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A Bayesian approach to tissue-fraction estimation for oncological PET segmentation

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Abstract. Tumor segmentation in oncological PET is challenging, a major reason being the partial-volume effects that arise due to low system resolution and finite voxel size. The latter results in tissue-fraction effects, i.e. voxels contain a mixture of tissue classes. Conventional segmentation methods are typically designed to assign each voxel in the image as belonging to a certain tissue class. Thus, these methods are inherently limited in modeling tissue-fraction effects. To address the challenge of accounting for partial-volume effects, and in particular, tissue-fraction effects, we propose a Bayesian approach to tissue-fraction estimation for oncological PET segmentation. Specifically, this Bayesian approach estimates the posterior mean of fractional volume that the tumor occupies within each voxel of the image. The proposed method, implemented using a deep-learning-based technique, was first evaluated using clinically realistic 2-D simulation studies with known ground truth, in the context of segmenting the primary tumor in PET images of patients with lung cancer. The evaluation studies demonstrated that the method accurately estimated the tumor-fraction areas and significantly outperformed widely used conventional PET segmentation methods, including a U-net-based method, on the task of segmenting the tumor. In addition, the proposed method was relatively insensitive to partial-volume effects and yielded reliable tumor segmentation for different clinical-scanner configurations. The method was then evaluated using clinical images of patients with stage IIB/III non-small cell lung cancer from ACRIN 6668/RTOG 0235 multi-center clinical trial. Here, the results showed that the proposed method significantly outperformed all other considered methods and yielded accurate tumor segmentation on patient images with Dice similarity coefficient (DSC) of 0.82 (95% CI: 0.78, 0.86). In particular, the method accurately segmented relatively small tumors, yielding a high DSC of 0.77 for the smallest segmented cross-section of 1.30 cm². Overall, this study demonstrates the efficacy of the proposed method to accurately segment tumors in PET images.

Keywords: Positron Emission Tomography, estimation, segmentation, partial-volume effects, tissue-fraction effects, multi-center evaluation

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3
4 **1. Introduction**

5
6
7 Reliable segmentation of oncological PET images is required for tasks such as PET-
8 based radiotherapy planning and quantification of radiomic and volumetric features
9 from PET images (Zaidi et al., 2009, Jha et al., 2017, Cook et al., 2018, Mena et al.,
10 2017). However, tumor segmentation in PET is challenging for several reasons such as
11 partial-volume effects (PVEs), system noise, and large variabilities in the shape, texture,
12 and location of tumors (Foster et al., 2014). Tumor segmentation can be performed by
13 having trained readers delineate the tumors manually. However, manual delineation
14 is both labor- and time-intensive, and suffers from intra- and inter-reader variability
15 (Foster et al., 2014). To address these issues, computer-aided segmentation methods
16 have been developed. These include methods based on thresholding, region growing,
17 boundary detection, and stochastic modeling (Foster et al., 2014, Sridhar et al., 2014,
18 Kass et al., 1988, Layer et al., 2015). However, these methods suffer from limitations,
19 such as requiring user inputs, sensitivity to model assumptions (Belhassen and Zaidi,
20 2010), and limited ability to account for PVEs. Learning-based methods (Blanc-Durand
21 et al., 2018, Zhao et al., 2018) have been developed to address these issues. While these
22 methods have demonstrated promise, they typically require manual delineations for
23 training, which are likely affected by PVEs. Thus, accounting for PVEs remains an
24 important challenge in accurate delineation of PET images.

25
26 The PVEs in PET arise from two sources, namely the limited spatial resolution of
27 PET system and the finite voxel size in the reconstructed image (Soret et al., 2007). The
28 limited spatial resolution leads to blurred tumor boundaries. The finite voxel size results
29 in voxels containing a mixture of tumor and normal tissue. This phenomenon is referred
30 to as tissue-fraction effects (TFEs) (Rousset et al., 2007). A recently developed deep-
31 learning (DL)-based technique (Leung et al., 2020) has attempted to account for PVEs
32 arising due to the low system resolution. However, this method is not able to account
33 for the TFEs. This shortcoming arises because this method, similar to conventional
34 classification-based segmentation methods, is not designed or trained to model TFEs.
35 Instead, this method is designed and trained on the task of classifying each voxel in an
36 image as belonging to a single region. Note that while these learning-based methods
37 can output a probabilistic measure of a voxel belonging to a region, that probability
38 is unrelated to TFEs. Similarly, other probabilistic techniques, such as simultaneous
39 truth and performance level estimation (STAPLE) technique (Dewalle-Vignion et al.,
40 2015), can yield a probabilistic estimate of the true segmentation. However, again, this
41 probabilistic estimate has no relation to TFEs. Fuzzy PET segmentation methods have
42 attempted to account for TFEs by assigning different fuzzy levels to voxels that are
43 partially occupied by the tumor (Hatt et al., 2007, 2009). However, the goal of these
44 methods is not to directly estimate the tumor-fraction volume within each voxel. Thus,
45 they are not able to explicitly model TFEs.

46
47 To address the challenge of accounting for PVEs, and in particular, TFEs, while
48 performing tumor segmentation in PET, in this manuscript, we propose a Bayesian

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4
5 approach to tissue-fraction estimation. Specifically, the segmentation problem is posed
6 as a task of estimating the fractional volume that the tumor occupies within each
7 voxel of an image. Through this strategy, we are able to explicitly model TFEs. The
8 proposed method was developed in the context of segmenting the primary tumor in
9 [¹⁸F]fluorodeoxyglucose (FDG)-PET images of patients with lung cancer.
10

11 In the next section, we develop a theoretical formalism for the proposed method.
12 Our evaluation of the method using both clinically realistic simulations and clinical
13 images of patients with stage IIB/III non-small cell lung cancer (NSCLC) from ACRIN
14 6668/RTOG 0235 multi-center clinical trial, is then presented in Sec. 3, followed by the
15 results of this evaluation, discussions, and conclusions.
16

17
18 **2. Method**

19 **2.1. Theory**

20
21 Consider a PET system imaging a radiotracer distribution, described by a vector $f(\mathbf{r})$,
22 where $\mathbf{r} = (x, y, z)$ denotes the spatial coordinates. We denote the tracer uptake in
23 the tumor by $f_s(\mathbf{r})$. The rest of the regions are referred to as background, and uptake
24 in the background is denoted as $f_b(\mathbf{r})$. Thus, the tracer uptake can be represented
25 mathematically as follows:
26

$$f(\mathbf{r}) = f_b(\mathbf{r}) + f_s(\mathbf{r}). \quad (1)$$

27
28 We define a support function for the tumor region as $s(\mathbf{r})$, i.e.
29

$$s(\mathbf{r}) = \begin{cases} 1, & \text{if } f_s(\mathbf{r}) > 0. \\ 0, & \text{otherwise.} \end{cases} \quad (2)$$

30
31 The radiotracer emits photons that are detected by the PET system, yielding projection
32 data. Reconstruction with the projection data yields the reconstructed image, denoted
33 by an M -dimensional vector $\hat{\mathbf{f}}$. Thus, the mapping from the tracer distribution to the
34 reconstructed image is given by the operator $\Theta : \mathbb{L}_2(\mathbb{R}^3) \rightarrow \mathbb{E}^M$.
35

36 Denote the PET system by a linear continuous-to-discrete operator \mathcal{H} , and let the
37 vector \mathbf{n} describe the Poisson-distributed noise. Denote the reconstruction operator,
38 quite possibly non-linear, by \mathcal{R} . The eventual reconstructed image is given in operator
39 notation as follows:
40

$$\hat{\mathbf{f}} = \mathcal{R}\{\mathcal{H}\mathbf{f} + \mathbf{n}\}. \quad (3)$$

41 In the reconstructed image, denote the volume of each voxel by V and define the voxel
42 function as $\phi_m(\mathbf{r})$, i.e.
43

$$\phi_m(\mathbf{r}) = \begin{cases} 1, & \text{if } \mathbf{r} \text{ lies within the } m^{\text{th}} \text{ voxel of the PET image.} \\ 0, & \text{otherwise.} \end{cases} \quad (4)$$

44 The fractional volume that the tumor occupies in the m^{th} voxel, denoted by v_m , is given
45 by
46

$$v_m = \frac{1}{V} \int d^3\mathbf{r} s(\mathbf{r})\phi_m(\mathbf{r}). \quad (5)$$

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5 Our objective is to design a method that estimates this quantity v_m from the
6 reconstructed image $\hat{\mathbf{f}}$ for all M voxels. Denote the estimate of v_m by \hat{v}_m . Further,
7 denote the M -dimensional vector $\{v_1, v_2, \dots, v_M\}$ by \mathbf{v} , and denote the estimate of \mathbf{v}
8 by $\hat{\mathbf{v}}$.
9

10 Estimating \mathbf{v} from the reconstructed image is an ill-posed problem due to the null
11 spaces of the \mathcal{H} and \mathcal{R} operator. Thus, we take a Bayesian approach to estimate $\hat{\mathbf{v}}$. We
12 first need to define a cost function that penalizes deviation of \mathbf{v} from $\hat{\mathbf{v}}$. A common cost
13 function is the ensemble mean squared error (EMSE), which is the mean squared error
14 averaged over noise realizations and the true values \mathbf{v} . However, in our case, the variable
15 \hat{v}_m is constrained to lie within $[0, 1]$, and the EMSE loss does not directly incorporate
16 this constraint. In contrast, using the binary cross-entropy (BCE) loss as the penalizer
17 allows us to incorporate this constraint on \hat{v}_m directly, as also suggested in Creswell
18 et al. (2017). The BCE loss between v_m and \hat{v}_m , denoted by $l_{BCE}(v_m, \hat{v}_m)$, is given by
19
20

$$l_{BCE}(v_m, \hat{v}_m) = -v_m \log(\hat{v}_m) - (1 - v_m) \log(1 - \hat{v}_m). \quad (6)$$

21
22 We define our cost function $C(\mathbf{v}, \hat{\mathbf{v}})$ as the negative of aggregate BCE loss over all
23 voxels averaged over the joint distribution of true values \mathbf{v} and noise realizations $\hat{\mathbf{f}}$. The
24 cost function is then given by
25
26

$$\begin{aligned} C(\mathbf{v}, \hat{\mathbf{v}}) &= - \int d^M \hat{\mathbf{f}} \int d^M \mathbf{v} \text{pr}(\hat{\mathbf{f}}, \mathbf{v}) \sum_{m=1}^M l_{BCE}(v_m, \hat{v}_m) \\ &= - \int d^M \hat{\mathbf{f}} \text{pr}(\hat{\mathbf{f}}) \int d^M \mathbf{v} \text{pr}(\mathbf{v}|\hat{\mathbf{f}}) \sum_{m=1}^M l_{BCE}(v_m, \hat{v}_m), \end{aligned} \quad (7)$$

