Dose prescription complexity versus tumor control probability in biologically conformal radiotherapy

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Purpose: The technical feasibility and potential benefits of voxel-based non-uniform dose prescriptions for biologically heterogeneous tumors have been widely demonstrated. In some cases, an “ideal” dose prescription has been generated by individualizing the dose to every voxel within the target, but often this voxel-based prescription has been discretized into a small number of compartments. The number of dose levels utilized, and the methods used for prescribing doses and assigning tumor voxels to different dose compartments have varied significantly. We present an investigation into the relationship between the complexity of the dose prescription and the tumor control probability (TCP) for a number of these methods.

Methods: The linear quadratic model of cell killing was used in conjunction with a number of modelled tumors heterogeneous in clonogen density, oxygenation, or proliferation. Models based on simple mathematical functions, published biological data and biological image data were investigated. Target voxels were assigned to dose compartments using (i) simple rules based on the initial biological distribution; (ii) iterative methods designed to maximize the achievable TCP; or (iii) methods based on an “ideal” dose prescription.

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Results: The relative performance of the simple rules was found to depend on the form of heterogeneity of the tumor, whilst the iterative and “ideal” dose methods performed

25 comparably for all models investigated. In all cases the maximum achievable TCP was approached within the first few (typically 2-5) compartments.

Conclusion: Results suggest that irrespective of the pattern of heterogeneity, the optimal dose prescription can be well approximated using only a few dose levels, but only if both the compartment boundaries and prescribed dose levels are well chosen.

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Key words: tumor control probability, radiation therapy, treatment planning, dose painting, functional imaging

I. INTRODUCTION

There has been much discussion in recent years of the use of deliberately non-uniform dose distributions in radiotherapy¹⁻³, and both the technical feasibility and potential benefits of “dose-painting” have been widely demonstrated⁴⁻¹². There are a number of possible approaches to the incorporation of radiobiological modelling into the treatment planning process. One such methodology is to use a model predicting tumor response to generate a non-uniform dose prescription to the target⁸. This prescription can then be used in conjunction with dose constraints for normal tissue (which can be dose-volume based or radiobiological and may take into account functional heterogeneity of organs at risk) to generate a clinical treatment plan. A schematic diagram of this methodology is presented in figure 1. An alternative is to use models predicting both tumor response and normal tissue damage to directly optimise a treatment plan using a metric such as the probability of uncomplicated tumor control, known as P_+ ^{4,13}. We have adopted the former methodology to enable us to consider the model predicting tumor response independent of that predicting normal tissue response. In this work we consider only the first stage of this process, the generation of a dose prescription (shown within the dashed box in figure 1). With information on biological variations within a tumor, obtained using functional imaging, it is possible to individualize the dose prescription to each imaged voxel within the target^{8,12,14,15}. However, more commonly the target has been divided into a small number of compartments such that the quasi-continuous optimal dose distribution is quantized into a few discrete dose levels^{5-7,9,16}. The aim of this work is to investigate the relationship between the complexity of a treatment prescription, measured by the number of prescribed dose levels, and the quality of the plan, represented by the TCP.

For an inhomogeneous tumor, the TCP can be increased with respect to a uniform dose distribution by redistributing dose without increasing the integral dose to the target. In general, under these conditions the TCP is expected to increase as the number of dose levels is increased. For any given target, the precise form of this relationship will depend on the heterogeneity of the tumor, the positioning of the boundaries between different compartments, and the choice of prescribed dose levels. The key practical questions are therefore: (i) how many dose levels are worthwhile; (ii) what is the optimal method for assigning voxels to different compartments; and (iii) how should we set the prescribed doses to those compartments? We have addressed these questions by investigating the behaviour of a number of model tumors with a variety of forms of biological heterogeneity.

