Abstract—Glioblastoma is a highly invasive brain tumor, whose cells infiltrate surrounding normal brain tissue beyond the lesion outlines visible in the current medical scans. These infiltrative cells are treated mainly by radiotherapy. Existing radiotherapy plans for brain tumors derive from population studies and scarcely account for patient-specific conditions. Here we provide a Bayesian machine learning framework for the rational design of improved, personalized radiotherapy plans using mathematical modeling and patient multimodal medical scans. Our method, for the first time, integrates complementary information from high resolution MRI scans and highly specific FET-PET metabolic maps to infer tumor cell density in glioblastoma patients. The Bayesian framework quantifies imaging and modeling uncertainties and predicts patient-specific tumor cell density with confidence intervals. The proposed methodology relies only on data acquired at a single time point and thus is applicable to standard clinical settings. An initial clinical population study shows that the radiotherapy plans generated from the inferred tumor cell infiltration maps spare more healthy tissue thereby reducing radiation toxicity while yielding comparable accuracy with standard radiotherapy protocols. Moreover, the inferred regions of high tumor cell densities coincide with the tumor radioresistant areas, providing guidance for personalized dose-escalation. The proposed integration of multimodal scans and mathematical modeling provides a robust, non-invasive tool to assist personalized radiotherapy design.

Index Terms—Glioblastoma, radiotherapy planning, Bayesian inference, FET-PET, multimodal medical scans.

I. INTRODUCTION

Glioblastoma (GBM) is the most aggressive and most common type of primary brain tumor, with a median survival of only 15 months despite intensive treatment [1]. The standard treatment consists of immediate tumor resection, followed by combined radio- and chemotherapy targeting the residual tumor. All treatment procedures are guided by magnetic resonance imaging (MRI). In contrast to most tumors, GBM infiltrates surrounding tissue, instead of forming a tumor with a well-defined boundary. The central tumor, which is visible on the medical scans, is commonly resected. However, the distribution of the infiltrating residual tumor cells in the nearby healthy-appearing tissue, which are likely to contribute to tumor recurrence, is not known.

Current radiotherapy (RT) planning handles these uncertainties in a rather rudimentary fashion. Guided by population-level studies, standard-of-care RT plans uniformly irradiate the volume of the visible tumor extended by a uniform margin [1]–[3], which is referred as the clinical target volume (CTV). However, the extent of this margin varies by few centimeters even across the official RT guidelines [4]. Moreover, GBM infiltration is anisotropic and thus a uniform margin very likely does not provide an optimal dose distribution. In addition, GBM invasiveness is highly patient-specific, and thus not all patients benefit equally from the same margin, which impairs comparison and advancement of RT protocols. Despite treatment almost all GBMs recur [5]. Biopsies [6] and post-mortem studies [7] show that tumor cells can invade beyond the CTV, which reduces RT efficiency, and is a possible cause of recurrence. At the same time radioresistance of tumor cells inside the CTV can also reduce RT efficiency. Radioresistance tends to occur in regions with complex microenvironment and hypoxia [8], both of which are commonly encountered in areas of high tumorcellularity. To address tumor radioresistance, several studies have suggested local dose-escalations [8]–[10]. In these approaches, a boosted dose is delivered into a single or multiple co-centered regions defined by adding uniform margins to the tumor outlines visible in MRI scans [11]. The Radiation Therapy Oncology Group (RTOG) phase-I trial [10] showed an increase in median survival of 8 months with dose-escalation. However, no benefit in progression-free survival was observed, indicating
a complex relationship between the true progression of the underlying disease and the tumor extent visible in MRI scans. Alternatively, positron emission tomography (PET) scans, which map tumor metabolic activities targeted by specific tracers, can be used to identify radioreistant regions. A promising tracer used in GBM imaging is 18F-fluoro-ethyl-

A prospective phase-II-study demonstrated that dose-escalation based on FET-PET enhancement delineates the tumor structure better than uniform margins, thus leading to lower radiation toxicity. Still, FET-PET based dose-escalation did not increase progression-free survival. One possible explanation is that PET enhances mainly the tumor core, which is usually resected, while the PET uptake values in the remaining tumor periphery coincide with the baseline signal from the healthy tissue. This, together with a rather low resolution of PET scan limits its ability to fully target radioreistant tumor residuals. This is also consistent with our results.