27
28 where in the second step we have expanded $\text{pr}(\hat{\mathbf{f}}, \mathbf{v})$ using the conditional probability.
29 Inserting Eq. (6) into Eq. (7), we obtain
30
31

$$C(\mathbf{v}, \hat{\mathbf{v}}) = \int d^M \hat{\mathbf{f}} \text{pr}(\hat{\mathbf{f}}) \int d^M \mathbf{v} \text{pr}(\mathbf{v}|\hat{\mathbf{f}}) \left[\sum_{m=1}^M v_m \log(\hat{v}_m) + (1 - v_m) \log(1 - \hat{v}_m) \right]. \quad (8)$$

32
33 To estimate the point at which this cost function is minimized, we differentiate the
34 cost function with respect to the vector $\hat{\mathbf{v}}$ and set that equal to zero. Because $\text{pr}(\hat{\mathbf{f}})$
35 is always nonnegative, the cost function is minimized by setting the derivative of inner
36 integral in Eq. (8) equal to zero, i.e.
37
38

$$\frac{\partial}{\partial \hat{\mathbf{v}}} \int d^M \mathbf{v} \text{pr}(\mathbf{v}|\hat{\mathbf{f}}) \left[\sum_{m=1}^M v_m \log(\hat{v}_m) + (1 - v_m) \log(1 - \hat{v}_m) \right] = 0. \quad (9)$$

39
40 This is then equivalent to performing component-wise differentiation and setting each
41 differentiated component to 0 (Barrett and Myers, 2013). For the m^{th} component of
42
43

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5 Eq. (9), we get

$$\begin{aligned} & \frac{\partial}{\partial \hat{v}_m} \int dv_m \text{pr}(v_m|\hat{\mathbf{f}}) [v_m \log(\hat{v}_m) + (1 - v_m) \log(1 - \hat{v}_m)] \\ &= \frac{\partial}{\partial \hat{v}_m} \int dv_m \text{pr}(v_m|\hat{\mathbf{f}}) [v_m \{\log(\hat{v}_m) - \log(1 - \hat{v}_m)\} + \log(1 - \hat{v}_m)] \\ &= 0. \end{aligned} \quad (10)$$

14 Since $\int dv_m \text{pr}(v_m|\hat{\mathbf{f}}) = 1$, the solution to Eq. (10), denoted by \hat{v}_m^* , is given by
15

$$\hat{v}_m^* = \int dv_m \text{pr}(v_m|\hat{\mathbf{f}}) v_m. \quad (11)$$

19 Equivalently, in vector notation, we get
20

$$\hat{\mathbf{v}}^* = \int d^M \mathbf{v} \text{pr}(\mathbf{v}|\hat{\mathbf{f}}) \mathbf{v}, \quad (12)$$

24 which is simply the posterior-mean estimate of \mathbf{v} . Note that the same estimator is
25 obtained when the cost function is the EMSE between \mathbf{v} and $\hat{\mathbf{v}}$. Thus, by minimizing the
26 cost function in Eq. (8), we obtain an optimal estimator that achieves the lowest mean
27 squared error among all possible estimators. We can further show that this estimator is
28 unbiased in a Bayesian sense (proof provided in Appendix B).
29
30

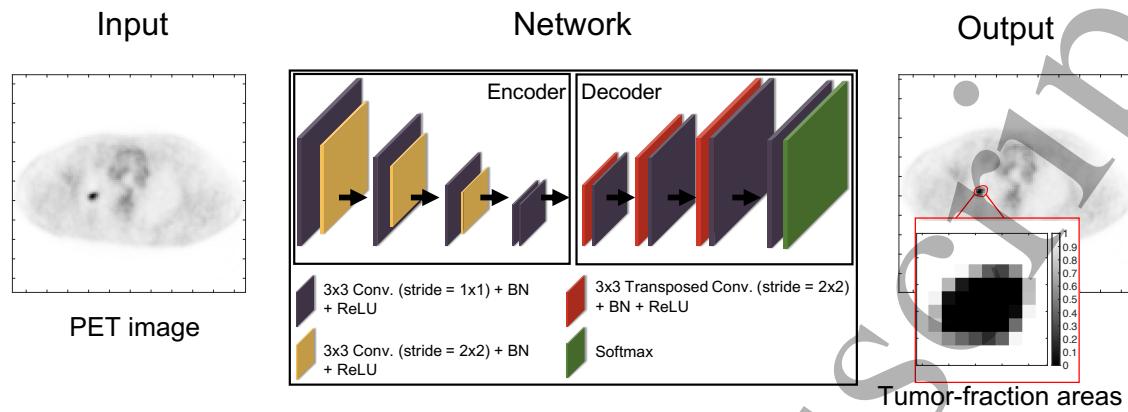
31 In summary, we have shown that by developing an optimization procedure that
32 minimizes the cost function defined in Eq. (8), we obtain a posterior-mean estimate of the
33 tumor-fraction volumes in each voxel of the reconstructed image. This estimator yields
34 the lowest mean squared error among all possible estimators. Further, this estimator is
35 unbiased in a Bayesian sense.
36
37

39 2.2. Implementation of the proposed technique

41 While we have developed the theoretical formalism in 3-D, in this manuscript, the
42 method was implemented and evaluated on a simplified per-slice basis. Thus, for each
43 pixel in the 2-D reconstructed image, the optimizer was designed to yield the posterior
44 mean estimate $\hat{\mathbf{a}}^*$ of the true tumor-fraction area (TFA), which we denote by \mathbf{a} . We
45 now describe the procedure to implement this optimizer.
46
47

48 Estimating the posterior mean $\hat{\mathbf{a}}^*$ requires sampling from the posterior distribution
49 $\text{pr}(\mathbf{a}|\hat{\mathbf{f}})$. Sampling from this distribution is challenging as this distribution is high-
50 dimensional and does not have a known analytical form. To address this issue,
51 the proposed method was implemented using a supervised learning-based approach.
52 Specifically, an encoder-decoder network was constructed, as shown in Fig. 1. During
53 the training phase, this network is provided with a population of PET images, and the
54 corresponding ground-truth TFA map, i.e. the vector \mathbf{a} for each image, as described
55 in Sec. 2.1. The network, by minimizing the cost function defined in Eq. (8) over this
56 population of images, becomes trained to yield the posterior-mean estimate of \mathbf{a} given
57 the input PET image.
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6



19
20 Figure 1: Illustration of the developed optimization procedure by constructing an
21 encoder-decoder network. Conv.: convolutional layer; BN: batch normalization; ReLU:
22 rectified linear unit.
23
24

25 The network architecture is similar to those for estimation tasks, such as image
26 denoising (Creswell et al., 2017) and image reconstruction (Nath et al., 2020). To
27 summarize, the network is partitioned into a contracting and an expansive path. The
28 contracting path learns the spatial information from the input PET images and the
29 expansive path maps the learned information to the estimated TFA map for each input
30 image. Skip connections with element-wise addition were applied to feed the features
31 extracted in the contracting path into the expansive path to stabilize the training and
32 improve the learning performance (Mao et al., 2016). In the final layer, the network
33 yields the estimate of the TFAs. A detailed description of the network architecture is
34 provided in Appendix A (Table A1).
35
36

37 As outlined in Sec. 1, the goal of the proposed method is to explicitly model
38 the TFEs while performing tumor segmentation. Our training strategy and network
39 architecture are specifically designed for this goal by defining the ground truth as the
40 TFAs for each image. We contrast this to the conventional DL-based segmentation
41 methods, where, in the ground truth, each pixel is exclusively assigned to the tumor
42 or the normal tissue class and the network is trained to classify each pixel as either
43 tumor or background. Further, as mentioned above, while the conventional DL-based
44 methods can output a probabilistic estimate for each image pixel, this estimate is only
45 a measure of classification uncertainty, and thus has no relation to TFEs, unlike the
46 proposed method.
47
48

49 The network was trained via the Adam optimization algorithm (Kingma and Ba,
50 2014). In the various experiments mentioned later, the network hyperparameters
51 were optimized on a training set via five-fold cross validation. The network training
52 was implemented in Python 3.6.9, Tensorflow 1.14.0, and Keras 2.2.4. Experiments
53 were performed on a Linux operating system with two NVIDIA Titan RTX graphics
54 processing unit cards.
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5 **3. Evaluation**
6

7 Evaluating the proposed method requires access to ground truth where either the
8 ground-truth TFA map or a surrogate for the true TFA map, such as tumor delineations
9 defined by trained readers, are known. In Sec. 3.2, we first evaluated the proposed
10 method using clinically realistic simulation studies, where the ground-truth TFA map
11 was known. In these studies, the support of tumor can be described at a very high
12 resolution, simulating $s(\mathbf{r})$ in Eq. (2). From this high-resolution description, the true
13 TFA within each image pixel can be computed using Eq. (5), thus providing the
14 TFA map. Realistic simulation studies also model imaging physics and variability in
15 patient populations. Thus, these studies provide a rigorous mechanism to evaluate
16 the method. However, we recognize that simulation studies may have limitations
17 in modeling all aspects of system instrumentation, patient physiology, and patient-
18 population variability, especially in multi-center settings, accurately. Thus, it is
19 important to assess the performance of the method using patient studies, ideally with
20 multi-center trial data. For this purpose, in Sec. 3.3, we evaluated the proposed method
21 on clinical images from the ACRIN 6668/RTOG 0235 multi-center clinical trial, where
22 trained-reader-defined segmentations were used as the surrogate ground truth. We first
23 describe the performance metrics used to quantitatively evaluate the proposed method.
24
25

26 **3.1. Evaluation metrics**
27
28

29 Since the proposed method is an estimation-based segmentation approach, our
30 evaluation used performance metrics for both the task of estimating the true TFA map
31 and of segmenting the tumor.