II. METHODS

II.A. Radiobiological Modelling

If radiation response is described by the linear-quadratic model, the surviving fraction (SF) of tumor cells following irradiation to dose D in f fractions is given by:

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

where α and β are the linear and quadratic parameters of cell kill, T is the overall treatment time and γ the repopulation rate, with repopulation beginning T_k days after the start of treatment. The tumor control probability (TCP) is found by assuming Poisson statistics and calculating the probability of there being no viable tumor cells remaining. Considering a tumor divided into N equal-sized voxels each of volume v , the probability of killing all tumor cells within a single voxel i is given by:

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

80 where ρ_i is the clonogenic cell density in voxel i and D_i the dose delivered to voxel i . Note that the radiosensitivity parameters are also allowed to vary spatially to account for local variations in oxygenation^{17,18}. The overall TCP for the whole tumor is then the product of the TCPs for all voxels²:

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

85 The local values of the linear and quadratic terms of radiosensitivity are given by intrinsic radiosensitivity terms α and β multiplied by factors A_i and B_i respectively, such that

$$\begin{aligned} \alpha_i &= A_i \alpha \\ \beta_i &= B_i \beta \end{aligned} \quad (4)$$

where A_i and B_i are functions of the local oxygenation. The oxygen dependence takes the form proposed by Wouters and Brown¹⁹:

$$\begin{aligned} A_i &= \left(\frac{1}{OER_{\alpha_{max}}} \right) \cdot \left[\frac{(p_i \cdot OER_{\alpha_{max}}) + K_m}{p_i + K_m} \right] \\ B_i &= \left(\frac{1}{OER_{\beta_{max}}} \right)^2 \cdot \left[\frac{(p_i \cdot OER_{\beta_{max}}) + K_m}{p_i + K_m} \right]^2 \end{aligned} \quad (5)$$

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.

For simplicity, we assume an idealized situation where we can precisely deliver
95 any desired dose distribution, with the resolution of the biological imaging voxels. For the purposes of this analysis, we can then simply consider a tumor as a series of N voxels with differing biological properties and dose prescriptions. We also assume knowledge of

the intrinsic radiosensitivity parameters α and β for the individual tumor¹⁵, enabling us to use single values of α and β rather than a population distribution. However, we subsequently consider the impact of variations in these parameters.

II.B. Dose Optimization

In order to allow a fair quantitative comparison between plans of differing complexity, we used a method which maximizes the TCP by redistributing dose between compartments, subject to a fixed integral dose^{8,16,20}. This method has been previously described by the authors¹⁵.

II.C. Tumor Models

The key biological parameters affecting the TCP in a given voxel are the clonogen density, the oxygenation and the proliferation rate. We have investigated the behavior of simple model tumors in which either clonogen density, oxygenation or proliferation is allowed to vary across the tumor, with that variation taking the form of four different simple mathematical functions. We also present data for models in which variations in oxygenation are based on published oxygen partial pressure histograms for a number of tumor types. Finally, we constructed tumor models from a number of clinical ¹⁸F-fluorodeoxyglucose (FDG) PET data sets. Whilst it would be inappropriate to use FDG uptake as a surrogate for clonogen density, hypoxia or proliferation, it is believed to be influenced by all these factors²¹⁻²⁶. We have therefore used FDG-PET data from 3 lung tumors, not to demonstrate a clinical application, but merely to indicate typical patterns of biological heterogeneity. For each scan we created models taking the PET data to represent variations in clonogen density, oxygenation, or a combination in order to

investigate whether the predictions for these models fell within the range of the mathematical models presented.

We have chosen radiobiological parameters from the literature to represent a typical lung tumor: $\alpha = 0.35 \text{ Gy}^{-1}$; $\alpha/\beta = 10 \text{ Gy}$; $\gamma = 0.231 \text{ day}^{-1}$ (equivalent to a potential doubling time of 3 days); $T_k = 28 \text{ days}^{27}$; $OER_{\alpha_{\max}} = 2.5$; $OER_{\beta_{\max}} = 3.0$; and $K_m = 3.28 \text{ mmHg}^{19}$. TCPs are calculated for treatments which deliver an integral dose equivalent to a uniform irradiation of 64 Gy in 32 fractions, delivered over 44 days (i.e. treated 5 days per week).

II.C.1. Simple Models

The simple mathematical models each contain 1000 voxels, across which clonogen density, oxygenation or proliferation varies as a linear, exponential, sigmoidal or logarithmic function of voxel number. For models with heterogeneous clonogen density the oxygen pressure has been set to a uniform 100 mmHg. To aid comparison the tumors have been normalized so that they all have a minimum density of 10^5 clonogens per voxel (which is approximately the lower detection limit using current PET techniques²¹), and all contain a total of 10^9 clonogens²⁸. This means that a uniform dose gives the same total TCP for each model.