The standard RT plans can be improved by incorporating information from computational tumor models. These models, calibrated against patient medical scans, provide estimates of tumor infiltration that extend the information available in medical images and can guide the personalized RT designs. Despite extensive development of tumor growth models and calibration strategies, their translation into clinical practice remains very limited. We postulate that there are (at least) three translational weak-ness: 1) Most model calibrations rely on data not commonly available in the clinical practice. For example, in medical scans with visible tumor progression from at least two time points are used for the model calibration. However, for GBM patients only scans acquired at single preoperative time point are available. 2) Models are based on simplified assumptions motivated by in-vitro studies. For instance, it is frequently assumed that the tumor cell density is constant along the tumor borders visible on MRI scans. 3) Even if advanced calibration techniques as in are used, it is not clear how robust the model predictions are and what benefits they offer over the standard treatment protocols.

Here, we address these translational issues and provide clinically relevant patient-specific tumor predictions to improve personalized RT design. We present a Bayesian machine learning framework to calibrate tumor growth models from multimodal medical scans. We show that an integration of information from complementary structural MRI and functional FET-PET metabolic maps enables the robust inference of the tumor cell densities from scans acquired at single time point. To the best of our knowledge, this is the first study making joint use of FET-PET and MRI scans for the patient-specific calibration of a tumor growth model. Our Bayesian approach infers modeling and imaging parameters under uncertainties arising from measurement and modeling errors. We propagate these uncertainties through the computational tumor model to obtain robust estimates of the tumor cell density together with confidence intervals that can be used for personalized RT design. The patient-specific tumor estimates offer an advantage in determining margins of CTV as well as regions for dose-escalation. A clinical study is used to assess benefits of the personalized RT design over the standard treatment protocols. In the remainder of the paper, Section II introduces the Bayesian framework for model calibration, including the tumor growth and imaging models. The results are presented in Section III where the framework is applied to synthetic and clinical data, followed by personalized RT study. The conclusion is presented in Section IV. Additional technical details are given in Supplementary Materials (SM).

II. BAYESIAN MODEL CALIBRATION

The Bayesian framework we develop combines deterministic model $M_a$ for tumor growth with a stochastic imaging model $M_{I}$ relating model predictions with tumor observations available from patient medical scans. Bayes theorem is used to estimate probability distribution of the unknown parameters of the both models, accounting for modeling and measurement uncertainties. Identified parametric uncertainties are propagated to obtain robust patient-specific tumor predictions. An overview of the framework is given in Fig. I.

A. Tumor growth model

Many tumor growth models are based on Fisher-Kolmogrov (FK) equation , which captures the main tumor behaviour: proliferation and infiltration. We use FK equation to describe the tumor model $M_{u}$. The equation is solved in a patient-specific brain anatomy reconstructed from the MRI scans, where each voxel corresponds to one simulation grid point. Let $\Omega \in \mathbb{R}^3$ be the brain anatomy consisting of white and grey matter and $u_i(t) \in [0, 1]$ be normalized tumor cell density at time $t$ and voxel $i$ at location $(i_x, i_y, i_z) \in \Omega$. Where $i = \{1, \cdots, N\}$ is index across all voxels. The dynamics of the tumor cell density $u := \{u_i(t)\}_{i=1}^N$ is modeled as:

$$\frac{\partial u}{\partial t} = \nabla \cdot (\nabla u) + \rho u (1 - u) \quad \text{in } \Omega, \quad \nabla u \cdot \vec{n} = 0 \quad \text{in } \partial \Omega. \quad (1)$$