32 **3.1.1. Evaluation on estimation performance** Performance on the estimation task was
33 evaluated using the EMSE between the true and estimated TFA maps. EMSE provides
34 a combined measure of bias and variance over the distribution of true values and noise
35 realizations, and is thus considered as a comprehensive figure of merit for estimation
36 tasks (Barrett and Myers, 2013). The error in the estimate of the TFA maps and
37 the tumor area was quantified using the pixel-wise EMSE and normalized area EMSE,
38 respectively. Denote $\langle \dots \rangle_X$ as the expected value of the quantity in the brackets when
39 averaged over the random variable X . The pixel-wise EMSE is given by
40
41

$$42 \text{Pixel-wise EMSE} = \left\langle \left\langle \|\hat{\mathbf{a}} - \mathbf{a}\|_2^2 \right\rangle_{\hat{\mathbf{f}}|\mathbf{a}} \right\rangle_{\mathbf{a}}. \quad (13)$$

43 The normalized area EMSE denotes the EMSE between the true and estimated areas of
44 each tumor, normalized by the true areas. The true and estimated areas, denoted by A
45 and \hat{A} , are given by the L_1 norms of \mathbf{a} and $\hat{\mathbf{a}}$, respectively. The normalized area EMSE
46 is then given by
47
48

$$49 \text{Normalized area EMSE} = \left\langle \left\langle \frac{|\hat{A} - A|^2}{A^2} \right\rangle_{\hat{\mathbf{f}}|A} \right\rangle_A. \quad (14)$$

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5 We have shown (Eq. (B4) in Appendix B) that the proposed method yields an
6 unbiased estimate of \mathbf{a} in a Bayesian sense. To verify this, the ensemble-average bias
7 was computed. This term, denoted by $\bar{\mathbf{b}}$, is an M -dimensional vector $\{\bar{b}_1, \bar{b}_2, \dots, \bar{b}_M\}$,
8 with the m^{th} element of the vector quantifying the average bias of the estimated TFA
9 within the m^{th} pixel. Consider a total of P tumor images and N noise realizations for
10 each tumor image. Let a_{mnp} and \hat{a}_{mnp} denote the true and estimated TFA within the
11 m^{th} pixel for the n^{th} noise realization in the p^{th} tumor image. The m^{th} component of
12 ensemble-average bias, \bar{b}_m , is then given by
13
14

$$\bar{b}_m = \frac{1}{P} \sum_{p=1}^P \frac{1}{N} \sum_{n=1}^N [\hat{a}_{mnp} - a_{mnp}] . \quad (15)$$

15
16 The proximity of the elements of $\bar{\mathbf{b}}$ to 0 would indicate that the estimator was unbiased
17 in a Bayesian sense.
18
19

20
21 3.1.2. *Evaluation on segmentation performance* The proposed method estimates the
22 TFA within each pixel, which is a continuous-valued output. For evaluation of
23 segmentation methods that yield such non-binary output, as in Taha and Hanbury
24 (2015), the spatial-overlap-based metrics can be derived based on the four cardinalities
25 of confusion matrix, namely the true positives (TP), false positives (FP), true negatives
26 (TN), and false negatives (FN). The four cardinalities are given by
27
28

$$\begin{aligned} \text{TP} &= \sum_{m=1}^M \min(\hat{a}_m, a_m) & \text{FP} &= \sum_{m=1}^M \max(\hat{a}_m - a_m, 0) \\ \text{TN} &= \sum_{m=1}^M \min(1 - \hat{a}_m, 1 - a_m) & \text{FN} &= \sum_{m=1}^M \max(a_m - \hat{a}_m, 0) . \end{aligned} \quad (16)$$

29
30 The spatial-overlap metric of Dice similarity coefficient (DSC) and Jaccard similarity
31 coefficient (JSC) were used to measure the agreement between the true and estimated
32 segmentation. The DSC and JSC are defined as
33
34

$$\text{DSC} = \frac{2\text{TP}}{2\text{TP} + \text{FP} + \text{FN}}, \quad \text{JSC} = \frac{\text{TP}}{\text{TP} + \text{FP} + \text{FN}}. \quad (17)$$

35
36 Higher values of DSC and JSC indicate higher segmentation accuracy. These metrics
37 were reported as mean values with 95% confidence intervals (CIs). Statistical
38 significance was assessed via a paired sample t -test, with a p -value < 0.01 inferring
39 statistically significant difference.
40
41

42 We also qualitatively evaluated the performance of the proposed method on the
43 task of estimating the TFA map. For this purpose, ground-truth and estimated tumor
44 topographic maps were first constructed from the true and estimated TFA maps using
45 the contour function in MATLAB (MathWorks, Natick, Mass). Specifically, the tumor
46 topographic map shows the topography of the TFA map by means of isocontours. Then,
47
48

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5 isocontours corresponding to the true and estimated TFA maps were plotted for the TFA
6 values of 0, 1/3, 2/3, and 1. A TFA of 0 implies that no area within that pixel contains
7 the tumor, while a TFA of 1 implies that the entire pixel area is the tumor.
8
9

10 *3.2. Evaluation of the proposed method using clinically realistic simulation studies*
11

12 This evaluation study was conducted in the context of segmenting the primary tumor
13 in FDG-PET images of patients with lung cancer. The study quantitatively evaluated
14 the accuracy of the method, compared the method to existing techniques, studied the
15 sensitivity of the method to PVEs, and also studied the performance of the method for
16 different clinical-scanner configurations. In each evaluation, clinically realistic simulated
17 PET images with known ground-truth tumor properties were generated, as described
18 in Sec. 3.2.1. The generated data was split into training and test sets. The proposed
19 method was trained and cross-validated using the training set. The performance of the
20 method was then evaluated using the independent test set. The evaluation study used
21 clinical images, was retrospective, IRB-approved, and HIPAA-compliant with a waiver
22 of informed consent.
23
24

25 *3.2.1. Generating realistic simulated PET images* The simulation strategy advances
26 on a previously proposed approach to simulate PET images (Leung et al., 2020).
27 Briefly, in the first step, realistic tumor-tracer distribution was simulated at a very high
28 resolution, so that the simulated tumor can be described potentially as a continuous
29 object, equivalent to $f_s(\mathbf{r})$ in Eq. (1), except that $\mathbf{r} = (x, y)$ is a 2-D vector. Specifically,
30 the pixel size in the simulated tumor image was 0.13 mm. This was 1/32 of the resolution
31 in the patient image. The shapes, sizes, and intensities of simulated tumors were sampled
32 from the corresponding distribution derived from clinical images, so that the simulated
33 tumors had variabilities as observed in patient populations. An advancement on the
34 approach proposed in Leung et al. (2020) was to simulate intra-tumor heterogeneity
35 using a stochastic lumpy object model (Rolland and Barrett, 1992). Existing clinical
36 PET images containing the lung region but with no tumor present were selected as
37 templates to ensure tumor-background realism and account for inter-patient variability.
38 The projection data for the simulated tumor and background were generated using a
39 PET simulation software (Leung et al., 2020). Since the simulated tumor had higher
40 resolution compared to the background, we had different projection models for the
41 tumor and background separately. The projection data for the tumor and background
42 were then added, enabling the impact of image reconstruction on the tumor appearance
43 and noise texture to be inherently incorporated (Ma et al., 2017). Reconstruction was
44 performed using a 2-D ordered subset expectation maximization (OSEM) algorithm.
45 We have validated the realism of the images simulated using this approach (Liu et al.,
46 2021a). Detailed simulation and reconstruction parameters will be provided for each of
47 the studies mentioned below.
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4 *3.2.2. Evaluating accuracy of the proposed method and comparing to other segmentation*
5 *methods* We quantitatively compared the proposed method to several commonly used
6 semi-automated PET segmentation methods, including 40% SUV-max thresholding
7 (Sridhar et al., 2014), active-contour-based Snakes (Kass et al., 1988), and Markov
8 random fields-Gaussian mixture model (MRF-GMM) (Layer et al., 2015, Jha et al.,
9 2010). The method was also compared to a fuzzy segmentation method, namely the
10 fuzzy local information C-Means clustering algorithm (FLICM) (Krinidis and Chatzis,
11 2010). Further, the method was compared to a U-net-based PET segmentation method
12 (Leung et al., 2020). The ground truth for training this U-net-based method was
13 defined such that each voxel was classified as either tumor or background. For all the
14 semi-automated segmentation methods, the tumor location was provided by manually
15 generating a rectangular region of interest (ROI) containing the tumor. In contrast,
16 the proposed and U-net-based method did not require any manual input and were fully
17 automated.

18 To generate the simulated images for this study, following the procedure in Sec.
19 3.2.1, we used 318 2-D slices from 32 patients for the background portion of the image.
20 The simulated PET system had a spatial resolution of 5 mm full width at half maximum
21 (FWHM). The projection data were reconstructed using the OSEM algorithm with 21
22 subsets and 2 iterations, similar to the PET reconstruction protocol for the patient
23 images. The reconstructed pixel size was 4.07 mm × 4.07 mm. The network was trained
24 and cross-validated using 9,540 images with 5-fold cross validation. Evaluation was then
25 performed on 2,070 completely independent test images, which were generated using 69
26 2-D slices from 7 patients.

27 *3.2.3. Evaluating sensitivity of the proposed method to PVEs* To conduct this
28 evaluation, similar to Le Pogam et al. (2011) and Leung et al. (2020), we studied
29 the performance of the method as a function of tumor area. For this purpose, all
30 test images were grouped based on the range of the true tumor area. Specifically, the
31 tumor areas were binned with a bin width of 2 cm². For each test image, PVEs-affected
32 tumor masks were generated by applying a rectangular filter to the ground-truth tumor
33 mask, following the strategy in Leung et al. (2020). This filter modeled the resolution
34 degradation due to the forward projection and the reconstruction process. The tumor
35 area measured using the proposed method and the PVEs-affected tumor area in all the
36 test images were obtained and divided by the true tumor area. A ratio of unity would
37 indicate that the output was insensitive to PVEs. A ratio lower or higher than unity
38 would indicate an underestimation or overestimation of the true tumor area, respectively,
39 showing that the segmentation output was affected by PVEs (De Bernardi et al., 2009).

