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A Statistical Modeling Approach to the Analysis of Spatial Patterns of FDG-PET Uptake in Human Sarcoma

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Abstract

Clinical experience with positron emission tomography (PET) scanning of sarcoma, using fluorodeoxyglucose (FDG), has established spatial heterogeneity in the standardized uptake values within the tumor mass as a key prognostic indicator of patient survival. But it may be that a more detailed quantitation of the tumor FDG uptake pattern could provide additional insights into risk. The present work develops a statistical model for this purpose. The approach is based on a tubular representation of the tumor mass with a simplified radial analysis of uptake, transverse to the tubular axis. The technique provides novel ways of characterizing the overall profile of the tumor,

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including the introduction of an approach for the measurement of its phase of development. The phase measure can distinguish between early phase tumors, in which the uptake is highest at the core, and later stage masses, in which there can often be central voids in FDG uptake. Biologically, these voids arise from necrosis and fluid, fat or cartilage accumulations. The tumor profiling technique is implemented using open-source software tools and illustrations are provided with clinically representative scans. A series of FDG-PET studies from 185 patients is used to formally evaluate the prognostic benefit. Significant ($p < 0.05$) improvements in the prediction of patient survival and progression are obtained from the tumor profiling analysis. After adjustment for other factors including heterogeneity, a typical one standard deviation increase in phase (as determined by the analysis) is associated with close to 20% more risk of progression or death. The work confirms that more detailed quantitative assessments of the spatial pattern of PET imaging data of tumor masses, beyond the maximum FDG uptake (SUV_{max}) and previously considered measures of heterogeneity, provide improved prognostic information for potential input to treatment decisions for future patients.

Keywords

Boundary surface extraction; human sarcoma; phase assessment; positron emission tomography; spatial statistics; tumor profiling

I. Introduction

Sarcomas are a diverse class of tumors affecting soft tissue, cartilage, and bone. Their treatment involves surgical resection, typically preceded by chemotherapy. The median survival time for patients with sarcoma is about five years from the time of surgery. A clinical study at the University of Washington (the major treatment center for sarcoma in the Pacific Northwest) has been using static positron emission tomography (PET) scanning with fluoro-deoxyglucose (FDG) to image tumors prior to treatment. This study, which is now in its 25th year, has provided a database of several hundred cases with FDG-PET images, clinical diagnostic information and patient outcome. The maximum standardized uptake value (SUV_{max}) in the tumor region of interest (ROI) has been routinely used for quantitation [7]. But the database provides the opportunity to identify novel quantitative summaries of FDG-PET imaging data that may enhance prognostic understanding, and ultimately treatment, in this patient population.

In previous work, we developed a measure of spatial heterogeneity of the FDG uptake within sarcoma [7], [17], [18]. This measure, which is based on the deviation of the uptake pattern from a simple ellipsoidal form, was shown to provide an independent prognostic indicator of duration of disease free status and time to death. Although spatial heterogeneity has prognostic merit, it does not provide a comprehensive evaluation of the uptake pattern in the tumor. A deeper understanding of the components of variation in the uptake pattern may be useful. To this end, the present work develops a flexible empirical model for description of the measured uptake pattern of FDG in the tumor mass. The approach leads to novel ways of quantifying the spatial pattern of uptake, by model-derived measures of tumor core nonlinearity, tumor phase of development and lack of fit of the uptake model. Remarkably,

the phase of development measure is found to enhance the prognostic benefit of the FDG imaging data—i.e., it significantly improves the prediction of patient outcome.

Our choice of model primarily arises from our own experience with FDG-PET data from sarcoma. Early stage sarcomas typically present as a localized area of high FDG uptake while later stage masses often show centrally diminished FDG uptake which rises and falls towards the periphery. In qualitative terms, this is similar to patterns of tumor growth observed in tumor spheroid work, and captured by standard convection-diffusion formulations used for their simulation in the mathematical biology literature [19], [21], [22]. But clearly the vascular network and nutrient supply experienced by a human sarcoma will differ from the idealized environment of a tumor spheroid. Hence it is reasonable to expect that the shape pattern of FDG uptake might be more complex and nonspheroidal. This is our experience. The proposed model is based on a tubular or sausage-like representation of the sarcoma tumor mass, with the uptake intensity allowed to vary from the central core to the boundary. A principal component analysis is used to identify the major axis of the tumor and, using this, a 3-D curve corresponding to the central core/spine of the tumor is extracted. Principal components help to make the approach less sensitive to the orientation of the tumor relative to the scanning geometry. Transverse to the central axis of the tumor the uptake pattern is examined using an adaptive radially contoured model. This model allows the amplitude, scale and profile of uptake to be evaluated along the axial direction of the tumor. A standardized (Gaussian) representation of the radial profile on transverse slices is used. The ordinate of the profile is used as a measure of phase of development—more negative phase values in the core capture central voids in the FDG uptake that typically arise in later stages of the disease process. The use of a common Gaussian profile allows the phase characteristics of the tumor to be readily compared across different cases (patients). Potential new prognostic variables for risk assessment are produced. These include core nonlinearity, phase characteristics, and a new heterogeneity measure. An analysis of a set of 185 cases is used to evaluate the prognostic potential of these new variables. The core phase is found to add significantly to prognosis, which is a key practical justification for the empirical modeling considered. Although well beyond the scope of this work, to the extent that the model provides a parsimonious description of the FDG uptake pattern, there may be an opportunity to use it to help identify/guide the selection of a tumor growth model for simulation of the future behavior of its FDG uptake under different treatment options—cf. Atuegwu *et al.* [1].

The outline of the paper is as follows. The model and techniques used for its estimation are developed in Section II. Section III has a set of illustrative examples that emphasize the ability to visualize the tumor mass using widely accessible open-source software tools [15], [20]. Our emphasis is on PET data as this represents the vast majority of our imaging data. However, in order to demonstrate broader applicability, two PET/CT cases are also included for illustration. Detailed clinical evaluation is presented in Section IV, showing improvement gained over previous work in terms of enhanced prognostic capability. We conclude with some discussion including potential refinement and generalization of the technique.

II. Methodology

We consider the analysis of static imaging data based on PET scan acquisition over a 45–60 min period following venous injection of the FDG radiotracer. Details of scanning are provided in Section III. We begin with some notation, including a description of coordinate systems used. The proposed model for representation of the within-tumor FDG uptake is described (Section II-B) and summary characterizations of the tumor derived from the model are defined. Procedures used for estimation of the model are then presented. These are illustrated with explanatory figures and an overall flowchart.