The term $\rho [1/day]$ denotes proliferation rate. The tumor infiltration into the surrounding tissues is modeled by the tensor $\mathbb{D} = \{D_{ij}\}_{i,j=1}^3$ where $I$ is a $3 \times 3$ identity matrix and

$$D_{ij} = \begin{cases} p_w D_w + p_g D_g & \text{if } i \in \Omega \\ 0 & \text{if } i \notin \Omega \end{cases} \quad (2)$$

The terms $p_w$ and $p_g$ denote percentage of white and grey matter at voxel $i$, while $D_w$ and $D_g$ stand for tumor infiltration in the corresponding matter. We assume $D_w = 10D_g [mm^2/day]$ . The skull and ventricles are not infiltrated by the tumor cells and act as a domain boundary with an imposed no-flux boundary condition $\nabla u \cdot \vec{n} = 0$, where $\vec{n}$ is the outward unit normal to $\partial \Omega$. The tumor is initialized at voxel $(i_{x_0}, i_{y_0}, i_{z_0})$ and its growth is modeled from time $t = 0$ until detection time $t = T [day]$. The parameters $\theta_u = \{D_w, \rho, T, i_{x_0}, i_{y_0}, i_{z_0}\}$ are considered unknown and patient-specific. The model is implemented in a 3D extension.
I) Medical Images

II) Computational Medicine

III) Bayesian Inference

IV) Personalised Radiotherapy

Fig. 1. Overview of the inference framework. I) Medical images show preoperative patient scans; (LA) a 3D reconstruction of T1Gd images and (LB) slices across all modalities. Tumor observations (e.g., segmentations) extracted from each modality are illustrated in (IC). II) Computational medicine includes a tumor growth model $M_s$ (II,B), which simulates tumor evolution in the patient anatomy (II,A), and imaging model $M_i$ (II,E) which relates the image observations (II,D) with the modeled tumor cell density $u$. The dotted line in (II,D) shows a schematic representation of the actual tumor cell density along the dashed line shown in (II,C) and its relation to each tumor observation available from the medical scans. The unknown, patient-specific parameters for each model are listed in Tables (II.C,F). III) Bayesian inference is used to identify the probability distributions of the unknown parameters, accounting for the modeling and measurement uncertainties. Parametric uncertainties are then propagated to obtain robust predictions about patient-specific tumor cell densities. The most probable estimate, given by a maximum a posterior (MAP) density, is shown in (IIIA,B), while the mean and standard deviation (std) are shown in (IIIB,B). IV) Personalised Radiotherapy uses the patient-specific predictions to improve dose-distribution and escalation design. A comparison of a standard and personalized dose distributions is shown in (IVB-C). The regions of estimated high tumor cell densities are marked by the orange isocontour in (IV/F). Observed tumor recurrences in T1Gd and FLAIR, marked by the pink and yellow curves in (IV/E,F), are used to compare treatment plan. The personalized plan spares more healthy tissue, while achieving tumor coverages comparable to the standard protocol, and guides the design of personalized dose escalation plans.
of the multi-resolution adapted grid solver \cite{25} with typical simulation time 1-3 minutes with 2 cores. An overview of the model \(M_u\) and its parameters is shown in Fig. 1 (II. A-C).

B. Multimodal imaging model

We consider routinely acquired T1 gadolinium enhanced (T1Gd) and fluid attenuation inversion recovery (FLAIR) MRI scans in combination with FET-PET maps. A stochastic imaging model \(M_I\) is designed to relate model predictions of the tumor cell density \(u\) and the tumor observation \(D = \{\hat{y}_{T1Gd}, \hat{y}_{FLAIR}, \hat{y}_{FET}\}\) available from the medical scans. See Fig. 1 for an overview of all the imaging modalities (I.B), corresponding tumor observations (I.C) and their relation to tumor cell density \(u\) (II.D).

The MRI scans provide a morphological information about the visible tumor in the form of binary segmentations. The MRI scans in combination with FET-PET maps. A stochastic imaging model \(M\) is designed to link model predictions of the tumor cell density \(u\) and the tumor observation \(D = \{\hat{y}_{T1Gd}, \hat{y}_{FLAIR}, \hat{y}_{FET}\}\) available from the medical scans. See Fig. 1 for an overview of all the imaging modalities (I.B), corresponding tumor observations (I.C) and their relation to tumor cell density \(u\) (II.D).