For models with heterogeneous oxygenation, the partial pressure of oxygen is allowed to vary linearly, exponentially, sigmoidally and logarithmically between 1 and 100 mmHg. Additional models are derived by linearly interpolating published oxygen partial pressure histograms for squamous cell carcinomas, breast cancers and gastric adenocarcinoma²⁹. For these hypoxic models, the total number of clonogens has been chosen such that: (i) a uniform irradiation to 64 Gy results in the same TCP for each

model; (ii) the maximum achievable TCP is significantly greater than 0; and (iii) clonogen densities fall within a clinically realistic range for all models. When the
145 uniform-dose TCP is 0.001, the total clonogen number ranges from 1.03×10^5 for the sigmoidal model to 1.95×10^6 for the logarithmic model, and the maximum achievable TCP is greater than 0.9 in each case.

For models with a heterogeneous proliferation rate, γ has been allowed to vary by a factor of 100 from a maximum value of 0.231 day^{-1} , with variations taking linear,
150 exponential, sigmoidal and logarithmic forms. The partial pressure of oxygen is set to a uniform 100 mmHg and again the total number of clonogens is normalized such that uniform irradiation results in the same TCP for each model. Figure 2 shows the variation in clonogen density, oxygenation or proliferation rate for each of these models.

II.C.2. PET-Based Models

155 The PET-based models were created by extracting a cuboid of data from a clinical ^{18}F -FDG PET scan, centred on a lung tumor. Background voxels were removed using a threshold of 15% of the peak voxel value, and the remaining voxels sorted into order of intensity. For all models, this threshold was within ± 0.5 of the absolute SUV threshold of 2.5 proposed by Paulino and Johnstone for the segmentation of tumors³⁰ and we
160 determined that our results were insensitive to variations in this threshold (data not presented). We consider models in which variations in voxel intensity are taken to reflect variations in either clonogen number or hypoxia, or both.

For models with heterogeneous clonogen density, image intensities were converted into clonogen numbers assuming a linear relationship between FDG uptake and
165 clonogen density^{21,22} and normalizing to give a minimum clonogen density of 10^5 per

voxel and a total clonogen number of 10^9 as before. The total number of tumor voxels varies between 237 and 2864 for these models. For models with heterogeneous oxygenation we have assumed that FDG uptake is negatively correlated with oxygenation²³⁻²⁵. Oxygen partial pressures have been allowed to vary within a range of 1 to 100 mmHg and we have again chosen a clonogen density for each model which results in a TCP of 0.001 for a uniform irradiation to 64 Gy. This combination of parameters again allows a significant TCP to be achieved by redistributing dose whilst keeping all parameters within a clinically realistic range. Finally, for models in which both clonogen density and oxygenation are allowed to vary, the clonogen distribution from the first PET model is combined with the oxygen distribution from the second for each tumor. It should be noted that these models imply that hypoxia is inversely related to clonogen density, which is unlikely to be clinically realistic as it suggests that hypoxic cells are more viable than normoxic cells. However, they are included in order to present a worst-case scenario in which variations in clonogen density and oxygenation interact constructively, as this is the situation in which the greatest dose heterogeneity will be required. Figure 3 shows PET images taken through the centre of each tumor and the derived clonogen and oxygen distributions for each of the PET models.

II.D. Setting Compartment Boundaries

II.D.1. Heterogeneous Clonogen Density

In general a non-uniform dose distribution is designed by allocating tumor voxels to a number of compartments, then optimizing the prescribed doses to those compartments. For models in which only clonogen density varies between voxels, the optimal dose distribution can be directly calculated for any number of compartments, as

described above¹⁵. We investigated a number of methods for allocating voxels to different

190 compartments. These methods fall into three categories: simple rules based on the
clonogen density distribution; numerical optimizations in which the boundary positions
are iteratively adjusted to maximize the total TCP; and methods in which the optimal
dose distribution is calculated with an individualized dose to every voxel, and
compartments are designed based on this ideal dose distribution.

195 *II.D.1.a. Simple Methods*

Equal volumes (Vol): the boundaries are set such that each compartment contains the
same number of voxels.

Equal clonogens (Clons): the boundaries are set such that each compartment contains
the same total number of clonogens.

200 **Evenly spaced clonogen density thresholds (Thresh):** compartments have evenly-
spaced boundaries between the pre-determined maximum and minimum clonogen density
limits.