A. Data and Principal Axis Transformation

The data are represented by an array $\{(y_i, x_i), i = 1, 2, \dots, N\}$ corresponding to measurements of the FDG-PET uptake (y_i) over a set of N voxels in a 3-D region (Ω) containing tumor mass. The raw uptake data are in units of counts (kBq/ml). These counts are converted to standardized uptake values (SUVs) for our analysis this is done by scaling counts by the dose (MBq) per unit weight (kg) of the patient. The voxel coordinates are $x_i = (x_{1i}, x_{2i}, x_{3i})^t$. Sarcomas tend to have a tubular or sausage-like pattern, whose orientation within the subject, relative to the field of view (FOV) of the scanner, will be somewhat variable. A principal component analysis is used to define an objective coordinate system for modeling the uptake pattern. This transformation is designed to make the analysis less dependent on the tumor orientation within the scanner, which clearly is not fully under the control of the imaging technician. We refer to this as *principal axis sampling (PAS)*. PAS is based on the uptake-weighted mean and covariance of the data

$$\mu = \frac{\sum_{i=1}^N y_i x_i}{\sum_{i=1}^N y_i}; \quad \Sigma = \frac{\sum_{i=1}^N y_i (x_i - \mu)(x_i - \mu)^t}{\sum_{i=1}^N y_i}. \quad (1)$$

Spectral decomposition of the covariance matrix gives $\Sigma = \Gamma \Lambda \Gamma^t$ with a diagonal matrix with diagonal entries and the corresponding orthonormal $\Lambda = \begin{bmatrix} \lambda_1 & & \\ & \lambda_2 & \\ & & \lambda_3 \end{bmatrix}$ and $\Gamma = [\gamma_1, \gamma_2, \gamma_3]$ the corresponding orthonormal eigenvectors. The PAS coordinates are

$\tilde{x}_i = \Gamma^t (x_i - \mu) = (\gamma_1^t (x_i - \mu), \gamma_2^t (x_i - \mu), \gamma_3^t (x_i - \mu))^t$. This provides an array $\{(y_i, \tilde{x}_i), i = 1, 2, \dots, N\}$. We refer to $h = \tilde{x}_3$ as the long-axis of the tumor, having values within $[a, b]$ (the tumor ends); the short-axis coordinates are $(\tilde{x}_1, \tilde{x}_2)$. Were there an accepted reference shape for all sarcomas, one could consider transformation into the coordinate system of that reference as an alternative to PAS. In the context of brain function studies this is usually the first step of analysis techniques like statistical parametric mapping (SPM) [10].

Tumor Core, Cylindrical Coordinates, and Boundary Surface—Our approach to the evaluation of the within-tumor uptake pattern involves an examination via contour surfaces that are defined via the central core and boundary surface of the mass. While the core and boundary might be identified in an interactive fashion, for objectivity and reproducibility there are advantages to a computer-based algorithm. We propose one possibility for this in Section II-C1 below (other possibilities are noted in the discussion). Before elaborating these aspects and describing the uptake analysis, we need to introduce

some notation. Let $c_h = (c_{1h}, c_{2h})^t$ represent the short-axis coordinates of the central core of the tumor as a function of the long-axis coordinate h . The PAS coordinates $\tilde{x} = (\tilde{x}_1, \tilde{x}_2, \tilde{x}_3)$ are transformed to a cylindrical form by (r, θ, h) by

$$\begin{aligned} r &= \sqrt{(\tilde{x}_1 - c_{1h})^2 + (\tilde{x}_2 - c_{2h})^2} \\ \theta &= \tan^{-1} \left(\frac{\tilde{x}_2 - c_{2h}}{\tilde{x}_1 - c_{1h}} \right); \quad h = \tilde{x}_3. \end{aligned} \quad (2)$$

In these coordinates a star-shaped contour is given by a function specifying its polar radius as a 2π -periodic function of angle. For concreteness, we fix on contours that are identified with a particular uptake level—the tumor boundary contour on each long-axis slice. Let the collection of these contours as a function of the long-axis be denoted by $\{(\sigma_h(\theta), \theta, h), \text{ for } \theta \in [-\pi, \pi] \text{ and } h \in [a, b]\}$. Table I summarizes these coordinates and notations. Note that while we adopt a cylindrical coordinate system, it is possible that a spherical system in which h were identified with the cosine of latitude could also be used. We have not explored if there would be a loss of efficiency with such an approach.

B. Within-Tumor FDG Uptake Model

Our approach represents uptake by a function whose contours on each short-axis PAS slice are a simple dilation or contraction of the reference contour specified $\sigma_h(\theta)$. The uptake level for the dilated or contracted contour is determined by three-parameter adjustment of a fixed reference radial uptake pattern g , which here we take to be the Gaussian form $g(u) = e^{-(u^2)/(2)}$. This leads to the uptake at the cylindrical coordinate (r, θ, h) being described by

$$y(r, \theta, h) = \beta_h g \left(\tau_h + \phi_h \frac{r}{\sigma_h(\theta)} \right) + \text{error} \quad (3)$$

where $\beta_h = 0$, $\phi_h = 0$, and τ_h represent long-axis slice-specific adjustments of the amplitude, scale and phase of the uptake. The specification of τ_h as a phase parameter is because this parameter varies whether the radial uptake pattern has a simple monotonically decreasing or more complex unimodal structure. If τ_h is positive the radial uptake is monotonically decreasing from the central core to the boundary, while if τ_h is negative the radial uptake will increase from the core to a maximum before decreasing again towards the boundary. Some care is required because the absolute magnitude of τ_h is susceptible to the choice of β_h —a large value of β_h can be compensated by a large value τ_h . Thus, it is important that our estimation process penalizes large β_h values. Since early stage sarcomas typically present with a monotone radial pattern and later stage ones have reduced central uptake and unimodal radial patterns, it seems reasonable to refer to τ_h as a core-phase parameter. But in a similar fashion the argument of the function g in (3) defines a measure of the phase of development at other points as well. So the local phase at the point (r, θ, h) is defined as

$$u = \tau_h + \phi_h \frac{r}{\sigma_h(\theta)}. \quad (4)$$

Summary Characterization of the Tumor Uptake Pattern—We identify three particular summaries associated with the model in (3) that will be examined as prognostic variables in our clinical dataset.

i) Nonlinearity: This is assessed by the deviation of the central core from a linear function of the long-axis coordinate. The deviation is weighted according to the axial tumor burden (measured by FDG uptake) and defined by

$$\xi = \frac{\sqrt{\sum_{i=1}^N y_i \left((c_1 h_i - a_1 - b_1 h_i)^2 + (c_2 h_i - a_2 - b_2 h_i)^2 \right)}}{\sum_{i=1}^N y_i} \quad (5)$$

where the intercepts (a_1, a_2) and slopes (b_1, b_2) are adjusted to minimize ξ .

ii) Phase: The average uptake-weighted voxel-level phase is $\bar{u} = \sum_{i=1}^N y_i u_i / \sum_{i=1}^N y_i$ [here u_i is defined by (4)]. The distribution of phase values over voxels can be evaluated in more detail. Of particular interest is the core phase, which may provide an indication of central low metabolism tissues associated with necrosis and fluid, fat or cartilage accumulations.

