beta_i \ln TCP_i} \right] \left\{ \left(\frac{f\alpha_i}{2\beta_i} \right)^2 + \frac{f}{\beta_i} \left[-\ln \left(-\frac{1}{\rho_i v_i} \ln TCP_i \right) + \gamma_i \Delta t \right] \right\}^{\frac{1}{2}} \quad (\text{A.8})$$

so

$$\begin{aligned} TCP_i \frac{\partial D_i}{\partial TCP_i} &= - \left(\frac{f}{2\beta_i \ln TCP_i} \right) \left\{ \left(\frac{f\alpha_i}{2\beta_i} \right)^2 + \frac{f}{\beta_i} \left[-\ln \left(-\frac{1}{\rho_i v_i} \ln TCP_i \right) + \gamma_i \Delta t \right] \right\}^{\frac{1}{2}} \\ &= \left\{ -\rho_i v_i \exp \left[-\alpha_i \left(1 + \frac{D_i}{f \left(\frac{\alpha_i}{\beta_i} \right)} \right) D_i + \gamma_i \Delta t \right] \right\}^{-1} \\ &\quad \cdot \left\{ \alpha_i^2 - \frac{4\beta_i}{f} \left[-\alpha_i \left(1 + \frac{D_i}{f \left(\frac{\alpha_i}{\beta_i} \right)} \right) D_i + \frac{4\beta_i \gamma_i \Delta t}{f} \right] \right\}^{\frac{1}{2}} \end{aligned} \quad (\text{A.9})$$

Let

$$Z_i = \alpha_i \left(1 + \frac{D_i}{f \left(\frac{\alpha_i}{\beta_i} \right)} \right) D_i - \gamma_i \Delta t \quad (\text{A.10})$$

Then

$$TCP_i \frac{\partial D_i}{\partial TCP_i} = \frac{1}{\rho_i v_i \exp(-Z_i)} \left\{ \alpha_i^2 - \frac{4\beta_i}{f} Z_i \right\}^{\frac{1}{2}} = TCP_{ref} \frac{\partial D_{ref}}{\partial TCP_{ref}} \quad (\text{A.11})$$

If voxel size is constant,

$$\exp(-Z_i) \cdot \left(\alpha_i^2 + \frac{4\beta_i}{f} Z_i \right)^{\frac{1}{2}} = \frac{\rho_{ref}}{\rho_i} \exp(-Z_{ref}) \cdot \left(\alpha_{ref}^2 + \frac{4\beta_{ref}}{f} Z_{ref} \right)^{\frac{1}{2}} \quad (\text{A.12})$$

We can solve Eq. (A.12) numerically for Z_i using Newton's method, and hence derive

desired voxel doses as follows:

- 1) Set D_{ref} to an initial estimated value. We have used the uniform final phase dose D_{unif} .
- 2) Set $Z_i = Z_{init}$, calculated using an initial estimate of the optimal dose distribution.

Here we have chosen to use $D_i = D_{ref} \cdot \frac{\rho_i}{\rho_{max}}$

- 3) Repeating the following steps (a. to e.) converges to a solution for Z_i within a few iterations:

$$\text{a. Let } fn(Z_i) = \exp(-Z_i) \cdot \left(\alpha_i^2 + \frac{4\beta_i}{f} Z_i \right)^{\frac{1}{2}} \quad (\text{A.13})$$

$$\text{b. Let } \Delta fn = \left[\frac{\rho_{ref}}{\rho_i} \exp(-Z_{ref}) \cdot \left(\alpha_{ref}^2 + \frac{4\beta_{ref}}{f} Z_{ref} \right)^{\frac{1}{2}} \right] - fn(Z_i) \quad (\text{A.14})$$

$$\begin{aligned} \text{c. } \frac{\partial fn}{\partial Z_i} = & - \left[\exp(-Z_i) \cdot \left(\alpha_i^2 + \frac{4\beta_i}{f} Z_i \right)^{\frac{1}{2}} \right] \\ & + \left[\exp(-Z_i) \left(\frac{2\beta_i}{f} \right) \cdot \left(\alpha_i^2 + \frac{4\beta_i}{f} Z_i \right)^{-\frac{1}{2}} \right] \end{aligned} \quad (\text{A.15})$$

$$\text{d. Let } \Delta Z_i = \frac{\Delta fn}{\left(\frac{\partial fn}{\partial Z_i} \right)} \quad (\text{A.16})$$

$$\text{e. set } Z_i \rightarrow Z_i + \Delta Z_i$$

- 4) Eq. (A.10) can then be rearranged to find D_i .
- 5) Calculate the resultant sum of voxel doses $S = \sum_i D_i$ and compare with the intended

$$\text{value } S_{int} = n \cdot D_{unif}$$

$$\text{6) Set } D_{ref} \rightarrow D_{ref} \cdot \frac{S_{int}}{S}$$

The iteration of steps 1) to 6) rapidly converges to a solution for the optimal dose distribution.

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