II.D.1.b. Iterative Methods

Exhaustive search (Exh): the dose distribution is optimized to give the maximum
205 achievable TCP for every possible combination of boundary positions, and the set of
positions resulting in the highest TCP is chosen.

Gradient ascent (Grad): boundary positions are iteratively optimized using a gradient
ascent method to find the maximum overall TCP.

II.D.1.c. Ideal Dose Distribution Methods

210 **Evenly spaced dose levels (Dose):** initial compartment doses are set by averaging over the ideal dose distribution within each compartment, with boundaries chosen to give approximately evenly-spaced dose levels.

Optimum mean square quantizer (OMQ): this method calculates the compartment boundaries and dose levels which result in a dose profile which is the best fit to the ideal
215 dose distribution. This is analogous to the problem of designing multiple static fields to give the best fit to an optimal fluence profile^{31,32}. Details are given in the appendix.

In each case, once the boundaries have been set using one of these methods, the dose-levels are re-optimized to ensure that the maximum possible TCP is achieved for each configuration.

220 ***II.D.2. Heterogeneous Oxygenation or Proliferation Rate***

For tumors with heterogeneous oxygenation (with or without clonogen density variations), for small numbers of compartments the dose distribution was optimized by iteratively adjusting the boundary positions to maximize TCP. For each set of boundary positions, compartment dose is given by the average voxel dose delivered to a
225 compartment by the ideal dose distribution. Where the number of compartments was 7 or greater, it was found that setting compartment boundaries using the even dose levels approach gave TCPs within 0.5% of this iterative method in all cases. This method was therefore adopted for larger numbers of compartments as it reduced calculation times and eliminated the risk of being influenced by local minima. A similar approach was taken to
230 optimizing dose distributions for models with heterogeneous proliferation rates.

II.D.3. Sensitivity to Variations in Chosen Parameter Values

The calculated TCP values for all these models will be sensitive to variations in the precise value of each of the fixed parameters chosen for that model. In order to determine whether conclusions drawn from the behavior of these models are robust
235 against such variations, we also repeated our analysis for a subset of the models with previously fixed values allowed to vary. We would expect our results to be particularly sensitive to our choice of oxygen pressures. We present results for the following: the sigmoidal clonogen density model, with the uniform oxygenation allowed to vary; the sigmoidal oxygenation model, with the minimum partial pressure of oxygen allowed to
240 vary; the model based on the gastric adenocarcinoma oxygen histogram, with the radiosensitivity allowed to vary.

III. RESULTS

III.A. Simple Models

III.A.1. Heterogeneous Clonogen Density

245 Figure 4a shows an exhaustive search of boundary positions for the 2-compartment case for each of the simple mathematical tumor models, with the dose-levels optimized to give the maximum achievable TCP for each boundary position. This illustrates the importance of dividing the tumor in such a way as to enable the maximum possible benefit from a non-uniform dose distribution. It also shows that the potential
250 benefits of redistributing dose depend on the heterogeneity of the tumor – the improvements in TCP are much greater for tumors with exponential and sigmoidal variations in clonogen density than for the largely homogeneous logarithmic model. Of course in the extreme case of a uniform tumor, no improvement in TCP would be possible, since a uniform distribution is optimal in this case³³.

Figure 4b and c show the relationship between complexity and TCP for the equal volumes, equal clonogens, even clonogen density thresholds and even dose levels methods, for the exponential and sigmoidal tumor models. It is clear that the relative performance of the simple methods depends on the form of tumor heterogeneity. The even dose levels approach works consistently well compared with the other simple methods when there is significant inhomogeneity across the tumor.

Figure 4d shows again the even dose levels approach along with the iterative methods (exhaustive search and gradient ascent) and the OMQ for the same 4 tumor models. Again we see that the potential benefits of dose redistribution depend on the heterogeneity of the tumor, but also that for all these models, most of the benefit occurs within the first few compartments. In all cases greater than 99.5% of the maximum achievable TCP is reached within 4 compartments. The exhaustive search was only carried out for up to 3 compartments since beyond this it becomes extremely computationally intensive. All these methods generally achieve similar results, suggesting that the gradient ascent method is not significantly hampered by local maxima for these models, although this may not be true for all cases (indeed this method gives slightly sub-optimal results for the sigmoidal model in the 4 to 7 compartment range). The OMQ approach has the advantage that it is an analytical method, it is relatively fast and it appears stable provided the number of compartments is small compared to the number of voxels.