Two measures are considered: the uptake-weighted core phase $\left(\bar{u}_c\right)$ and the profile uptake-weighted core phase $(\tilde{u}_c)$. These are defined by

$$\bar{u}_c = \frac{\sum_{i=1}^N y_i \tau_{h_i}}{\sum_{i=1}^N y_i} \quad \text{and} \quad \tilde{u}_c = \frac{\sum_{i=1}^N y_i g(\tau_{h_i})}{\sum_{i=1}^N y_i}. \quad (6)$$

The phase pattern at an intermediate point between the core and boundary might be considered in a similar way. Apart from our own experience with sarcoma, there is a possible theoretical basis for relating the core uptake pattern to the phase of development. Indeed, some standard convection-diffusion models for tumor growth [21] evolve to have reduced concentrations of active cancer cells in the central core. This is illustrated in the discussion.

iii) Model Heterogeneity (H^*): Just as the lack of fit of the ellipsoidal contoured model was used to define the elliptical heterogeneity measure in [7], we use the lack of fit of this new model as a further measure of heterogeneity. Letting the model based predictions of uptake be denoted $\hat{y}_i$, this heterogeneity is

$$H^* = 1 - \frac{\sum_{i=1}^N [y_i - \hat{y}_i]^2}{\sum_{i=1}^N \left[y_i - \bar{y} \right]^2} \quad (7)$$

where $\bar{y}$ is the mean of values in the ROI.

C. Estimation Techniques

The uptake model in (3) depends on two sets of functional parameters: the structural set describing the core and boundary, and the uptake set specifying the axially varying

amplitude, scale and core phase. But while simultaneous optimization of these model parameters by consideration of an overall objective function, such as a regularized or penalized least squares [25], may have some attraction, this is not necessarily desirable. The reason is that we wish to ensure that the structural parameters reflect the core and boundary surface of the tumor. Were the parameters optimized in an overall objective function (which we have experimented with), there is no guarantee that they would retain their structural interpretation—the localized criteria relevant to specification of a boundary or core may be swamped out by the bulk of the data considered in an overall objective function. Thus our present approach involves an analysis in which the structural parameters are identified in a separate manner from the uptake parameters. Our own practical experience with clinical sarcoma FGD-PET data has lead us to develop an algorithm for computer-based extraction of structural parameters (see Section II-C1).

For estimation, we bin the data by percentiles of the long-axis coordinate and construct raw structural and uptake parameters for each bin. These raw values are smoothed to achieve stability. If the total number of bins is N_h , then the j th bin is $(h_{(j-1)}, h_{(j)}] = \text{Bin}j$, where $h_{(j)}$ is the $(jN')/(N_h)$ th-order statistic of the individual voxel long-axis coordinate values (h'_i) . The number of bins (N_h) is set so that the axial range of individual voxel h_i -values $(\bar{H} - \underline{H})$ divided by the number of bins is no smaller than the within-plane resolution of the imaging (Δ_x) , i.e., $N_h \approx (\bar{H} - \underline{H}) / (\Delta_x)$. The flowchart resented in Fig. 1 represents the main steps of the approach described hereafter.

1) Structural Parameter Estimation—For each axial bin a two-pass approach is used to extract the raw values for the center and boundary contour shape. Having constructed raw estimates for the center and boundary contour on each axial bin, smoothing across axial bins is used to produce final values. A weighted smoothing procedure with weights inversely proportional to the average misfit of the model per data point on each axial slice is used. The smoothing of boundary contours is done separately across a discretized set of angles with linear interpolation of the resulting contours used for evaluation at intermediate angles.

a) Central Core Estimates for Binned Long-Axis Data: Using an elliptical contour shape $\sigma_h^o(\theta) = (1 + e \cos(\theta - \varphi))$ for $\theta \in [-\pi, \pi]$ with the eccentricity (e) and orientation (φ) unknown, the uptake data within the axial bin is modeled as a nonparametric unimodal function of the elliptically adjusted radius $\rho_i = (r_i) / (\sigma_{h_i}^o(\theta_i))$ where, as in (2), r_i and θ_i depend on an assumed axial center (c_1, c_2) for the bin. Thus

$$y_i = f(\rho_i | c_1, c_2, e, \varphi) + \text{noise}. \quad (8)$$

For any particular choice of the four parameters controlling the center and contour shape $\alpha = (c_1, c_2, e, \varphi)$, let f_α represent the nonparametric unimodal function estimate based on the data pairs (ρ_i, y_i) . Our approach uses a simple isotonic regression [2] to postprocess the B-spline smooth [25] of y on ρ , after it has been divided into the components that are before and after

the maximum. This leads to an overall assessment of the α -parameters in terms of the residual sum of squares (RSS) deviation between the data and the fitted unimodal form

$$RSS(\alpha) = \sum_{i \in Bin} [y_i - f_\alpha(\rho_i | c_1, c_2, e, \varphi)]^2. \quad (9)$$

A steepest descent procedure is used to optimize this criterion with respect to the unknown α -values. In this procedure care is taken to ensure that the center values lie in the interior of the convex hull of the short-axis data in the bin. Specifically, using a quickhull¹ algorithm for computation of the convex hull of a planar set of points, we peel away a fraction of the short axis (x_1, x_2) data in the bin and make sure that choices for center values do not lie outside the convex hull of the remaining values. The procedure is illustrated in Fig. 2 for data taken from case study number 2 in Section III-B.

b) Boundary Surface for Binned Long-Axis Data: The boundary surface is associated with a particular uptake level (l) that is specified as a percentile (say p_l) of the uptake distribution—for our ROIs we find setting the level to the upper quartile of the data ($p_l = 75\%$) to be effective—see Section II-D for more explanation. For the boundary contouring method, we restrict to data on a fixed axial bin, as illustrated in Fig. 3. As the central core procedure has been complete, the center and a starting elliptical boundary shape $\sigma_{h_i}^o(\theta_i)$ are available as input. The short-axis data are converted to polar coordinates by (2) and are binned by angle to produce a set of sectorial subsets. The j th sectorial subset consists of values with angles in the interval $((2\pi(j-1))/(J), (2\pi j)/(J))$ for $j = 1, 2, \dots, J$. Here J is chosen to ensure an average number of values per sector—on the order of 10 data points per sector works well. Let the number of values in the j th sector be n_j and consider the collection of scaled radii $(\rho_i^j = (r_i) / (\sigma_{h_i}^o(\theta_i)))$ and uptake (y_i^j) values in the sector as a data array for $\{(\rho_i^j, y_i^j) \text{ for } i=1, 2, \dots, n_j\}$. Since these data are noisy, the radial value corresponding to the desired level is not well determined. To address this we fit a parametric unimodal function g (a Gaussian is used) to the data and use the fitted curve to solve for the (largest) radius corresponding to the specified level, i.e.,

$$\bar{\rho}_j = \frac{g^{-1}\left(\frac{l}{\hat{\beta}}\right) - \hat{\tau}}{\hat{\phi}} \quad (10)$$

where $(\hat{\beta}, \hat{\tau}, \hat{\phi})$ are found by nonlinear least squares (NLS) minimization [3], [20] of

$$RSS(\beta, \tau, \phi) = \sum_i \left[y_i^j - \beta g\left(\tau + \phi \rho_i^j\right) \right]^2. \quad (11)$$