The updated posterior PDF is computed by the Bayes theorem:

\[P(D|\theta, M) \propto P(D|\theta, M) \cdot P(\theta|D),\]

where \(P(D|\theta, M)\) is the likelihood of observing data \(D\) from the model \(M\) for a given value of \(\theta\). Since each of the medical scans captures a different physiological process, the tumor observations are assumed independent and the likelihood function can be expressed as:

\[P(D|\theta, M) = P(\hat{y}_{T1Gd}|\theta, M) \cdot P(\hat{y}_{FLAIR}|\theta, M) \cdot P(\hat{y}_{FET}|\theta, M).\]

The prior PDF is assumed uniform with details specified in the SM. Since an analytical expression for Eq. (8) is not available, sampling algorithms are used to obtain samples \(\theta(l), l \in \{1, \ldots, S\}\) from the posterior \(P(\theta|D, M)\). We use Transitional Markov Chain Monte Carlo (TMCMC) algorithm \cite{27} which iteratively constructs series of intermediate PDFs:
Table I

Results of the Bayesian calibration for the synthetic case generated with the ground truth (GT) values. Reported is maximum a posteriori (MAP), mean and standard deviation (std). The units are $D_w \sim \text{mm}^2/\text{day}$; $\rho \sim 1/\text{day}$; $T \sim \text{day}$; and $ic_0$, $ic_y$, $ic_z \sim \text{mm}$.

|       | $D_w$ | $\rho$ | $T$ | $ic_0$ | $ic_y$ | $ic_z$ | $\sigma$ | $b$ | $u^{\text{GT}}$ | $u^{\text{FLAIR}}$ | $\sigma_b^2$ |
|-------|-------|--------|-----|--------|--------|--------|---------|----|----------------|------------------|------------|
| GT    | 0.1300| 0.0250 | 302.00 | 80.64 | 171.52 | 128.00 | 0.0230 | 0.8800 | 0.7000 | 0.2500 | -        |
| MAP   | 0.1226| 0.0296 | 271.13 | 80.61 | 171.55 | 127.92 | 0.0280 | 0.9884 | 0.8440 | 0.4874 | 0.0502  |
| mean  | 0.1543| 0.0361 | 253.85 | 80.64 | 171.47 | 127.80 | 0.0294 | 0.9775 | 0.8325 | 0.4841 | 0.0505  |
| std   | 0.0530| 0.0125 | 107.59 | 0.1280 | 0.1024 | 0.2048 | 0.0022 | 0.0139 | 0.0132 | 0.0076 | 0.0004  |

Fig. 2. Synthetic test case. Orange box: A 2D slice of the synthetic ground truth (GT) tumor cell density (A) and corresponding image observations (B); the normalized FET-PET signal with additive noise (red-blue color scale) and the outlines of the T1Gd (yellow) and FLAIR (pink) binary tumor segmentations. Blue box: Results of the Bayesian calibration with multimodal data. The results are in close agreement with GT data. Green box: Calibration results using only the MRI data, which do not provide enough information to recover the tumor cell density profile correctly.

A. Sensitivity study

The model $M_\mu$ is used to generate a 3D synthetic tumor in a brain anatomy obtained from [29] using the parameters reported in Table I. A 2D slice of the simulated ‘ground-truth’ (GT) tumor cell density is shown in Fig. 2 (A). The synthetic T1Gd and FLAIR tumor segmentations are constructed by thresholding the GT tumor cell density at $u^{\text{T1Gd}}_0 = 0.7$ and $u^{\text{FLAIR}}_0 = 0.25$. The FET-PET signal is designed by taking the GT tumor cell density within the T1Gd and FLAIR segmentations, adding Gaussian noise with zero mean and standard deviation (std) $\sigma$, and normalizing the result. The value of $\sigma$ is chosen as average std of the FET signal from the healthy brain tissue. The generated synthetic image observations are shown in Fig. 2 (B).