40 *3.2.4. Evaluating accuracy of the proposed method for different clinical-scanner*
41 *configurations* For this purpose, we simulated two PET systems with configurations
42 similar to the Siemens Biograph 40 and Biograph Vision scanners. The PET images
43 reconstructed from these two scanners had different pixel sizes, as dictated by the
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2 *A Bayesian approach to tissue-fraction estimation for oncological PET segmentation* 11
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5 protocol. The Biograph 40 generated images of 128×128 pixels, while the Biograph
6 Vision generated images of 192×192 pixels. Details of the PET scanner acquisition
7 and reconstruction parameters are provided in Appendix A (Table A2). Clinical PET
8 images of patients with lung cancer were obtained from these scanners. Using these
9 clinical scans and following the simulation procedure described in Sec. 3.2.1, a total of
10 5,520 and 6,120 simulated PET images were generated for each scanner, respectively.
11 These were used for optimizing and training the network. Next, the trained network was
12 tested on 1,200 and 1,320 independent simulated images, respectively. The performance
13 of the proposed method was also compared to the U-net-based method.
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17 *3.3. Evaluation of the proposed method using clinical multi-center PET images*
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20 We next evaluated the proposed method using clinical PET images. For this purpose, we
21 used de-identified patient data from the ACRIN 6668/RTOG 0235 multi-center clinical
22 trial (Machtay et al., 2013) available from The Cancer Imaging Archive (Clark et al.,
23 2013). In this evaluation study, FDG-PET images of 78 patients with inoperable
24 stage IIB/III NSCLC were included. Detailed patient demographics with clinical
25 characteristics are provided in Appendix A (Table A3). As in Machtay et al. (2013),
26 the standard imaging protocol involved recommended dose level from 10 to 20 mCi
27 and image acquisition beginning 50 to 70 minutes after FDG injection. PET images
28 were acquired from ACRIN-qualified clinical scanners (Scheuermann et al., 2009), with
29 attenuation, scatter, random, normalization, decay, and deadtime correction applied
30 in the reconstruction protocol. For all the 78 patients, the PET images were of size
31 128×128 , with the pixel size ranging from 4.69 mm to 5.47 mm. Detailed reconstruction
32 parameters are provided in Appendix A (Table A4).
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35 Evaluation of the proposed method would require the knowledge of true TFA maps.
36 For this purpose, a board-certified nuclear-medicine physician (J.C.M) with more than
37 10 years of experience in reading PET scans identified the primary tumor of each patient
38 by reviewing the PET, CT, and fused PET/CT images along axial, sagittal, and coronal
39 planes using MIM Encore (MIM Software, version 6.9.3). The radiologist was asked to
40 delineate a continuous (un-pixelated) boundary for each identified tumor. For each
41 tumor, the radiologist drew an external tumor boundary and considered the whole
42 volume within that boundary as belonging to the tumor class. A workflow was created
43 in MIM to assist the radiologist with this delineation task. The radiologist used a MIM-
44 based edge-detection tool to segment the tumor in 3-D on the fused PET/CT image,
45 by placing the cursor at the center of the tumor and dragging it out until the three
46 orthogonal guiding lines reached the tumor boundary. The radiologist then examined
47 and adjusted the segmentation to make it more accurate and also account for PVEs.
48 This manual segmentation was continuous and allowed for a voxel to consist of a mixture
49 of tumor and normal tissues. The segmentation was saved at a higher resolution than
50 that of the PET image.
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53 From this manual segmentation, we obtained a discrete version of the tumor mask,
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2 *A Bayesian approach to tissue-fraction estimation for oncological PET segmentation*
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5 $s(\mathbf{r})$, as defined in Eq. (2), for each 2-D PET slice and at a higher resolution than the
6 PET image. Specifically, the pixel size in the tumor mask was 1/8 of that in the PET
7 image. This resolution was chosen since more fine sampling did not cause changes in
8 the definition of the tumor mask. Let this high-resolution manual segmentation be an
9 N -dimensional vector ($N > M$), where we recall that M was the dimension of the PET
10 image. Denote the pixel function in this high-resolution space by $\phi_n^{manual}(\mathbf{r})$, following
11 the similar definition in Eq. (4). Define an N -dimensional vector $\psi(\mathbf{r})$ with each element
12 of this vector defined as
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$$\psi_n(\mathbf{r}) = \begin{cases} 1 & \text{if pixel } n \text{ in the manual segmentation is assigned to} \\ & \text{tumor class.} \\ 0 & \text{otherwise.} \end{cases} \quad (18)$$

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21 Denote the pixel area of the PET image by A . We computed the ground-truth TFA
22 within each image pixel as follows:
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25
$$a_m = \frac{1}{A} \sum_{n=1}^N \psi_n(\mathbf{r}) \int d^2\mathbf{r} \phi_n^{manual}(\mathbf{r}) \phi_m(\mathbf{r}), \quad (19)$$

26

27
28 where the integral computes fractional area that n^{th} pixel in the manual segmentation
29 occupies within the m^{th} pixel of the PET image. The network was then trained to
30 estimate the posterior mean of a_m for the m^{th} image pixel, following the training strategy
31 described in Sec. 2.2.
32

33 The network was trained and cross-validated using 565 2-D slices from 61 out of
34 78 patients. The trained network was then evaluated on 140 completely independent 2-
35 D slices from the remaining 17 patients. The performance of the proposed method
36 was compared to the other segmentation methods, described in Sec. 3.2.2, both
37 quantitatively and qualitatively, using the procedure and metrics described in Sec. 3.1.2.
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40 **4. Results**
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42 *4.1. Evaluation of the proposed method using clinically realistic simulation studies*

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44 *4.1.1. Evaluating accuracy of the proposed method and comparing to other segmentation*
45 *methods* Quantitatively, the proposed method significantly outperformed ($p < 0.01$)
46 all other considered methods, including the U-net-based method, on the basis of the
47 pixel-wise EMSE, normalized area EMSE, DSC, and JSC (Fig. 2, Table A5 in Appendix
48 A). The proposed method yielded the lowest pixel-wise EMSE, the lowest normalized
49 area EMSE of 0.02, the highest DSC of 0.90 (95% CI: 0.90, 0.91), and the highest JSC of
50 0.83 (95% CI: 0.83, 0.84). In addition, all the elements of the ensemble-average bias map
51 were close to 0, providing the evidence that the method yielded an unbiased Bayesian
52 estimate of the TFA map, as shown in Sec. 2.1. Further, the proposed method accurately
53 segmented relatively small tumors, and in particular, yielded high DSC of 0.84 for the
54 smallest segmented tumor axial cross-section of 0.88 cm^2 in area. The diameter of this
55 tumor was approximately twice the FWHM of the system resolution.
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A Bayesian approach to tissue-fraction estimation for oncological PET segmentation 13

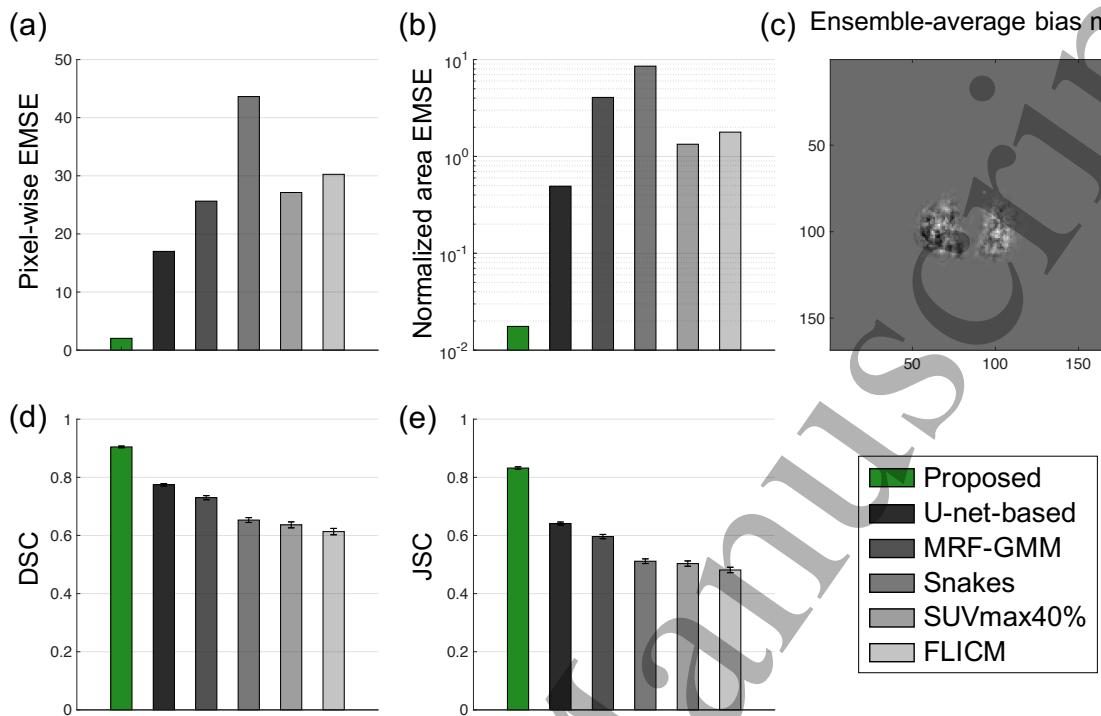


Figure 2: Evaluation result using clinically realistic simulation studies: (a) the pixel-wise EMSE between the true and estimated tumor-fraction areas; (b) the normalized area EMSE between the measured and true tumor areas (plot displayed in log scale on y-axis for better visualization); (c) the ensemble-average bias of the proposed method; the (d) Dice similarity coefficient and (e) Jaccard similarity coefficient between the true and estimated segmentations.

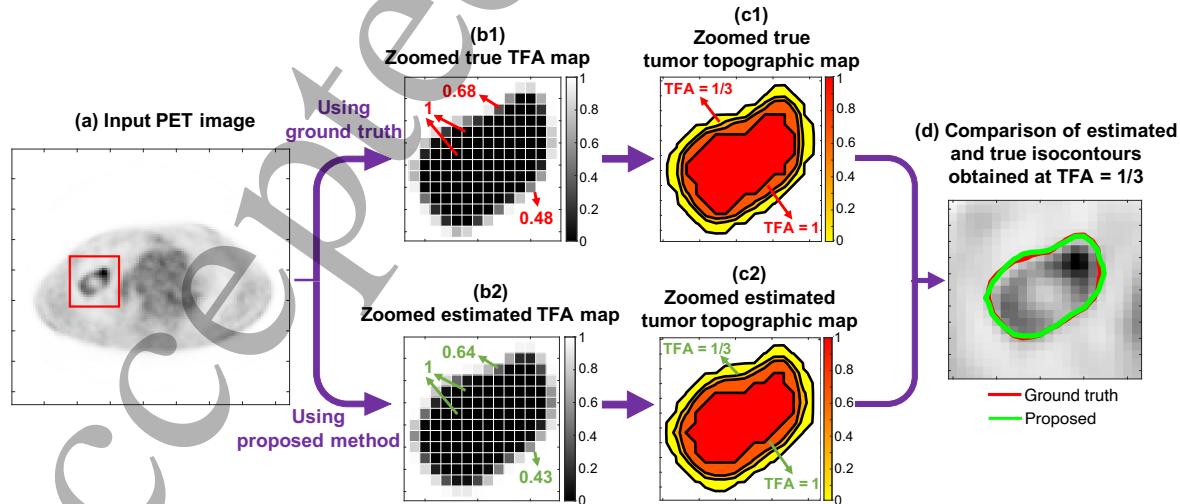
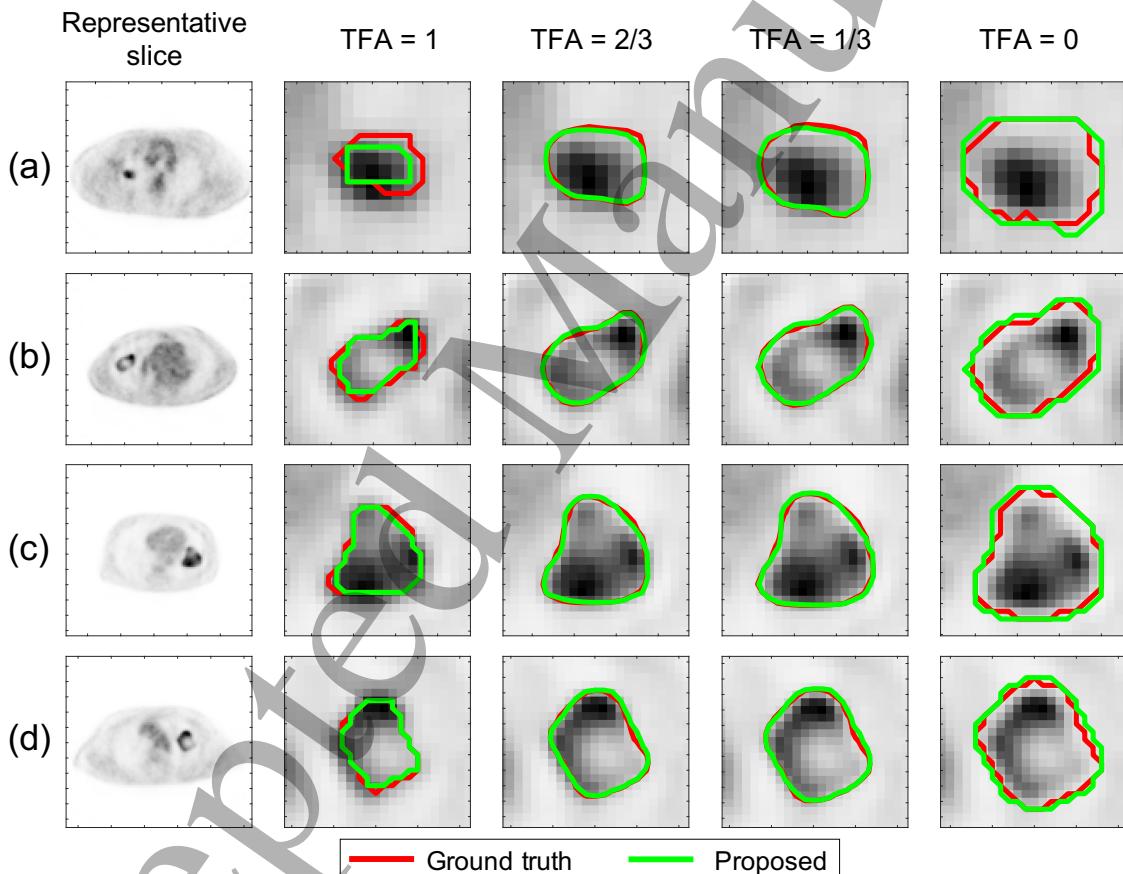