¹Quickhull algorithms incrementally construct the hull of a set of planar points by addition of vertex points that are farthest away from the set of edges of the current hull (see <http://www.cse.unsw.edu.au/~lambert/java/3d/quickhull.html> for a helpful illustration). The implementation here is in R [20]. It uses Eddy [8]'s quick sort procedure for determination of vertex addition at each stage.

The variance of $\bar{\rho}_j \left(\bar{w}_j^{-1} \right)$ is obtained by propagation of errors [3]. Repeating this process for each sector gives an array of values $\left\{ \left(\bar{\theta}_j, \bar{\rho}_j, \bar{w}_j \right), \text{ for } j=1, 2, \dots, J \right\}$. Nonparametric spline smoothing [20], [25] of the $\bar{\rho}$ -values as a function of $\bar{\theta}$ with weights $\bar{w}$ is used to produce a correction $\mathcal{A}(\theta|h)$ to the initial elliptical contour. This yields the boundary contour $\sigma_h(\theta) = \sigma_h^o(\theta) \cdot \vartheta(\theta|h)$. The procedure is illustrated in Fig. 3.

2) Uptake Model Parameter Estimation—With the structural parameters specified, it remains to obtain estimates for the functional amplitude, scale and phase parameters in the uptake model (3). Again the procedure involves analysis of the binned long-axis data using NLS to obtain raw estimates and then smoothing over bins with smoothing splines to obtain the set of functional parameters. As larger values of core-phase (τ) in (3) can be compensated by correspondingly larger amplitudes (β), a penalized least squares criterion is used for estimation within each axial bin

$$RSS_{\gamma}(\beta, \tau, \phi) = \sum_{i \in \text{Bin}} \left[y_i - \beta g \left(\tau + \phi \frac{r_i}{\sigma_{h_i}(\theta_i)} \right) \right]^2 + \gamma \beta^2 \quad (12)$$

where $\gamma > 0$. Choosing γ in proportion to the squared coefficient of variation (cov) of the uptake data in the bin appears to work quite well; we use $\gamma = 0.1 \cdot \text{cov}^2$ but values in the range [0.1, 1.0] typically produce very similar results. The penalty term is entered as an additional residual so a standard NLS code [4], [20] can be directly applied for optimization. Raw NLS estimates from each axial bin are smoothed to obtain the final set of uptake parameters. A simple cubic spline smoother is used [20], [25].

D. Implementation Details

The technique is readily implemented in mainstream programming environments. In what follows we present illustrations and numerical results that were obtained using open-source software. AMIDE (A Medical Imaging Data Examiner) is an open-source multimodality image display and analysis computer package [15]. It has a number of easy-to-use features including co-registration and rudimentary 3-D ROI drawing. AMIDE ROI data can be exported for more detailed analysis in other systems. For statistical analysis we use R [20]. This is also an open-source computing environment in which many statistical techniques are implemented. R has a good system for interactive data analysis and a convenient scripting language that allows access to functions for nonlinear optimization and regression [3], [4] and smoothing [25]. Using these features the implementation of the various components of the methods described above is straightforward. All analyses reported here use a common boundary contour level set at the upper quartile of the uptake distribution ($p_l = 75\%$). This value is motivated by the fact that we use an AMIDE elliptical cylinder ROI to specify the region that bounds the tumor. So if the tumor were truly ellipsoidal, its fractional volume in the AMIDE elliptical cylinder would be expected to be at most $(\pi)/(4) = 0.78$ (i.e., the ratio of the area of a circle to the bounding square). Sensitivity analysis was conducted on this choice, and values in the range 60%–80% provided very similar results. Rudimentary tools for display of analysis results, including some useful projections of the wire-frame

representations of the boundary surface and the radial uptake pattern, are also readily constructed in the R environment. No doubt there are a variety of other software solutions that could also be used for our analysis, but the functionality and open-source status of AMIDE and R are appealing.

III. Illustrations

We present results from the application of our approach to data from on-going imaging of sarcoma at the University of Washington Medical Center. We show four cases from FDG-PET imaging using GE Advance (two cases) and a GE Discovery LS PET/CT (two cases) scanners. Scanning followed standard clinical protocols as previously described [6]. Patients received 18F-FDG (259–370 MBq) intravenously 45–60 min before emission and attenuation-scan acquisition of the tumor fields of view. Images were reconstructed using standard filtered backprojection algorithms. While the vast majority of cases in which we have extensive clinical follow-up have GE Advance scans, cases with the GE Discovery are included to demonstrate the ability to process PET/CT sets. The higher resolution and level of detail of PET/CT imaging data may be useful for our approach. In particular it may be used to obtain finer resampling and contour information, and better assess specific features, such as spatial heterogeneity, or whether an inactive core is due to the presence of bone structure rather than necrosis. However, our selection of examples is chosen to illustrate the applicability of the approach across a range of commonly encountered clinical cases and older as well as more recent PET scanners. While the presentation here is graphical, Section IV provides an in-depth prognostic evaluation of approach over a series of PET Advance scanner cases in which we have more extensive (statistically powerful) follow-up information. Validation of the approach for PET/CT imaging data will be carried out when a larger number of clinical studies, with sufficient outcome information, become available.

A. Visualization Scheme

Here, we detail the common format used in Section III-B, with components presenting the raw image data, the tumor morphology, representative transaxial analyses and the axial uptake structure.

A) Raw Images—Mid-plane sections of the tumor volume (transverse, sagittal, and coronal) including an outline of the AMIDE-generated 3-D elliptical cylinder ROI containing tumor.