III.A.2. Heterogeneous Oxygenation or Proliferation Rate

Figure 5 (a) and (b) show the relationship between TCP and number of dose levels for the mathematically derived and clinically derived hypoxic models respectively.

Figure 5 (c) shows results for the mathematical models with varying proliferation rate.

Once again the majority of the benefit occurs within the first few compartments for all

280 these models.

III.A.3. Sensitivity to Variations in Chosen Parameter Values

Figure 6 shows the complexity versus TCP curve for a number of the models previously presented, with a key fixed parameter allowed to vary in each case. In figure 6 (a), the analysis for the sigmoidal clonogen density model is repeated with the uniform partial pressure of oxygen varying between 20 and 100 mmHg. Figure 6 (b) shows results for the sigmoidal oxygenation model, with the minimum partial pressure of oxygen varying between 0 and 10 mmHg. The total clonogen number was fixed equal to that used for the original model. Figure 6 (c) shows the effect of varying the radiosensitivity parameters on the behaviour of the hypoxic model based on the gastric adenocarcinoma oxygen histogram. In this case α was varied between 0.15 and 0.5 Gy⁻¹ with the α/β ratio fixed at 10 and the uniform clonogen density scaled to give the same TCP in each case for a uniform dose of 64Gy. In each case investigated, whilst a change of parameter values affected the absolute TCP values and the initial slope of the curve, the overall shape of the curve was largely unaffected.

295 III.B. PET-Based Models

Comparing the distributions of uptake in figure 3 with the simple models in figure 2, we would expect the results for the PET model tumors to fall within the range of the results for the mathematical models investigated. Figure 7 shows results of the gradient ascent method for each of the PET models. The resulting dose prescription maps are also shown for 1 to 5 compartments, and for the optimal dose distribution in each case. Note that

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these maps represent a single slice through each tumor, and that although the most heterogeneous slice of each model has been chosen, in some cases not all the available dose levels are present on the slice displayed. It is clear that where both clonogen density and oxygenation vary across the tumor, hypoxia is the dominant effect in determining the most effective dose distribution. Again, the majority of the benefit is attained within the first few compartments for all the models investigated.

IV. DISCUSSION

The results presented above suggest that, for a wide range of heterogeneous biological distributions, the vast majority of the benefit of dose redistribution can be attained using very few dose levels. However, this is only true if both the prescribed dose levels and the dividing lines between compartments are well chosen. Due to the uncertainties inherent in interpreting biological image data, previous work demonstrating the feasibility of dose-painting has tended to link the biological image intensities and subsequent dose prescription levels somewhat arbitrarily, often quantizing either biological parameters or dose into very few levels^{5-9,16}. For example, Yang and Xing⁹ present an elegant method for optimizing a non-uniform dose prescription on the voxel scale, but demonstrate it using models in which the biological variations are quantized into a few discrete levels. Das *et al*⁷ consider continuously varying biological distributions and dose prescriptions but generate their prescription by setting dose proportional to PET voxel intensity. Sovik *et al*¹¹ used very similar radiobiological models to those presented here to investigate the impact of varying the number of dose levels on the benefit of redistributing dose for 4 hypoxic tumor models. We have

expanded upon this work to investigate a wide range of theoretically and clinically
325 derived biological distributions to determine whether their conclusions are generally
applicable. Taking into account variations in clonogen density, oxygenation and
proliferation rate, our results are consistent with their observation that increasing the
number of dose levels beyond 4 yields little additional benefit. We have however
demonstrated a number of methods to approximate the optimal dose prescription for any
330 number of discrete dose levels for a given non-uniform tumor.

We have made the simplifying assumption that any desired dose distribution can
be accurately delivered. Whilst this is clearly not a realistic expectation, beam-shaping
devices with a resolution comparable to that of most functional images are now widely
available. For example, multi-leaf collimators with an effective leaf width of 3 to 5mm
335 are not uncommon, giving the capability to produce fluence modulations at the same
scale as a typical PET voxel. Whilst the steepest achievable dose gradients will be
fundamentally limited by the penumbra of the beam-shaping device, and small-field
dosimetry remains problematic, we would nevertheless expect to be able to deliver a
close approximation to the desired dose distribution in the majority of cases³⁴. The major
340 limiting factors for dose-painting therefore remain the quantification of biological
parameters from functional imaging and the validation of models predicting tissue
response³⁵.