A sensitive study for the number of samples is performed, indicating 6000 samples as adequate for the model. The manifold of the inferred probability distribution is presented in Fig. 3 and the calibrated parameters are given in Table I. As seen from the probability distribution manifold, tumor observations from a single time point do not contain enough information to infer time dependent parameters ($D_w$, $\rho$, $T$) exactly, since different combinations of these parameters can generate the same tumor cell density as shown in Fig. 3. This pose a challenge for calibration approaches searching only for

Fig. 3. The results of the Bayesian calibration for the synthetic case. Above the diagonal: Projection of the TMCMC samples of the posterior distribution $P(\theta|D, M)$ in 2D space of the indicated parameters. The colors indicate likelihood values of the samples. The number in each plot shows the Pearson correlation coefficient between the parameter pairs. The colored triangles mark four selected parameters used in Fig. 4. Diagonal: Marginal distributions obtained with Gaussian kernel estimates. Boxplot whiskers demarcate the 95% percentiles. Below the diagonal: Projected densities in 2D parameter space constructed by 2D Gaussian kernel estimates. The black dots mark the values used to generate the synthetic data.

Fig. 4. Insensitivity of the tumor cell distribution to the speed of the growth. Shown are slices of the tumor cell densities computed with different combinations of parameters ($D_w$, $\rho$, $T$) as listed at the bottom of each plot. These correspond to the colored triangles in Fig. 3. Despite significant variation in the parameter values, all combinations lead to very similarly-appearing tumors. In the absence of temporal information, the model calibration cannot distinguish between compensating effects among the parameters that affect the dynamics, e.g., tumors with similar $D_w/\rho$ and $T/\rho$ values are very similar to one another as shown here ($D_w/\rho \approx 4.5$, $T/\rho \approx 7.7$). Hence, the Bayesian calibration identifies the probability distribution of all the plausible values.
a single value of $\theta$. Instead, the Bayesian calibration provides a more fair estimate. The inferred probability distribution shows a strong correlation between the parameters $(D_w, \rho, T)$, while the high std values imply low confidence in these parameters. On the other hand, parameters that affect the tumor spatial pattern, e.g. $(\hat{c}_x, \hat{c}_y, \hat{c}_z)$, are identified with high accuracy, which is reflected by their low std. The image related parameters $(\hat{c}^{\text{TGI}}, \hat{c}^{\text{FLAIR}})$ are slightly overestimated due to the assumed correlation length and the effect of the complex brain anatomy. The role of the anatomy is discussed further in the SM.

The inferred parametric uncertainties are propagated to obtain robust posterior predictions about the tumor cell density shown in Fig. 2 (C-E). Despite the large parametric uncertainties, the MAP and mean tumor cell density estimates are almost indistinguishable from the GT tumor. The low std values imply that, with the present Bayesian formulation, the information contained in multimodal data is sufficient to infer tumor cell density from single time point scans.

For comparison, if the model calibration is performed only with the MRI data, i.e. $D = \{\hat{y}^{\text{TGI}}, \hat{y}^{\text{FLAIR}}\}$, the estimated tumor cell densities shown in Fig. 2 (F-G) deviate from the GT tumor mainly in the central part of the lesion, which is also consistent with the regions of high std shown in Fig. 2 (H). Nonetheless, the outlines of the predicted tumor are similar to those of the GT tumor. This is because the tumor morphology is mainly constrained by the MRI data, since the FET-PET signal coincides with the baseline signal of the healthy tissue in the regions of lower tumor infiltration.

On the other hand, the FET-PET signal constrains the tumor cell density profile in the regions of high tumor infiltration. This highlights the importance of integrating structural and functional image information for the model calibration when dealing with single time point data.