B) Morphology—The boundary surface of the tumor is defined by the set

$$\mathcal{B} = \{(c_{1h} + \sigma_h(\theta) \cos(\theta), c_{2h} + \sigma_h(\theta) \sin(\theta), h) \mid \theta \in (-\pi, \pi] \text{ and } h \in [a, b]\}. \quad (13)$$

A uniform sampling of axial (h) and angular values (θ) provides a set of mesh 3-D points for wire-frame representation of this surface. Wires are constructed as lines of equal latitude (h) and longitude (θ). Using standard analysis (the QR-decomposition in R), the wire frame can be projected onto a plane perpendicular to any desired viewing position, giving a 2-D plot. Sagittal and coronal PAS views are obtained by projection onto the $x_1\tilde{x}_3\tilde{}$ and $x_2\tilde{x}_3\tilde{}$ planes. This is perhaps the most revealing presentation of the tumor structure. More complex views

are obtained by re-mapping into the original image coordinates. For example, sagittal ($x_2 - x_3$) and coronal ($x_1 - x_3$) views, allowing comparison with the raw image data, can be obtained in this way. Using the PAS transformation parameters ($\mu \Gamma$), these views are achieved by projection of the points $\mathcal{A} = \mu + \Gamma \mathcal{B} = \{\mu + \Gamma \tilde{x} \text{ for } \tilde{x} \in \mathcal{B}\}$. It is helpful to use the same wires when viewing the tumor surface in the PAS ($\mathcal{B}$) or original ($\mathcal{A}$) domains. Using alternative colors (black and grey) to distinguish wire segments whose outward normals point toward or away from the view position is helpful.

C) Representative Analysis of Long-Axis Data—Two long-axial bins (33rd and 66th percentiles) are considered and plots of the PAS transformed voxel coordinates ($x_1 \tilde{x}_2$) with points color-coded by uptake intensity range are provided (top row of quadrant C). We identify (by cross-hairs in plots) the computed core-centers for the data in each bin and the estimated boundary contour for each plane is also included. In the bottom row of quadrant C the uptake on individual voxels within the selected axial bin is plotted against the computed adjusted polar radius ($r_i/(\sigma_{h_i}(\theta_i))$) and the smoothed pattern (using a uni-modal constraint) and threshold value l (cf. Section II-C2) used are identified.

D) Axial Uptake Structure—Our analysis summarizes the ($x_1 \tilde{x}_2$) uptake pattern as a radial function of the scaled polar radius ($r/(\sigma_h(\theta))$) (top-left plot in quadrant D). To present the raw radial uptake on any long-axis bin (h), the observed uptake is averaged over contractions of the fitted boundary contour. Thus for any long-axis coordinate h and $c \in [0, 1]$ the image uptake values can be averaged over the set

$$\mathcal{B}^c(h) = \{(c_{1h} + \sigma_h(\theta) \cos(\theta), c_{2h} + \sigma_h(\theta) \sin(\theta)), \text{ for } \theta \in (-\pi, \pi]\} \quad (14)$$

to provide a representative uptake value at a contraction (c) of the boundary. Since the average radius of the boundary contour is $\bar{\sigma}_h = 1/(2\pi) \int_{-\pi}^{\pi} \sigma_h(\theta) d\theta$, $c\bar{\sigma}_h$ is the average radius of the contracted contour. Letting R be the maximum of the long-axis radius of the boundary contour we bin $[0, R]$ into N_R equal intervals

$I_k^R = ((k-1)R)/(N_R), (kR)/(N_R)]$ for $k = 1, 2, \dots, N_R$. The long-axis domain (assume a range $[\underline{H}, \bar{H}]$) is similarly binned into N_H intervals (I_j^H), so as to construct an $N_H \times N_R$ array, denoted y_{rad} , representing the radially-averaged uptake as a function of the long-axis and radial dimension of the tumor

$$y_{rad,jk} = \frac{1}{|B_{jk}|} \sum_{x_i \in B_{jk}} y_i \quad (15)$$

where B_{jk} is the set

$$B_{jk} = \bigcup_{\{h \in I_j^H, c \in I_k^R\}} \mathcal{B}^c(h)$$

and $|B_{jk}|$ is the number of voxels whose centers lie in B_{jk} . An image of y_{rad} provides an overview of the radial pattern as a function of the axial position in the tumor. As constructed

the array also encodes the average transaxial radial extent of the tumor as a function of the long-axis dimension.

Having fitted our model structure, the phase measurement (4) ($u_i = \tau_{h_i} + \phi_{h_i} \cdot r_i / (\sigma_{h_i}(\theta_i))$) is available for each voxel. After adjustment for axial amplitude (i.e., dividing uptake by the corresponding estimated β -value, i.e., $z_i = y_i / \hat{\beta}_{h_i}$) uptake is plotted against phase (top-right plot in quadrant D) to give an assessment of the overall radial profile of the tumor. This plot provides a direct view of the structure of the radial-function in our model. So comparison with the assumed Gaussian form can be made. Some care is needed in interpreting this plot because the sampling is not uniform in the phase, and the variance of the adjusted uptake

values is inversely related to the magnitude of the fitted amplitude ($\hat{\beta}_{h_i}$). To address this, we provide a non-parametric estimate of the trend (incorporating a unimodality constraint and taking account of the variance issue). We use weights $\tilde{w}_i = \hat{\beta}_{h_i} / (1 + (u_i) / \max_i(u_i))$. A smoothing spline [20], [25] is applied to smooth z_i as a function of u_i with weights $\tilde{w}_i$. This function is then processed using isotonic least-squares regression [2], [20], pre- and post- the maximum to produce a uni-modal curve. Examples of these curves are shown as green lines in component D of the following Figs. 4–7. Note that these trend lines are not used in a quantitative manner.

The bottom-left plot of quadrant D shows the axial phase pattern of the core of the tumor (left-most curve) and the first, second and third quartiles of the phase distribution (remaining curves, respectively from left to right). These shed light on the parts of the tumor where the radial tumor profile is at different stages. In tumors with central areas of low FDG uptake (associated with necrosis or fluid, fat or cartilage buildup), the core-phase would be negative although there might be deviation from this towards the extremities of the axial dimension. The bottom-right plot of quadrant D shows a measure of heterogeneity, defined as the axial deviation of the fitted uptake model from the observed uptake.

B. Four Cases

1) Inner Thigh Tumor Imaged With a GE-Advance—The tumor is located on the inner thigh. The boundary surface grid pattern [Fig. 4(B)] shows that the mass is well aligned with the PET scanning geometry. The resampled (33rd and 66th percentiles) transverse slices (Fig. 4(C), top row) show an active core, in agreement with the information imaged in Fig. 4(A). The corresponding uptake profiles also indicate this pattern with a decreasing curve (bottom row). In Fig. 4(D), the tumor profile (top row) shows little decline in uptake towards the central core. The core-phase (bottom-left) is slightly negative in the middle of the axial dimension, although remaining close to zero, and the quantiles of the phase are similar at all axial levels. This indicates a relatively uniform, active tumor core. The 3-D uptake pattern is well described by the model—the heterogeneity is generally low except at the axial extremities where the uptake declines (bottom-right).