Figure 3: Illustration of the procedure to obtain isocontours from the ground-truth TFA map and the TFA map estimated by the proposed method.

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2 *A Bayesian approach to tissue-fraction estimation for oncological PET segmentation* 14
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5 We next qualitatively show the performance of the proposed method on the task
6 of estimating the TFA map, following the procedure described in Sec. 3.1.2. We first
7 illustrate the procedure to obtain the isocontours from the ground-truth and estimated
8 TFA maps for a representative tumor (Fig. 3). We then followed this procedure to
9 obtain the isocontours from the TFA maps for different cases. In Fig. 4, the comparisons
10 between the true and estimated isocontours for representative slices at four different TFA
11 values are shown. We observe that the proposed method yielded isocontours close to the
12 true isocontours at different considered TFA values. In addition, the method yielded
13 accurate segmentation for different tumor types, including those with substantial intra-
14 tumor heterogeneity as best observed in Fig. 4(b-d).
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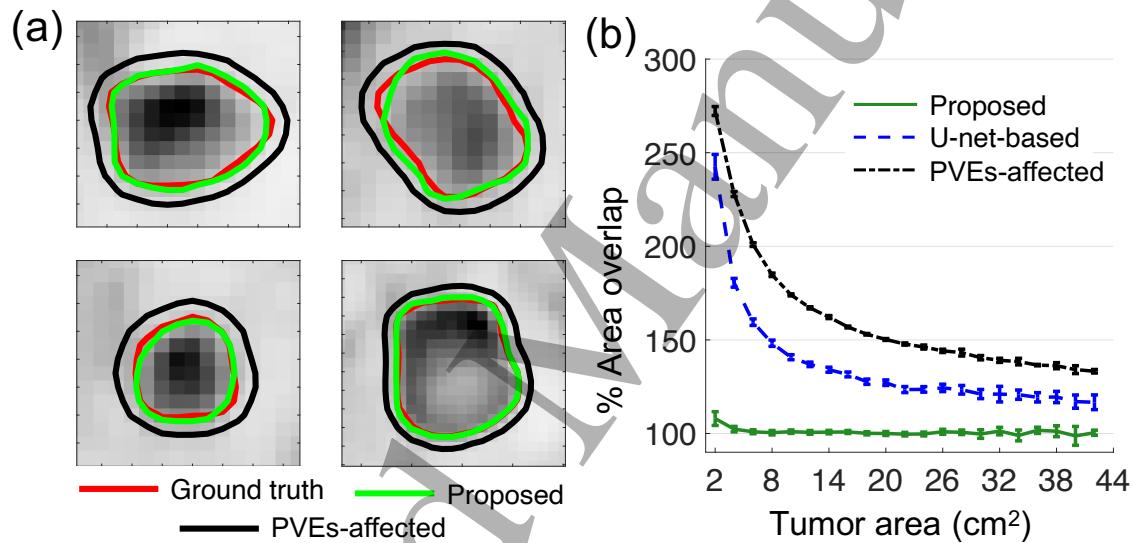