B. Patient study

A retrospective clinical study is conducted on 8 patients diagnosed with GBM. Scans of the patients P1-P8 are shown in Fig. 5 and the details about acquisition protocols are reported in the SM. All patients received the standard treatment, surgery followed by combined radio- and chemotherapy. There was no visible tumor after the treatment and patients were regularly monitored for progression. The preoperative scans shown in Fig. 5 (A-D) are used for the Bayesian inference. The calibrated parameters are reported in Table 1 in the SM and the posterior, patient-specific predictions for the tumor cell densities are shown in Fig. 5 (E-G). These patient-specific predictions provide estimates about the possible tumor cell migration pathways in the surrounding of the visible tumor, constrained by the patient anatomy and the available tumor observations. The predicted tumor infiltration pathways can be validated by the patterns of the first detected tumor recurrence shown in Fig. 5 (H), where the outlines of the predicted infiltrations (blue) and recurrence tumors (pink) are depicted. For the patients P5, P7, P8 the model accurately predicts tumor infiltration also inside the healthy-appearing collateral hemisphere, whereas for cases P1-P4 the tumor predictions are correctly restricted only to one hemisphere. Moreover, despite a similar appearance of the preoperative tumors in the patients P1 and P2, the model correctly predicts more infiltrative behaviour for the patient P1, which is consistent with the recurrence pattern. The high confidence in the predictions is reflected by low std shown in Fig. 5 (F).

C. Personalized radiotherapy design

The patient-specific tumor cell density predictions can be used to design margins of the CTV and to identify high cellularity regions that could mark areas of increased radioresistance. The personalized RT plan can be based either on the most probable scenario given by MAP estimate or the worst case scenario given as a sum of the mean and std of the tumor cell density. Since in the present study, the mean and MAP estimates are very similar, and the std values are small, the MAP estimates are used. An overview of the proposed personalized RT design is shown in Fig. 1 (IV), while the details are described in the following subsections. The tumors recurrence patterns are used to assess the benefits of the proposed RT plan over the standard treatment protocol. For evaluation purposes, all recurrence scans are registered to the preoperative anatomy. To prevent registration errors arising from mapping the anatomy with the resection cavity to the preoperative brain, rigid registration is used. This provides a sufficient mapping for most cases, however it cannot capture the post-treatment tissue displacement around the ventricles in patients P7-P8, making the mapping less accurate in these regions. The design of methods that provide robust registration between pre- and post-operative brain anatomies is still an open problem.

1) Dose distribution: An ideal CTV covers all the residual tumor, including infiltrating tumor cells that are invisible on the pretreatment imaging scans, while sparing healthy tissue. We use tumor recurrence pattern to evaluate efficiency ($\eta^{\text{CTV}}$) of the CTV, defined here as the relative volume of the recurrence tumor ($V^{\text{REC}}$) contained within the CTV:

$$\eta^{\text{CTV}} = \frac{V^{\text{REC}}}{{V^{\text{REC}}} \cap CTV} \times 100\%.$$ (11)

Figure 3 (H) shows the FLAIR scans with the first detected tumor recurrence outlined by the pink lines. The margin of the administrated $CTV^{\text{RTOG}}$, designed by the standard RTOG protocol with a $2\text{cm}$ margin around the visible tumor, is marked by the green lines in (E,F,H). The personalized CTV, referred as $CTV^{\text{MAP}}$, is constructed by thresholding the MAP tumor cell density at $u = 0.1\%$ for all patients. (This value was chosen so that the efficiency of the $CTV^{\text{MAP}}$ is comparable to that of the $CTV^{\text{RTOG}}$). The outlines of the proposed $CTV^{\text{MAP}}$ are shown as the blue isocountres in Fig. 5 (H-I). A visual comparison of the CTVs shown in Fig. 5 (H) and Fig. 1 (IV), and a quantitative comparison presented in Fig. 6 show that the proposed personalized plans spare more healthy tissue, hence reducing radiation toxicity, while maintaining the efficiency of the standard RTOG protocol.