2) Pelvic Region Tumor Imaged With a GE-Advance Scanner—The tumor is centered on an area which has overlap with the urinary bladder and streak artifacts arising from the bladder degrade the overall image quality [Fig. 5(A)]. The boundary surface grid

pattern [Fig. 5(B)] shows that the mass, while having a simple shape, is not so well aligned with the PET scanning geometry. Representative transverse slices [Fig. 5(C)] show good agreement with the PET scans and exhibit a less active core. The analysis [Fig. 5(D)] also reveals a tumor profile which notably declines towards the central core (top row). Although the quantiles in phase show little variation with axial level, there is a marked negativity in core-phase towards the middle of the axial extent of the mass. This indicates a stronger difference in uptake rate between the tumor core and its more active boundaries. This is consistent with a more developed sarcoma. The 3-D uptake pattern is well described by the model—the heterogeneity is generally low except at the axial extremities where the uptake declines [Fig. 5(D)].

3) Extended Leg Tumor Mass Imaged With a PET/CT Scanner—This tumor has distinct masses above and below the kneejoint. The mass below the knee is more elongated [Fig. 6(A)]. The surface grid pattern [Fig. 6(B)] is substantially the same in both the original and transformed coordinates. There is a marked nonlinearity reflecting the way in which the leg is flexed in the scanner. The tumor profile [Fig. 6(D)] is strongly concentrated towards its core where the phase is very close to zero. The axial pattern of radial uptake highlights the nodular structure of the tumor with gaps between areas of high FDG uptake—the gap at the knee is the most extensive. Outside of the gaps, quantiles in phase show little variation with axial level. Representative transverse slices [Fig. 6(C)] are in good agreement with the model and apart of the gaps where the radial uptake is low, the 3-D uptake pattern is well described by the model—heterogeneity is low except when the uptake is low (i.e., at lesion separations), indicating that all lesions remain relatively homogeneous.

4) Upper Body Tumor Imaged With a PET/CT Scanner—This tumor is located in the upper arm and is not well aligned with the scanning geometry [Fig. 7(A) and (B)]. The surface grid pattern [Fig. 7(B)] pattern is complex in the original coordinates but the PAS transformation simplifies the visualization of the structure. Both the two transverse uptake curves [Fig. 7(C)] and the tumor profile [Fig. 7(D)] indicate some areas with low core uptake (especially within (0, 5) on the z-axis). There is a significant degree of deviation from the mean phase profile, which corresponds with a more advanced development. As a result the model heterogeneity is generally high (bottom-right). The axial pattern of radial uptake shows a concentrated mass at the base of the axial dimension becoming diffuse and more photopenic as observation moves upwards through the mass.

IV. Prognostic Evaluation

The above procedures were used to analyze a set of 185 GE-Advance FDG-PET scans from sarcoma patients treated at the University of Washington over a 15 year period. Each scan set has a volume with between 35 and 105 image planes with 128×128 voxels in each image. These data were previously used to report on prognostic characteristics of an elliptic heterogeneity measure [7]. In the current analysis, the previous hand-drawn tumor ROIs, which had been constructed with reference to conventional diagnostic imaging CT or MRI, were supplemented by cruder elliptical cylinder ROIs constructed in AMIDE. These new AMIDE ROIs largely overlap with the previous hand-drawn ones. Typical examples are shown above. While extensive collections of GE-Advance and PET/CT scanning have been

carried out, the detailed hand-drawn ROIs are only available on the selected GE-Advance cohort. In statistical terms, this cohort, which has the most extensive follow-up (70 deaths and 95 disease progression events), offers obvious advantages for prognostic evaluation of potential imaging variables. AMIDE ROI sets were processed using an R script. Each analysis produced a set of five new variables—core nonlinearity, three phase measurements and the model heterogeneity. We also calculated three elliptical heterogeneity values—one for the original hand-drawn ROI, one for the elliptical cylinder ROI and a third for the subregion selected through the boundary analysis technique. These data enable us to evaluate how alternative calculations of elliptical heterogeneity affect prognostic utility.

We use a multivariate Cox proportional hazards regression [20], [24] for analysis. Table II reports results for models which include standard diagnostic variables (grade and the widely used maximum standardized tumor uptake SUV_{max}) together with a single additional variable (five values from the current tumor synthesis as well as three elliptical heterogeneity values). Hazard ratios show the change in risk associated with an increase of one standard deviation in the variable considered. So a 70%–80% increase in risk of death is associated with higher heterogeneity tumors and tumors with higher core phase (lower metabolism) have 20%–30% less risk of death or disease progression. These results demonstrate the potential prognostic utility of the variables defined by our spatial analysis, but the core phase and the model heterogeneity assessments stand out. A more detailed multivariate analysis finds good support for a model with heterogeneity based on the AMIDE-generated elliptical cylinder ROI and the core-phase variables (u_c , $\tilde{u}_c$). The results are reported in Table III. Even after adjusting for overall heterogeneity and other important factors, core-phase status is seen to be strongly associated with risk. Adding other covariates (including the previous heterogeneity based on hand-drawn ROIs) does not significantly improve prognostic accuracy. Each of the elliptical heterogeneity measures and the model-based heterogeneity are strong prognostic factors, but there is little difference between the prognostic utility of any of the four different heterogeneities considered. The fact that almost 80% of the variation in the heterogeneity measures computed from the hand-drawn ROIs (H_o) is explained by the covariates used in Table III explains this finding. This is important because it allows adequate heterogeneity evaluations to be based on a much cruder (and more easily implemented) ROI definition. The survival and progression-free patterns for high (top 33%), intermediate (middle 34%), and low (lowest 33%) risk groups identified by the fitted Cox models are compared in Fig. 8. Using the core-phase information there is a noticeable increase in differentiation between the progression-free patterns of high, intermediate and low risk patients. The impact of core-phase on overall survival is not as apparent, although better separation between low and intermediate risk groups is seen. The marked improvements over cruder uses of the PET imaging information (SUV_{max}) are seen in Fig. 8.