50 Figure 4: Evaluation result using clinically realistic simulation studies: comparison
51 between the estimated isocontours using the proposed method (green) and the ground-
52 truth isocontours (red), defined from set of points at four TFA values (0, 1/3, 2/3,
53 1).
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56 4.1.2. *Evaluating sensitivity of the proposed method to PVEs* Fig. 5 shows that the
57 method yielded percent area overlap close to 100% for all considered tumor sizes,
58 including small tumors with axial cross-section less than 2 cm². For these smaller
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2 *A Bayesian approach to tissue-fraction estimation for oncological PET segmentation* 15
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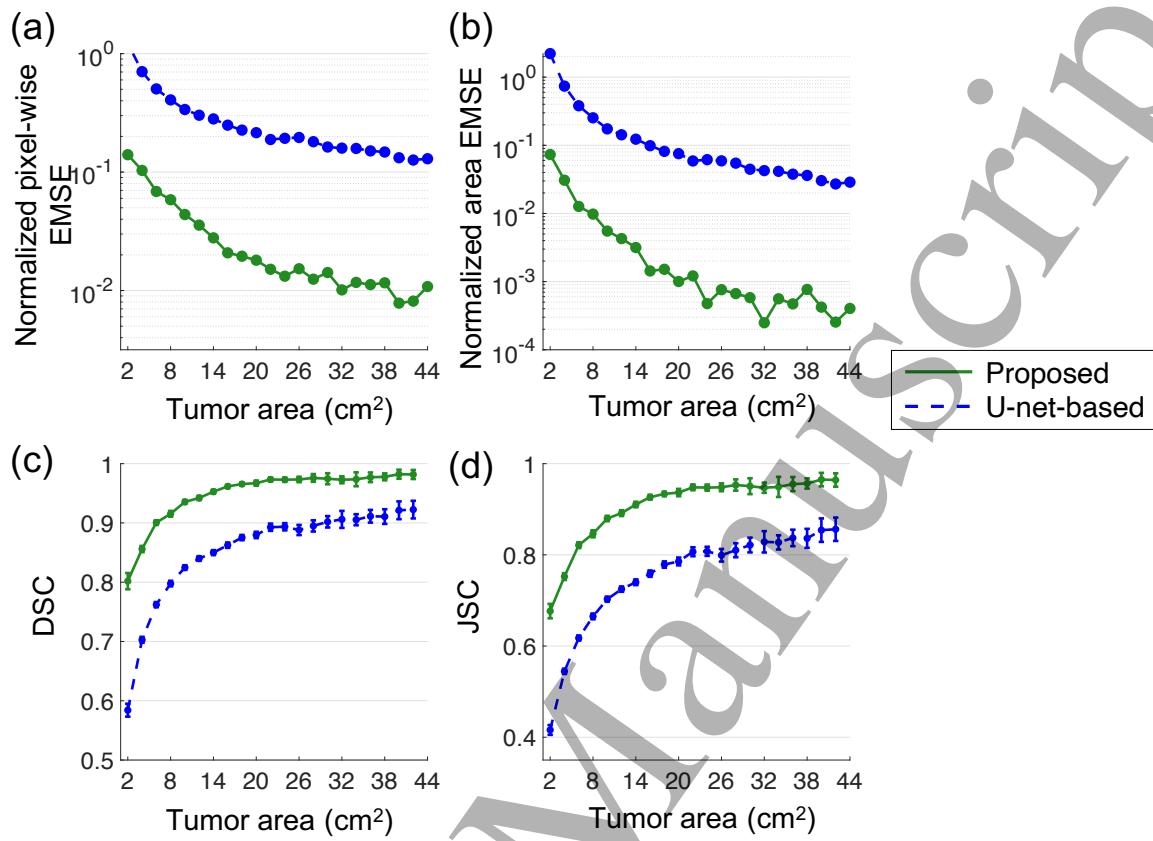
5 tumors, the diameter was approximately less than 3 times the FWHM of the system
6 resolution. This was unlike the PVEs-affected tumor areas, which, as expected, were
7 significantly overestimated for smaller tumors. In addition, the proposed method
8 yielded high DSC and JSC for these small tumors, indicating accurate segmentation
9 performance. Further, the proposed method significantly outperformed the U-net-based
10 method. Overall, these results demonstrate the relative insensitivity of the proposed
11 method to PVEs when segmenting relatively small tumors. Further, Fig. 6 shows
12 that the proposed method consistently yielded lower pixel-wise EMSE and lower area
13 EMSE normalized by the true tumor areas, compared to the U-net-based method. The
14 proposed method also yielded higher DSC and JSC for all tumor sizes.
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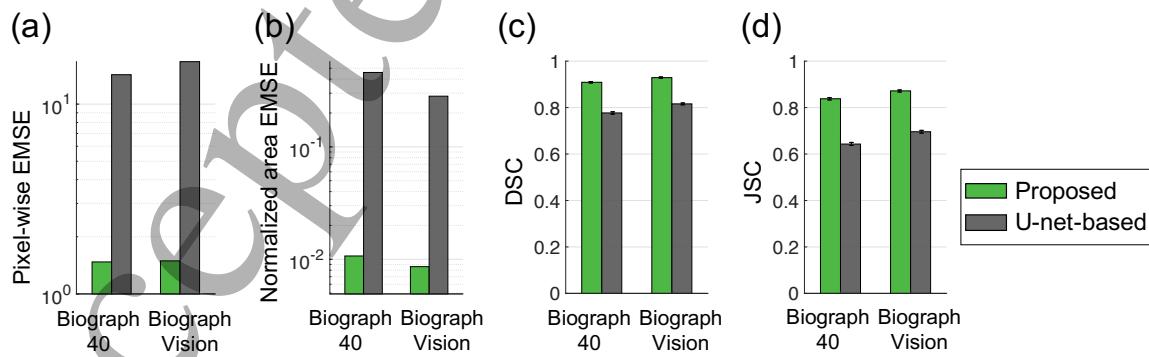
38 Figure 5: Evaluation result using clinically realistic simulation studies: (a) qualitative
39 comparison between the isocontours generated from the PVEs-affected TFA maps and
40 the isocontours generated from the estimated TFA maps using the proposed method.
41 The isocontours were defined as the set of points with TFA equal to 0.5. (b) quantitative
42 evaluation of the sensitivity of the proposed method to PVEs. Results obtained using
43 the U-net-based method are also shown.
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48 4.1.3. *Evaluating accuracy of the proposed method for different clinical-scanner*
49 *configurations* Fig. 7 shows the comparison of the segmentation accuracy between the
50 proposed and the U-net-based method for two different clinical-scanner configurations,
51 as described in Sec. 3.2.4. The proposed method significantly outperformed the U-net-
52 based method for both clinical settings, on the basis of pixel-wise EMSE, normalized
53 area EMSE, DSC, and JSC.
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34 Figure 6: Evaluation result using clinically realistic simulation studies: effects of varying
35 the tumor size on the task of (a) estimating the tumor-fraction areas, (b) estimating
36 the whole tumor areas, and (c-d) segmenting the tumor. Plots (a-b) are displayed in
37 log scale on y-axis for better visualization.
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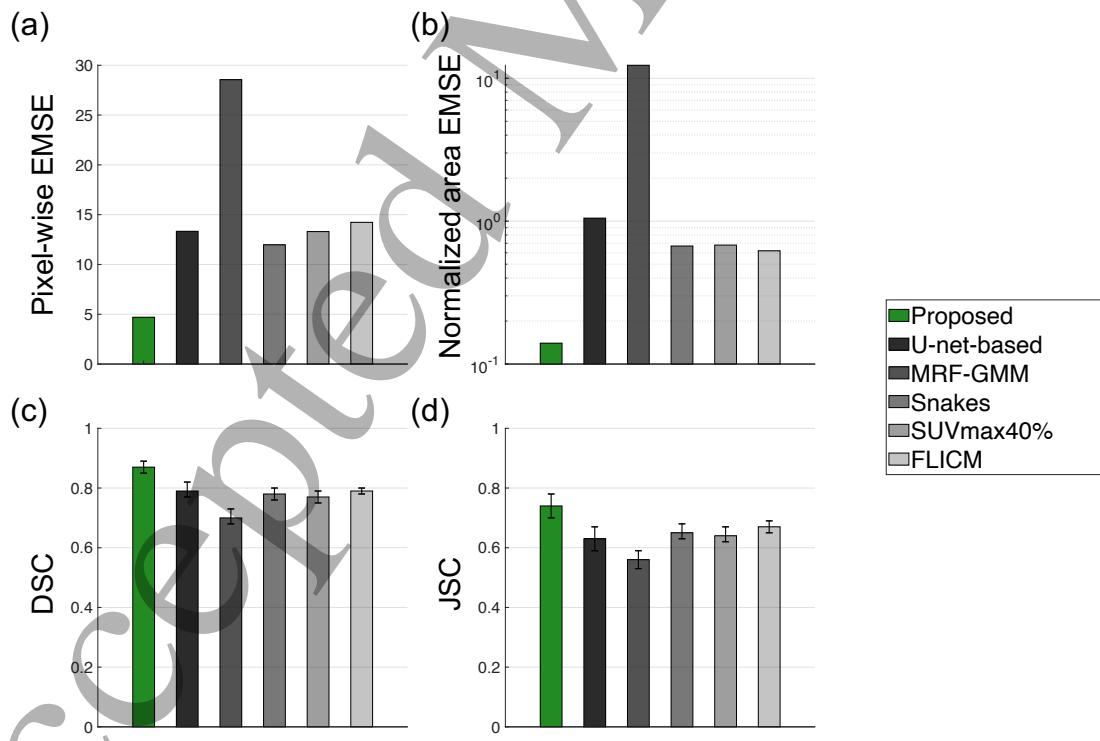
52
53 Figure 7: Evaluation result using clinically realistic simulation studies: evaluation of
54 the segmentation performance for different clinical-scanner configurations on the basis
55 of (a) pixel-wise EMSE, (b) normalized area EMSE, (c) Dice similarity coefficient, and
56 (d) Jaccard similarity coefficient.
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5 *4.2. Evaluation of the proposed method using clinical multi-center PET images*
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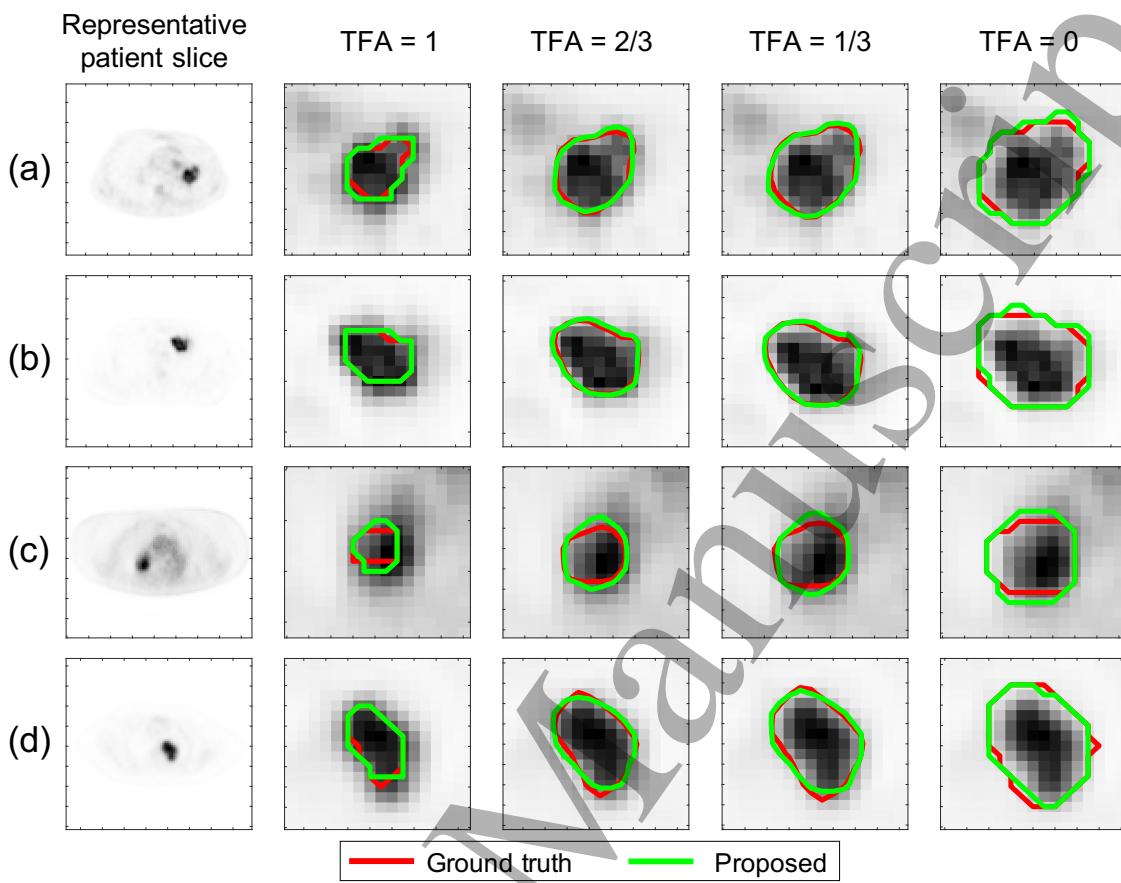
7 Quantitatively, the proposed method yielded reliable segmentation with DSC of 0.82
8 (95% CI: 0.78, 0.86). For 16 out of 17 test patients (94.2%), both the proposed and U-
9 net-based method yielded correct tumor localization in all 2-D slices. When considering
10 the patient cases with correct tumor localization, as shown in Fig. 8 (with details
11 provided in Table A6 in Appendix A), the proposed method significantly outperformed
12 ($p < 0.01$) all other considered methods, yielding the lowest pixel-wise EMSE, the
13 lowest normalized area EMSE of 0.14, the highest DSC of 0.87 (95% CI: 0.85, 0.89),
14 and the highest JSC of 0.74 (95% CI: 0.70, 0.78). In addition, the proposed method
15 accurately segmented relatively small tumors and yielded high DSC of 0.77 for the
16 smallest segmented tumor axial cross-section of 1.30 cm^2 in area.
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19 Qualitatively, we observe in Fig. 9 that the proposed method yielded an accurate
20 match to the true isocontours defined at different considered TFA levels, following the
21 strategy in Sec. 3.1.2 with illustration in Fig. 3. Further, Fig. 10 shows that the
22 method accurately segmented tumors with small sizes (a, e), tumors with convex shape
23 (b, f), tumors surrounded by regions with high uptake (c, d, g, h), and tumors with
24 substantial intra-tumor heterogeneity (b, d, f, h).
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53 Figure 8: Evaluation result using clinical multi-center PET images: (a) the pixel-wise
54 EMSE between the true and estimated tumor-fraction areas; (b) the normalized area
55 EMSE between the measured and true tumor areas (plot displayed in log scale on y-axis
56 for better visualization); the (c) Dice similarity coefficient and (d) Jaccard similarity
57 coefficient between the true and estimated segmentations.
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33 Figure 9: Evaluation result using clinical multi-center PET images: comparison between
34 the estimated isocontours using the proposed method (green) and the ground-truth
35 isocontours (red), defined as set of points at four TFA values (0, 1/3, 2/3, 1).
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40 **5. Discussion**
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43 In this manuscript, we proposed a Bayesian approach to tissue-fraction estimation for
44 segmentation in oncological PET. Conventional segmentation methods are typically
45 classification-based, i.e. classifying each voxel in the image as belonging to a certain
46 tissue class. Thus, these methods are inherently limited in modeling TFEs. While
47 probabilistic techniques can provide estimates of probabilities that each image voxel
48 belongs to a tissue class, these probabilistic estimates are unrelated to TFEs. We address
49 this inherent limitation by framing the segmentation task as an estimation problem,
50 where the fractional volume that the tumor occupies in each voxel is estimated. Through
51 this strategy, we are able to explicitly model the TFEs while performing segmentation.
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54 Quantitatively, the proposed method yielded accurate performance on estimation of
55 the ground-truth TFA maps and on segmentation tasks, and significantly outperformed
56 the considered segmentation methods, yielding the lowest pixel-wise EMSE and
57 normalized area EMSE, and the highest DSC and JSC, as evaluated using both
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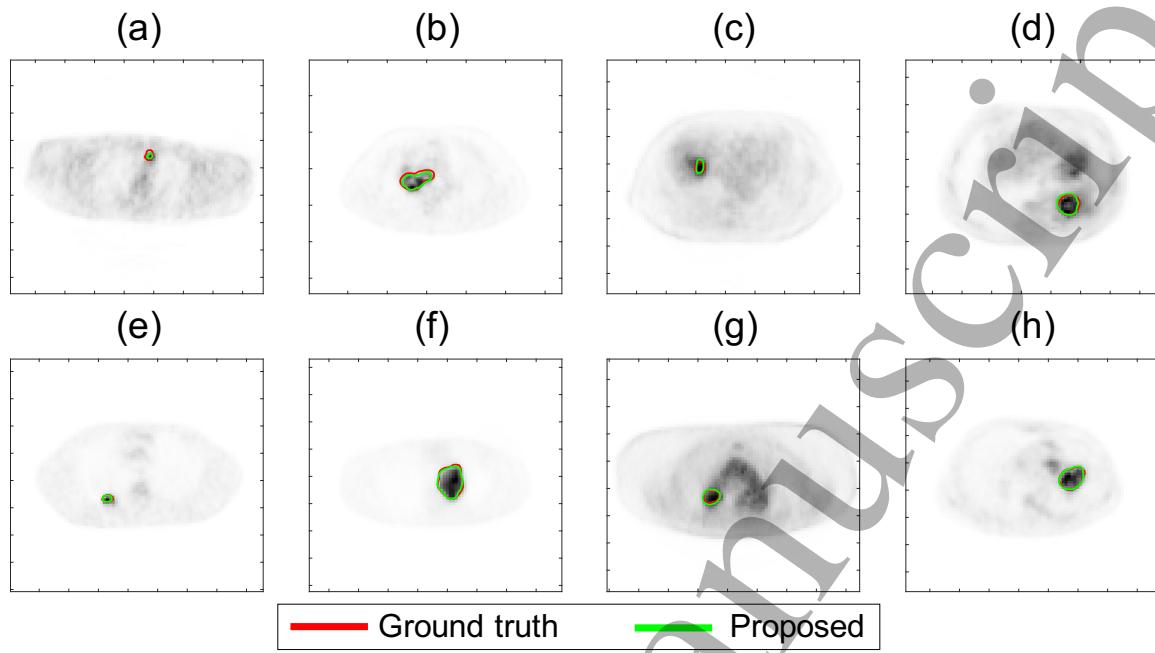