Both plans show reduced efficiency for patients P7-P8, mainly around the ventricles, which may be caused by misalignment

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Fig. 5. Results of the Bayesian calibration for patients P1-P8. Orange box: Preoperative scans showing (A) T1Gd; (B) FLAIR; (C) Tumor segmentations: T1Gd (yellow) and FLAIR (pink); (D) FET-PET. Blue box: (E) MAP and (F) std of the inferred tumor cell densities shown in the preoperative FLAIR scans. The CTV\textsuperscript{RTOG} margin is shown as the green curves. (G) The 3D reconstructions show outlines of the MAP tumor (blue) together with tumor extent visible on the scans (orange) in the preoperative anatomy (white). Green box: Scans of the first detected tumor recurrence. (H) FLAIR tumor recurrence (pink), CTV\textsuperscript{RTOG}(green), and CTV\textsuperscript{MAP}(blue) margins. (I) T1Gd tumor recurrence (yellow) and the dose-escalation outlines proposed by FET enhancement (magenta) and MAP estimates (orange). (J) Multilevel dose-escalation designed by MAP estimates.
between the preoperative and recurrence anatomy. These preliminary results imply that the regions predicted as a tumor-free by the model, remain tumor-free and thus the model predictions have potential to guide personalized CTV design. The standard or hospital-specific protocols can be updated by the model predictions to spare brain tissue not infiltrated by the tumor. This can lead to significant savings in the healthy tissue, especially in the cases of large lesions or lesions close to hemispheres separation and other anatomical constrains.

2) Dose-escalation: No dose-escalation plan for GBM patients has been yet approved by phase-III-clinical trials. Here, we present a theoretical comparison of two escalation plans targeting high tumor cellularity regions identified by: 1) FET-PET enhancement as proposed in [5] and 2) MAP estimates. We evaluate the efficiency of an escalation plan by its capability of targeting T1Gd-enhanced tumor recurrence regions. In these regions, the recurrent tumor has high cellularity, despite having received the full radiation dose, suggesting tumor radioresistance. Figure 5(I) shows the T1Gd scans with the first detected tumor recurrence. The margins of the T1Gd-enhanced tumor recurrence are marked by the yellow lines, while the outlines of the dose-escalation plans designed by the FET-PET enhancements are shown in magenta. The FET enhancements do not fully cover the T1Gd recurrent tumor in patients P4-P7, providing a possible explanation for why improvements in progression-free survival have not been observed in [5]. In comparison, the MAP estimates, calibrated by the FET-PET signal, extend the information about the tumor cell density in the periphery of the visible lesion. Figure 5 shows two possible dose-escalation plans based on the inferred MAP tumor cell density: (I) a single-level dose-escalation based on the thresholded MAP solution with threshold \( u = 30\% \) marked by the orange lines and (J) a cascaded four-level escalation plan constructed by thresholding the MAP tumor cell density at \( u = [0.1, 25, 50, 75] \%). The optimal design of a personalized dose-escalation plan would require more extensive studies. However, these preliminary results show that the inferred high cellularity regions coincide with the areas of tumor recurrence better than those suggested by the FET-PET enhancement alone. The presented inference framework thus provide a promising tool for a rational dose-escalation design.

### IV. Conclusion

We have demonstrated that patient-specific, data-driven modeling can extend the capabilities of personalized RT design for infiltrative brain lesions. We combined patient structural and metabolic scans from a single time point with a computational tumor growth model through a Bayesian inference framework and predicted the tumor distribution beyond the outlines visible in medical scans. The patient-specific tumor estimates can be used to design personalized RT plans, targeting shortcomings of standard RT protocols. In future work, the basic FK tumor growth model could be replaced by more advanced models (e.g., [50]), however, it remains to be seen whether scans at a single time point would provide enough information to calibrate these models sufficiently. If not, then simpler, well-calibrated models may prove to be more informative. In addition, the computational framework developed here will be tested on a larger patient cohort and prospective clinical trials will be performed. In summary, the results presented here provide a proof-of-concept that multimodal Bayesian model calibration holds a great promise to assist the development of personalized RT protocols.

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