V. Discussion

We have developed a model for examination of PET measured FDG uptake patterns in human sarcoma. The proposed spatial model presents improvements upon more typical image processing methods for tumor volume extraction, as it provides a disease-specific scheme that does not require MR or CT data, and generates direct prognostically useful

measures of tumor risk. This contribution builds upon previous work [5]–[7], [17], [18] toward a more refined analysis of the FDG uptake pattern. The approach makes critical use of a principal axis rotation that transforms the 3-D uptake to a coordinate system in which modeling is possible. The proposed model involves a tubular representation of the sarcoma structure, with smooth contractions of the estimated boundary contour used to explore the planar patterns radially, transverse to the axial dimension. Employing a standardized Gaussian as a reference profile, a mechanism for assessment of the stage of development (phase) of any voxel in the tumor volume is developed. The result is a more comprehensive synthesis of the 3-D uptake pattern that incorporates novel variables, in addition to a companion measure of heterogeneity, into a methodology for prognostic assessment. This approach is readily amenable to implementation and visualization using only open-source software tools.

Analysis of PET imaging information requires preliminary determination of the tumor ROI within the scan, in a process that is in general time-consuming, and can be tedious and difficult to reproduce. A semi-automated tool for routine ROI generation facilitates both medical practice and computerized analysis. In this context standard image processing techniques do not best exploit PET information. There are a variety of other approaches that could potentially be adapted for refinement of the elliptical contour σ_h^o (in Section II-C), including snakes [13], [14], [23] and sophisticated change-point methods [9], [11]. Our construction is motivated by the particular form of the final model, which includes a unimodal description of radial uptake, and our methodology takes advantage of this assumption in the construction of the boundary. In statistical terms, more general purpose boundary tracking algorithms may not be as efficient when this uptake assumption is valid. This is a matter that could be explored in greater depth. It is possible that more experience with PET/CT scanning will change this outlook. We note that current practice in the analysis of fMRI neuro-imaging data has benefitted greatly from the existence of standardized anatomic atlases for analysis [10]. A reviewer has pointed to the possibility of constructing a standardized statistical shape pattern for sarcoma FDG-PET data, calibrated on the basis of our current clinical experience. This could provide a kind of sarcoma atlas that might be useful in analysis, even if it would lack internal fiducial markers which are a feature of brain atlases.

The implementation of the approach separates specification of structural parameters from the detailed analysis of the within tumor uptake. In other clinical applications, the possibility for the structural parameters to be specified based on expert medical input, including supplementary high-resolution diagnostic information (such as co-registered CT or MRI scans), could well be preferred to our proposed computer-based approach. Although our method is found effective in the sarcoma setting, its generalization to other contexts may benefit from a linkage to more general inference strategies. A more integrated approach to estimation may be possible in which the structural and uptake parameters are combined. For example, the estimation procedure could alternatively be formulated in terms of regularization. This would remove the post-hoc smoothing step. The functional parameter involved is $\psi = (\beta, \tau, \varphi)$, with $\psi(h) = (\beta(h), \tau(h), \varphi(h))$ for $h \in [a, b]$. Let $\lambda_\psi(r, \theta, h) =$

$\beta(h)g(\tau(h) + \varphi(h)r/(\sigma_h(\theta)))$ represent the model-based uptake prediction in cylindrical coordinates as a function of ψ . A natural regularization functional would be

$$l_{\gamma,\tau}(\psi) = \sum_{i=1}^N [y_i - \lambda_{\psi}(r_i, \theta_i, h_i)]^2 + \gamma \int_a^b \beta(h)^2 dh + \tau J_m(\lambda_{\psi}) \quad (16)$$

for $\gamma, \tau > 0$ and $J_m(\lambda_{\psi})$ is the m th-order 3-D Laplacian, expressed in cylindrical coordinates [25]. While this formulation provides a theoretical framework for analysis, post-hoc smoothing of localized maximum likelihood, which our methodology is an example of, is in many contexts highly effective [12], [16]. However, care may be needed in this so that the optimized parameters maintain their interpretation.

The analysis provides new diagnostic imaging variables for prediction of survival and disease progression. Notably the stage of development of the tumor measured by the core-phase parameter is a significant prognostic factor. The interpretation of this parameter as a measure of the stage of development of the tumor is grounded in our own clinical experience with sarcoma. But it is interesting that some simple theoretical constructs used for modeling the growth in tumor spheroid data demonstrate the same qualitative features of development as we find in sarcoma. Thus the methodology may have applicability to other tumors. Fig. 9 presents a simulation from a classical model used to describe solid tumor growth (see Roose *et al.* [21]). In this example we can see how the radial tumor profile evolves over time. Some points to note: 1) at each stage the profile is quite Gaussian in shape, 2) the amplitude (cf. β) and scale (cf. φ) of the profile decrease over time, and 3), the profile peak moves radially i.e., the core-phase (cf. τ) becomes more negative. This simplified example is somewhat provocative. It would be interesting to explore, through in-silico experimentation, what aspects of a tumor growth model can be determined from measurement of the radial profile at one point in time. Were it possible to shed light on the growth model then the possibility to develop simulations for the likely evolution of tumor under various treatment scenarios could be considered. This could be a step towards integration of mathematical biology concepts into clinical practice with PET as recently suggested by Atuegwu *et al.* [1]. But there are caveats. It would be necessary to develop and validate (*in vivo*) a suite of cancer growth models, formulated in terms of FDG -PET uptake, for a range of human cancers [19], [21], [22]. We should emphasize that these remarks and Fig. 9 are presented to stimulate thought on this topic.

The use of a tubular model, rather than a more regular structure, corresponds to an attempt to automatically adapt to tumor volumes that clearly depart from a smooth regular structure. Such examples may be found for instance with sarcomas developing near a joint (e.g., the knee) or against a bone structure. Moreover, this locally adaptive boundary identification and the underlying mathematical representation proposed within are used to define specific tumor characteristics that also account for such dispositions. These features are then used to assess the tumor activity and related prognosis. The third case study presented in Section III-B illustrates this concern: the tumor had broken down into separated, yet homogeneous lesions, which was well captured by the profiling methodology. However, such a representation does not allow for a comparison to standard shape models. An initial projection of the uptake data onto an ellipsoidal coordinate system would allow us to

implement such a methodology; this perspective will be given further consideration. Similarly, one may also argue that the proposed tubular model may not be suitable for tumors presenting a typical ellipsoidal volume. However, no constraints are being made on the tubular ends, so as to allow for a potentially smooth closure at the volume extremities. The approach is applied here to PET data, for which the resolution may not allow for a binning scheme fine enough to encompass such smooth extremities. This feature could be controlled further, but may not necessarily contribute to the prognostic assessment using the derived biomarkers, which remains our ultimate goal.

Certain other aspects of the model could also be refined. Angular variation in uptake could be introduced. Another possibility might be to consider bifurcating tubular structures. These variations, while not immediately critical for sarcoma, could prove useful in the context of other uptake structures. In particular given the established use of polar mapping for consideration of cardiac PET and SPECT imaging data, adaptation of the present work to that context might prove worthwhile. A further direction is how to adapt these methods for dynamic data. One possibility would be to base the analysis on a vector of derived kinetic parameters at each voxel. So we could let $\mathbf{y}$ represent the kinetic vector and to allow $\boldsymbol{\eta}_h$ be the corresponding vector of kinetic amplitudes. Some preliminary work of this type is currently underway.