It should be noted that our observations relate to a prescribed target dose
distribution, not to a final planned clinical dose. In the absence of normal tissue dose
345 constraints, we would expect these two distributions to be closely matched, as discussed
above. However, where organs at risk are present close to or overlapping with the target,

a reduction in the target dose may be necessary in these regions. This could of course lead to an increase in the number of dose levels present in the final planned target dose distribution.

350 The resolution of the dose prescription is limited by the PET resolution and/or the resolution with which we can physically modulate dose, whichever is coarser. Biological heterogeneities are likely to exist on a much finer scale than we can hope to either image non-invasively or modulate external-beam dose. Acquiring biological information on a finer scale than the dose prescription voxel size would result in the dose to each
355 prescription voxel being largely determined by the least radiosensitive region within that voxel. This means that our current approach, in which we take each PET voxel value to be representative of all cells within that PET voxel, is likely to underestimate both the heterogeneity of the optimal dose distribution and the potential benefit of dose redistribution³⁶. However, we have demonstrated that a wide range of optimal dose
360 distributions, optimized making a variety of assumptions, can be well approximated using very few dose levels and a small increase in the dose range of the optimal dose distribution is unlikely to affect this conclusion.

 It is clear that where significant hypoxia exists, this will dominate the dose prescription, and the increase in TCP achieved by dose redistribution is modest for the
365 models in which only clonogen density or proliferation vary. However, even an increase of 5% in TCP could be considered clinically important, particularly if it can be achieved with only a modest increase in the complexity of the plan. In the case of common cancers such as lung or prostate, even a small improvement in TCP could result in an improved outcome for a large number of patients.

370 The initial steepness of the TCP versus complexity curve for all significantly
inhomogeneous tumors indicates that a relatively simple dose prescription consisting of 2
to 5 dose levels will be sufficient to produce a dose distribution that is very close to
optimal. This will simplify the task of designing treatment planning systems capable of
fully utilizing biological information from functional imaging to optimize planned dose
375 distributions. Plotting this curve for individual tumors, taking into account variations in
clonogen density, oxygenation and proliferation, could assist in choosing the number of
dose levels to use in each specific case. This would also enable the identification of cases
for which the overall benefit of dose redistribution is minimal and a simple uniform
irradiation would be the most appropriate treatment. We have demonstrated a number of
380 methods for assigning dose levels which could easily be implemented within a treatment
planning system. The even dose levels method, the OMQ and the iterative approaches all
appear to give comparable results, so the most appropriate method will depend on the
relative importance of robustness and computational efficiency. The optimal approach is
likely to be one in which, for small numbers of dose levels, the boundaries are iteratively
385 optimized, whilst the even dose levels approach is used where larger numbers of dose
levels are required and iterative optimization becomes computationally prohibitive.

V. CONCLUSIONS

 When designing non-uniform dose prescriptions for biologically heterogeneous
390 tumors, only a few dose levels are required, provided these dose levels are well chosen.
The quantification of biological parameters from functional imaging remains the limiting
factor in the clinical implementation of dose painting.

ACKNOWLEDGMENTS

395 This work was supported by Cancer Research UK (CRUK). We acknowledge NHS funding to the NIHR Biomedical Research Centre. We would also like to thank Ros Perrin for her help in generating the PET-based models.

APPENDIX: OPTIMUM MEAN SQUARE QUANTIZER METHOD

400 A quantizer maps a continuous variable x onto a discrete variable x' , which takes values from a finite set of numbers. For a quantizer with L levels, this mapping is achieved by defining a set of “transition levels” $\{t_1, \dots, t_{L+1}\}$ and assigning “reconstruction levels” $\{r_1, \dots, r_L\}$ such that if $t_k < x < t_{k+1}$, then $x' = r_k$. The optimum mean square quantizer sets both transition and reconstruction levels so as to minimize the mean square error from the original distribution for a given number of quantization levels³¹. Let x be prescribed voxel dose, with a continuous probability density function $p_x(x)$ determined from the ideal dose distribution. The mean square error is then:

$$\mathcal{E} = \int_{t_1}^{t_{L+1}} (x - x')^2 p_x(x) dx = \sum_{i=1}^L \int_{t_i}^{t_{i+1}} (x - r_i)^2 p_x(x) dx \quad (\text{A1})$$