Figure 10: Evaluation result using clinical multi-center PET images: qualitative assessment of the performance of the proposed method in estimating the TFA maps for small tumors (a,e), for tumors with convex shape (b,f), for tumors surrounded by regions with high uptake (c-h), and for tumors with substantial intra-tumor heterogeneity (b,d,f,h). Isocontours were defined as set of points at TFA = 0.5.

clinically realistic simulation studies (Fig. 2) and clinical images from multi-center trial data (Fig. 8). With clinical images, the method yielded a DSC of 0.82 (95% CI: 0.78, 0.86). Qualitatively, the method yielded isocontours of close match to the ground-truth isocontours defined at different considered TFA values, as we observe from the results in Fig. 4 and Fig. 9. Additionally, as shown in Fig. 3 for a representative tumor with substantial intra-tumor heterogeneity, the proposed method correctly estimates the TFA value as unity for pixels that are within the tumor boundary but have relatively low intensity. This observation was consistent across different heterogeneous tumors, showing the reliable performance of the proposed method even with heterogeneous tumors. We believe that the method is reliable in this scenario because the method estimates the TFA by computing the conditional expectation of the TFA in that pixel given the entire reconstructed PET image, and not just the intensity of that pixel (Eq. (11)). All these results demonstrate the ability of the method to accurately estimate the TFA within each image pixel and yield accurate tumor segmentations.

The isocontours defined based on certain choices of TFA values were shown only to visually illustrate the performance of the proposed method on the task of estimating the TFA map. The proposed method yields the estimated TFA map as the final output. This allows the method to provide the end user, such as a physician or a radiation oncologist, the ability to visualize the TFAs within each PET-image pixel, which they

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2 *A Bayesian approach to tissue-fraction estimation for oncological PET segmentation* 20
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4 can use to make a decision based on their clinical use-case scenario.

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6 Further, the proposed method demonstrated the ability to accurately segment
7 relatively small tumors. In realistic simulation-based evaluation studies, the method
8 yielded a high DSC of 0.84 for the smallest segmented tumor, with an axial cross-section
9 of 0.88 cm^2 and a diameter approximately twice the FWHM of the system resolution.
10 With clinical images, for the smallest tumor axial cross-section of 1.30 cm^2 , the method
11 yielded a DSC of 0.77. This accuracy in segmenting small tumors is especially important
12 for clinical tasks such as radiotherapy planning, where an accurate segmentation for
13 small tumors is crucial to protect normal organs from radiations.
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16 While the U-net-based method had demonstrated the ability to account for PVEs
17 arising due to the low system resolution (Leung et al., 2020), the proposed method
18 significantly outperformed this method, emphasizing the significance of modeling the
19 TFEs in PET segmentation. This need to model TFEs was also demonstrated in the
20 results of evaluation using clinically realistic simulation studies, where the performance
21 of the method was assessed for different clinical-scanner configurations (Sec. 4.1.3). For
22 example, for the higher-resolution Biograph Vision scanner, the TFEs may be more
23 dominant compared to system-resolution-related blur. We observed in Fig. 7 that the
24 proposed method was more accurate compared to the U-net-based method for this
25 scanner. Further, for both clinical-scanner configurations, the proposed method yielded
26 similar performance in estimating the TFAs and segmenting the tumor, indicating that
27 the method was relatively insensitive to the changes in voxel size.
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30 Our evaluation of the proposed method with clinical images of patients with stage
31 IIB/III NSCLC shows that the method, when trained with 61 patients, yielded a reliable
32 segmentation performance with DSC of 0.82. When considering patient cases where the
33 tumor was localized correctly by the method (94.2%), the DSC further improved to 0.87.
34 These results demonstrate the accuracy of the method in clinical settings and motivate
35 further clinical evaluation of the method with even larger datasets and with delineations
36 defined by multiple readers. Further, the method is general, and the results motivate
37 the evaluation of the method for segmenting tumors other than the primary tumors,
38 including infiltrating tumors, and segmenting tumors at other stages of the disease,
39 including metastasis. In all these cases, the method would require the corresponding
40 definition of the ground-truth TFAs, or a surrogate for the ground truth, such as those
41 from manual delineations performed by trained readers.
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44 The results obtained with the proposed method also motivate further evaluation of
45 this method for PET-based clinical applications that require tumor delineation such as
46 PET-based radiotherapy planning (El Naqa et al., 2009, Zaidi et al., 2009). Further,
47 the results motivate evaluation of this method for the applications of computing PET-
48 based volumetric markers of metabolic tumor volume (MTV) and total lesion glycolysis
49 (Ohri et al., 2015, Chen et al., 2012), and radiomic features (Cook et al., 2018, Zhang
50 et al., 2017, Mena et al., 2017), each of which are being evaluated as prognostic and
51 predictive markers of therapy response. Such evaluation can be performed using task-
52 specific evaluation frameworks (Kupinski et al., 2006, Jha et al., 2012, 2017, Barrett
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5 et al., 2010). In this context, our initial results in both clinically realistic simulation
6 (Fig. 2(b)) and patient studies (Fig. 8(b)) on estimating the tumor area indicate the
7 promise of the proposed method on the task of quantifying MTV more accurately than
8 conventional methods.
9

10 Our study has some limitations. First, while the theory of the proposed method was
11 developed in the context of 3-D imaging, our evaluation studies were conducted on a per-
12 slice basis. This helped to increase the size of training data and was computationally less
13 expensive (Leung et al., 2020). However, implementing the method to 3-D segmentation
14 is relatively straightforward and would require only slight modifications to our network
15 architecture, such as the ability to be input 3-D images and output 3-D tumor-fraction
16 volume maps. Thus, the 2-D convolutional layers in the network would be replaced by
17 3-D convolutional layers. The overall network design would remain similar. In fact,
18 in the ongoing study on using an extended version of this method for segmenting 3-D
19 single-photon emission computed tomography (SPECT) images, we have seen that a
20 similar design was sufficient to perform 3-D segmentation (Moon et al., 2020, Liu et al.,
21 2021b). The results shown here and in the SPECT study suggest that the proposed
22 method will yield reliable performance for 3-D tumor segmentation in PET, and this is
23 an area of further research. Additionally, in this study, the proposed method was used
24 to segment the image into only two regions. However, the method is general, and in the
25 ongoing study of 3-D SPECT segmentation, we are applying this method to segment
26 the images into seven different regions. Another limitation is that our evaluation studies
27 currently consider cases where only the primary tumor is present in an image. However,
28 again, the method could be generalized to potentially segment multiple tumors present
29 in the same image slice. Confirming this though would require additional evaluation
30 studies. Further, respiratory motion of the lung, which may also cause blurring of
31 the tumor mask, was not considered in the proposed method. Extending the method
32 to account for lung motion is also an important research area. Finally, the method
33 does not incorporate tumor information from CT images while segmenting PET images.
34 Incorporating information from CT images can provide a prior distribution of the tumor-
35 fraction areas for the estimation task. Thus, investigating the incorporation of CT
36 images into the proposed method is another important research direction.
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38 We evaluated our method in the context of segmenting oncological PET images of
39 patients with lung cancer and demonstrated accurate tumor segmentation performance.
40 The method is general and thus, these results motivate the evaluation of the method
41 for other cancer types. However, segmenting tumors in the lung region could be easier
42 due to the scarce FDG uptake in the lung. In other cancer types, tumor-to-background
43 intensity ratios may be lower, which may make the segmentation task challenging. For
44 example, renal tumors often have similar FDG uptake as the normal renal cortex.
45 Further, there may be situations where the FDG uptake in tumor is lower than the
46 background, such as photon-deficient tumors on the liver. Thus, before application
47 to other cancers, corresponding validation studies would be needed. Additionally, the
48 method can be extended to segment PET images for other applications, such as those
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in cardiology and neurology. Further, the method can be extended to segment images from other imaging modalities that have low resolution, such as SPECT and optical imaging, with ongoing efforts in SPECT (Moon et al., 2020, Liu et al., 2021b).

10 **6. Conclusion**
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In this manuscript, we proposed a Bayesian approach to tissue-fraction estimation for oncological PET segmentation. We theoretically demonstrated that the proposed method yields a posterior-mean estimate of the tumor-fraction volume for each voxel in the PET image. Evaluation of the method using clinically realistic 2-D simulation studies demonstrated the capability of the method to explicitly model TFEs by accurately estimating the tumor-fraction areas. The method significantly outperformed the considered commonly used PET segmentation methods, including a U-net-based method. In addition, the method was relatively insensitive to partial-volume effects and demonstrated accurate segmentation performance for different clinical-scanner configurations. Further, the proposed method demonstrated accurate performance in segmenting clinical images of patients with stage IIB/III NSCLC, obtained from the ACRIN 6668/RTOG 0235 multi-center clinical trial data. For this dataset, the method yielded DSC of 0.82 (95% CI: 0.78, 0.86). In conclusion, this study demonstrates the efficacy of the proposed method for tumor segmentation in PET. Pending necessary permissions, we will publish the source code for the proposed method for wider usage by the image-science community (source code currently available at https://drive.google.com/drive/folders/1Kk0LvnSUccz6zkYoKJgX73Wd9pvUTJm_?usp=sharing).