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Fig. 1.
Flowchart of the tumor FDG uptake analysis (section numbers in parentheses).

Fig. 2.

Illustration of center core estimation for binned long-axis data. Left: Short-axis plot of voxel coordinates coded from lowest (grey) to highest (yellow) FDG uptake. The cross-hairs (black) indicate the extracted center location. Right: uptake information (black points) is plotted against the fitted scaled radii ρ_i and corresponding non-parametric fit of the uptake pattern (green). The height of the level used for boundary extraction is shown in red. Parameters (c_1, c_2, e, ϕ) are optimized using the RSS criterion (9).

Fig. 3.

Illustration of boundary contour estimation for binned long-axis data. A radial analysis (right) of a particular sectorial ray (blue arrow left) with the fitted model-derived estimates of the boundary radius value $[\bar{\rho}_j \text{ in } (10)]$. This corresponds to the level (l) shown in red. The collection of derived boundary points are shown as block dots (left) with the smoothed boundary contour ($\sigma_h(\theta)$).

Fig. 4.

Case 1: Inner thigh sarcoma (PET). (A)–(D) are described in detail in Section III-A.

Fig. 5.
Case 2: Pelvic region sarcoma (PET). (A)–(D) are described in detail in Section III-A.

Fig. 6.
Case 3: Extensive Leg Sarcoma (PET/CT). (A)–(D) are described in detail in Section III-A.

Fig. 7.
Case 4: Upper arm sarcoma (PET/CT). (A)–(D) are described in detail in Section III-A.

Fig. 8.

Kaplan-Meier Survival Patterns for high (upper 33%), intermediate (middle 34%), and low (bottom 33%) risk groups identified by Multivariate Cox Regression Analysis. Top row is for time-to-death; the bottom for time-to-disease progression. On the left-hand side heterogeneity, core-phase and grade are used as covariates; on the right-hand side only the SUV_{max} and grade are used as covariates.

Fig. 9.

Schematic representation of the evolution of a radially symmetric 2-D tumor growth model in which the concentration of alive (c_a) and dead (c_d) cells evolve according to a standard birth and death process [21]. Radiotracer activity (uptake) is assumed to be proportional to the concentration of alive tumor cells. The gray-scale images show the spatial distribution of uptake at different stages. The line graph shows the radial profile at different time-points in the evolution. Early, intermediate, and late time profiles are highlighted.

TABLE I

Coordinate Systems and Structural Parameters of the Tumor

Name	Notation	Definition	Structural Tumor Parameters
Raw Voxels	$x = (x_1, x_2, x_3)^t$	Scan Specification	Location and Spread $\mu, \Sigma = \Gamma \Lambda \Gamma^t$
Principal Axis (PAS)	$\tilde{x} \doteq (\tilde{x}_1, \tilde{x}_2, \tilde{x}_3)^t$	$x \doteq \Gamma^t(x - \mu)$	Central Core $(c_{1h}, c_{2h}, h); h \in [a, b]$
Cylindrical	(r, θ, h)	$r = \sqrt{\left(\tilde{x}_1 - c_{1h}\right)^2 + \left(\tilde{x}_2 - c_{2h}\right)^2}$ $\theta = \tan^{-1} \left(\frac{\tilde{x}_2 - c_{2h}}{\tilde{x}_1 - c_{1h}} \right); \quad h = \tilde{x}_3$	Boundary Surface $(\sigma_h(\theta), \theta, h); (\theta, h) \in [-\pi, \pi] \times [a, b]$

TABLE II

Evaluation of Heterogeneity and Tumor Profiling Variables as Individual Variable Additions to a Multivariate Cox Regression Which Includes Grade and the Maximum Uptake as Covariates.

Variable	Death		Progression	
	Hazard Ratio	95% C.I.	Hazard Ratio	95% C.I.
Heterogeneity (H_o)	1.76	[1.34,2.31]***	1.59	[1.25,2.02]***
Heterogeneity (H_Q)	1.80	[1.41,2.31]***	1.59	[1.28,1.97]***
Heterogeneity ($H_{Q'}$)	1.72	[1.36,2.17]***	1.53	[1.25,1.88]***
Heterogeneity (H^*)	1.90	[1.38,2.59]***	1.52	[1.18,1.96]**
Nonlinearity (ξ)	1.29	[1.12,1.48]***	1.22	[1.06,1.39]**
Core Phase (u_c)	0.82	[0.70,0.97]*	0.84	[0.73,0.96]*
Core Phase ($\bar{u}_c$)	0.70	[0.57,0.86]***	0.74	[0.62,0.88]***
Mean Phase ()	0.92	[0.76,1.12]	0.98	[0.83,1.16]

Hazard Ratios Record Proportional Changes in Risk Associated With a Standard Deviation (sd) Increase in the Variables ($e^{\beta \text{sd}}$ Where β Is the Regression Coefficient). H_o , H_Q , and $H_{Q'}$ Are Elliptical Heterogeneities Calculated for the Original, AMIDE, and Computer Generated ROIs. Definitions for the Other Variables Are in Section II-B [see (6) and (7)]. The Analysis Is Based on N = 185 Patients (70 Deaths and 95 Disease Progression Events). Symbols *, **, and *** Correspond to P-Values Below 0.05, 0.01, and 0.001, Respectively

TABLE III

Multivariate Cox Regression Results for Death and Progression.

Variable	Death		Progression	
	Hazard Ratio	95% C.I.	Hazard Ratio	95% C.I.
Grade:Intermediate vs Low	2.96	[0.68,12.9]	2.11	[0.85,5.24]
Grade:High vs Low	5.52	[1.29,23.6]*	3.54	[1.45,8.65]**
SUV _{max}	1.20	[0.93,1.56]	1.05	[0.83,1.33]
Heterogeneity (H_Q)	1.63	[1.24,2.14]***	1.45	[1.14,1.84]**
Core Phase ($\bar{u}_c$)	0.81	[0.66,0.99]*	0.82	[0.69,0.98]*

Hazard Ratios for Continuous Variables Record Proportional Changes in Risk Associated With a Standard Deviation (sd) Increase in the Variables ($e^{\beta \text{sd}}$ Where β Is the Regression Coefficient). H_Q Is the Elliptical Heterogeneity Calculated for the Simple AMIDE Generated ROI. Core Phase (6) Is defined in Section II-B. Analysis Is Based on N = 185 Patients (70 Deaths and 95 Disease Progression Events). Symbols *, **, and *** Correspond to p-Values Below 0.05, 0.01, and 0.001, Respectively