The error can be minimized by differentiating with respect to both t_k and r_k and setting the results to zero:

$$\frac{d\mathcal{E}}{dt_k} = (t_k - r_{k-1})^2 p_x(t_k) - (t_k - r_k)^2 p_x(t_k) = 0 \quad (\text{A2})$$

$$\frac{d\mathcal{E}}{dr_k} = \int_{t_k}^{t_{k+1}} (x - r_k) p_x(x) dx = 0 \quad (\text{A3})$$

$$1 \leq k \leq L$$

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This leads to the following:

$$t_k = \frac{(r_k + r_{k-1})}{2} \quad (\text{A4})$$

$$415 \quad r_k = \frac{\int_{t_k}^{t_{k+1}} x p_x(x) dx}{\int_{t_k}^{t_{k+1}} p_x(x) dx} \quad (\text{A5})$$

If we set t_l and t_{L+l} equal to the minimum and maximum voxel doses from the ideal distribution, equations A4 and A5 can be solved using an iterative method to give both transition levels and prescribed dose levels.

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FIG. 1. Schematic diagram of the proposed methodology for biologically conformal treatment planning. The aspects of the process considered in this work are contained within the dashed box.

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FIG. 2. (a) Clonogen distributions for the simple mathematical models (linear, exponential, sigmoid and logarithmic); (b) Oxygen distributions for the simple mathematical models; (c) Oxygen distribution for the models based on published oxygen partial pressure histograms: squamous cell carcinoma(SCC), breast cancer(BC) and gastric adenocarcinoma(GAC); (d) Proliferation rates for the simple mathematical models.

FIG. 3. Assumed clonogen (solid lines) and oxygen (dashed lines) distributions for tumor models based on 3 clinical ^{18}F FDG-PET scans. For each scan, models are presented for which PET voxel intensity represents: (a) clonogen density; (b) hypoxia and (c) both. Color scales indicate the initial PET voxel standardized uptake values (SUVs).

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FIG. 4. (a) The maximum achievable TCP as a function of boundary position for the 2-compartment case for each of the simple models with heterogeneous clonogen density (linear, exponential, sigmoid and logarithmic); (b) TCP as a function of complexity for the model with exponentially varying clonogen density using the equal volume, equal clonogens, evenly-spaced clonogen density threshold and evenly-spaced dose-level methods; (c) TCP as a function of complexity for the model with sigmoidally varying clonogen density using the equal volume, equal clonogens, evenly-spaced clonogen density threshold and evenly-spaced dose-level methods; (d) TCP as a function of complexity for the even dose levels (Dose), gradient ascent (Grad), optimum mean square quantizer (OMQ) and exhaustive search (Exh) methods for the simple models with heterogeneous clonogen density (linear, exponential, sigmoid and logarithmic).

FIG. 5. (a) TCP as a function of complexity for the simple mathematical models with heterogeneous oxygenation (linear, exponential, sigmoid and logarithmic); (b) TCP as a function of complexity for the simple models based on published oxygen partial pressure histograms: squamous cell carcinoma(SCC), breast cancer(BC) and gastric adenocarcinoma(GAC); (c) TCP as a function of complexity for the simple mathematical models with heterogeneous proliferation rate (linear, exponential, sigmoid and logarithmic).

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FIG. 6. (a) TCP versus complexity for the sigmoidal clonogen density model with the uniform partial pressure of oxygen varying between 20 and 100 mmHg; (b) TCP versus complexity for the sigmoidal oxygenation model with the minimum partial pressure of oxygen varying between 0 and 10 mmHg; (c) TCP versus complexity for the model based on the gastric adenocarcinoma oxygen histogram with the radiosensitivity α varying between 0.15 and 0.5 Gy⁻¹.

FIG. 7. TCP as a function of complexity for each of the PET-based models. The resulting dose prescription maps are also shown for 1 to 5 compartments, and for the optimal dose distribution for the cases in which PET uptake represents: (a) clonogen density; (b) hypoxia and (c) both.

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