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36 **Acknowledgments**
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5 **Appendix A.**
67 The architecture of the encoder-decoder network designed for the proposed method is
8 provided in Table A1.
910 Details of the simulated PET systems used in the evaluation of proposed method
11 for different clinical-scanner configurations are given in Table A2.
1213 Patient demographics with clinical characteristics and reconstruction parameters of
14 clinical scanners in the ACRIN 6668/RTOG 0235 multi-center clinical trial are provided
15 in Table A3 and Table A4, respectively.
1617 Evaluation results of the proposed method using clinically realistic simulation
18 studies and clinical images from multi-center clinical trial are given in Table A5 and
19 Table A6, respectively.
2021 **Table A1: Architecture of the encoder-decoder network.**
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	Layer Type	Filter Size	# of Filters	Stride	Input Size	Output Size
Layer 1	Conv.	3×3	32	1×1	$168 \times 168 \times 1$	$168 \times 168 \times 32$
Layer 2	Conv.	3×3	32	2×2	$168 \times 168 \times 32$	$84 \times 84 \times 32$
Layer 3	Conv.	3×3	64	1×1	$84 \times 84 \times 32$	$84 \times 84 \times 64$
Layer 4	Conv.	3×3	64	2×2	$84 \times 84 \times 64$	$42 \times 42 \times 64$
Layer 5	Conv.	3×3	128	1×1	$42 \times 42 \times 64$	$42 \times 42 \times 128$
Layer 6	Conv.	3×3	128	2×2	$42 \times 42 \times 128$	$21 \times 21 \times 128$
Layer 7	Conv.	3×3	256	1×1	$21 \times 21 \times 128$	$21 \times 21 \times 256$
Layer 8	Conv.	3×3	256	1×1	$21 \times 21 \times 256$	$21 \times 21 \times 256$
Layer 9	Transposed Conv.	3×3	128	2×2	$21 \times 21 \times 256$	$42 \times 42 \times 128$
Layer 9	Skip Connection (Add Layer 5)	-	-	-	$42 \times 42 \times 128$	$42 \times 42 \times 128$
Layer 10	Conv.	3×3	128	1×1	$42 \times 42 \times 128$	$42 \times 42 \times 128$
Layer 11	Transposed Conv.	3×3	64	2×2	$42 \times 42 \times 128$	$84 \times 84 \times 64$
Layer 11	Skip Connection (Add Layer 3)	-	-	-	$84 \times 84 \times 64$	$84 \times 84 \times 64$
Layer 12	Conv.	3×3	64	1×1	$84 \times 84 \times 64$	$84 \times 84 \times 64$
Layer 13	Transposed Conv.	3×3	32	2×2	$84 \times 84 \times 64$	$168 \times 168 \times 32$
Layer 13	Skip Connection (Add Layer 1)	-	-	-	$168 \times 168 \times 32$	$168 \times 168 \times 32$
Layer 14	Conv.	3×3	32	1×1	$168 \times 168 \times 32$	$168 \times 168 \times 32$
Layer 15	Conv.	3×3	2	1×1	$168 \times 168 \times 32$	$168 \times 168 \times 2$
Output	Softmax	-	-	-	$168 \times 168 \times 2$	$168 \times 168 \times 2$

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5 Table A2: Technical acquisition and reconstruction parameters of the PET systems
6 (FOV: field of view).
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Parameters	Biograph 40	Biograph Vision
Transaxial FOV (mm)	550	700
Axial FOV (mm)	216	260
Reconstruction method	OSEM	OSEM
Subsets	21	21
Iterations	2	2
Crystal pitch (mm)	4.00	3.30
FWHM (mm) @ 1 cm	5.90	3.70
Voxel size (mm ³)	4.30 × 4.30 × 4.25	3.65 × 3.65 × 3.27

32 Table A3: Patient demographics with clinical characteristics.
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Demographics / clinical characteristics	Value	Percent
Age: median (range)	67.5 (37 - 82)	-
Sex		
	Male	63% (49/78)
	Female	37% (29/78)
Race		
	White	90% (70/78)
	African American	5% (4/78)
	Asian	2.5% (2/78)
	Other/unknown	2.5% (2/78)
Performance status		
	Fully active	41% (32/78)
	Ambulatory	59% (46/78)
Clinical stage		
	IIB	5% (4/78)
	IIIA	55% (43/78)
	IIIB	40% (30/78)
Chemotherapy regimen		
	Carboplatin/paclitaxel	60% (47/78)
	Cisplatin/etoposide	27% (21/78)
	Other	12% (9/78)
	Not available	1% (1/78)
Radiation dose		
	< 50 Gy	1% (1/78)
	50-60 Gy	8% (6/78)
	60-70 Gy	58% (45/78)
	≥70 Gy	27% (21/78)
	Not available	6% (5/78)

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Table A4: Reconstruction parameters of PET/CT systems used in ACRIN
6668/RTOG 0235 multi-center clinical trial. (DLYD: delayed event subtraction; SING:
singles-based correction; N/A: not available)

Parameter	GE Discovery ST	GE Discovery STE	GE Discovery RX	CPS 1023	CPS 1024
Reconstruction method	OSEM	OSEM	OSEM	OSEM	OSEM
Subsets	N/A	N/A	N/A	8	8
Iterations	N/A	N/A	N/A	2	2
Attenuation correction	CT	CT	CT	CT	CT
Scatter correction	Convolution subtraction	Convolution subtraction	Convolution subtraction	Model-based	Model-based
Randoms correction	DLYD/SING	SING	SING	DLYD	DLYD
Pixel spacing (mm)	4.69×4.69 5.47×5.47	5.47×5.47	5.47×5.47	5.31×5.31	5.31×5.31
Slice thickness (mm)	3.27	3.27	3.27	2.50	3.38

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Table A5: Evaluation result using clinically realistic simulation studies: performance comparison between the proposed method and other considered segmentation methods.

Metrics	Proposed	U-net-based	MRF-GMM	Snakes	40% SUV _{max}	FLICM
Pixel-wise EMSE	2.04	17.00	25.64	43.63	27.13	30.26
Normalized area EMSE	0.02	0.49	4.07	8.55	1.34	1.78
DSC	0.90 (0.90,0.91)	0.77 (0.77,0.78)	0.73 (0.72,0.74)	0.65 (0.64,0.66)	0.64 (0.63,0.65)	0.61 (0.60,0.62)
JSC	0.83 (0.83,0.84)	0.64 (0.64,0.65)	0.60 (0.59,0.60)	0.51 (0.50,0.52)	0.50 (0.49,0.51)	0.48 (0.47,0.49)

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Table A6: Evaluation result using clinical multi-center PET images: performance comparison between the proposed method and other considered segmentation methods on the basis of quantitative figures of merit. Results here are reported for patient cases with correct tumor localization (94.2%).

Metrics	Proposed	U-net-based	MRF-GMM	Snakes	40% SUV _{max}	FLICM
Pixel-wise EMSE	4.70	13.33	28.55	13.30	14.23	11.97
Normalized area EMSE	0.14	1.05	12.33	0.68	0.62	0.67
DSC	0.87 (0.85,0.89)	0.79 (0.77,0.82)	0.70 (0.68,0.73)	0.78 (0.76,0.80)	0.77 (0.75,0.79)	0.79 (0.78,0.80)
JSC	0.74 (0.70,0.78)	0.63 (0.59,0.67)	0.56 (0.53,0.59)	0.65 (0.63,0.68)	0.64 (0.62,0.67)	0.67 (0.65,0.69)

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4 Appendix B.
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8 In this appendix, we provide the proof of showing that the optimal estimator minimizing
9 the cost function in Eq. (8) is unbiased in a Bayesian sense. To show this, we take the
10 average of the estimate $\hat{\mathbf{v}}^*$ over the joint distribution of noise realizations $\hat{\mathbf{f}}$ and true
11 values \mathbf{v} :
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$$\begin{aligned}\overline{\overline{\hat{\mathbf{v}}^*}} &= \int d^M \mathbf{v} \int d^M \hat{\mathbf{f}} \text{pr}(\hat{\mathbf{f}}, \mathbf{v}) \hat{\mathbf{v}}^* \\&= \int d^M \mathbf{v} \text{pr}(\mathbf{v}) \int d^M \hat{\mathbf{f}} \text{pr}(\hat{\mathbf{f}}|\mathbf{v}) \hat{\mathbf{v}}^* \\&= \int d^M \mathbf{v} \text{pr}(\mathbf{v}) \int d^M \hat{\mathbf{f}} \text{pr}(\hat{\mathbf{f}}|\mathbf{v}) \int d^M \mathbf{v}' \text{pr}(\mathbf{v}'|\hat{\mathbf{f}}) \mathbf{v}',\end{aligned}\quad (B1)$$

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21 where in the second step we have expanded $\text{pr}(\hat{\mathbf{f}}, \mathbf{v})$ using the conditional probability,
22 and in the third step we have inserted Eq. (12). By using the Bayes' theorem and
23 changing the order of integration, the above equation becomes
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$$\overline{\overline{\hat{\mathbf{v}}^*}} = \int d^M \hat{\mathbf{f}} \text{pr}(\hat{\mathbf{f}}) \int d^M \mathbf{v}' \text{pr}(\mathbf{v}'|\hat{\mathbf{f}}) \mathbf{v}' \int d^M \mathbf{v} \text{pr}(\mathbf{v}|\hat{\mathbf{f}}).\quad (B2)$$

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29 Since $\int d^M \mathbf{v} \text{pr}(\mathbf{v}|\hat{\mathbf{f}}) = 1$, Eq. (B2) becomes
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$$\overline{\overline{\hat{\mathbf{v}}^*}} = \int d^M \hat{\mathbf{f}} \text{pr}(\hat{\mathbf{f}}) \int d^M \mathbf{v}' \text{pr}(\mathbf{v}'|\hat{\mathbf{f}}) \mathbf{v}'.\quad (B3)$$

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35 Further, we can simplify the above equation using the law of total expectation and get
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$$\overline{\overline{\hat{\mathbf{v}}^*}} = \int d^M \mathbf{v}' \text{pr}(\mathbf{v}') \mathbf{v}' = \bar{\mathbf{v}}.\quad (B4)$$

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40 Thus, the average value of the estimate is equal to the average true value, so that the
41 estimator is unbiased in a Bayesian sense.
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