



# Automatic Lung Cancer Segmentation in [<sup>18</sup>F]FDG PET/CT Using a Two-Stage Deep Learning Approach

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## Abstract

**Purpose** Since accurate lung cancer segmentation is required to determine the functional volume of a tumor in [<sup>18</sup>F]FDG PET/CT, we propose a two-stage U-Net architecture to enhance the performance of lung cancer segmentation using [<sup>18</sup>F]FDG PET/CT.

**Methods** The whole-body [<sup>18</sup>F]FDG PET/CT scan data of 887 patients with lung cancer were retrospectively used for network training and evaluation. The ground-truth tumor volume of interest was drawn using the LifeX software. The dataset was randomly partitioned into training, validation, and test sets. Among the 887 PET/CT and VOI datasets, 730 were used to train the proposed models, 81 were used as the validation set, and the remaining 76 were used to evaluate the model. In Stage 1, the global U-net receives 3D PET/CT volume as input and extracts the preliminary tumor area, generating a 3D binary volume as output. In Stage 2, the regional U-net receives eight consecutive PET/CT slices around the slice selected by the Global U-net in Stage 1 and generates a 2D binary image as the output.

**Results** The proposed two-stage U-Net architecture outperformed the conventional one-stage 3D U-Net in primary lung cancer segmentation. The two-stage U-Net model successfully predicted the detailed margin of the tumors, which was determined by manually drawing spherical VOIs and applying an adaptive threshold. Quantitative analysis using the Dice similarity coefficient confirmed the advantages of the two-stage U-Net.

**Conclusion** The proposed method will be useful for reducing the time and effort required for accurate lung cancer segmentation in [<sup>18</sup>F]FDG PET/CT.

**Keywords** Lung cancer · Deep learning · Segmentation · PET/CT

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## Introduction

Lung cancer is one of the most common types of cancers and is the leading cause of cancer-related deaths in the USA [1] as well as other countries. Optimal and personalized management of lung cancer depends on the histological subtype, molecular characteristics, and tumor stage [2]. [<sup>18</sup>F]fluorodeoxyglucose ([<sup>18</sup>F]FDG) positron emission tomography/computed tomography (PET/CT), which allows visualization of the molecular features and anatomical abnormalities of the target lesion, is considered as an essential medical examination for lung cancer diagnosis and staging. Therefore, many guidelines recommend the use of [<sup>18</sup>F]FDG PET/CT for the evaluation of patients suffering from lung cancer [3–5].

Recently, deep learning algorithms have been actively applied to various tasks in medical image processing

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and analysis, including lesion and organ detection, segmentation, and image restoration [6–15]. Furthermore, attempts have been made to apply machine learning algorithms to [ $^{18}\text{F}$ ]FDG PET/CT analysis for lung cancer. In particular, various studies have been conducted to improve lesion detectability and predict the characteristics of the lesions [16–19]. Furthermore, accurate tumor segmentation is required to determine the functional volume of tumors in PET/CT [20]. However, studies related to improving the accuracy of tumor segmentation are limited [21].

U-Net [22] is one of the most widely used deep learning networks for medical image segmentation [23–26]. The deeply supervised encoder–decoder network, which crops and copies feature maps from the encoding units to the decoding units, processes the entire image in the forward pass to directly generate the segmentation maps [27, 28]. The two-dimensional (2D) U-Net, which converts 2D image slices into 2D slices, is simple and fast, but occasionally introduces discontinuity artifacts while stacking 2D network outputs to generate three-dimensional (3D) volume [29]. The discontinuity artifacts can be mitigated by employing 3D U-Nets [30]. However, they are computationally expensive and require a considerable computer memory. Therefore, the limited computation resources, which are generally used to process the large 3D datasets, would lead to suboptimal network architecture and training.

Therefore, in this study, we propose a two-stage U-Net architecture to enhance the lung cancer segmentation performance in FDG PET/CT. In this method, a global 3D U-Net that may be suboptimal for the given task is applied to select the candidate lung cancer regions, and 2.5D U-Net, which is a compromise between the 2D and 3D U-Nets and employs a multislice input, is applied for the final lung cancer segmentation. In the following sections, the details of the two-stage U-Net architecture and its training and testing methods are described.

## Materials and Methods

### Datasets

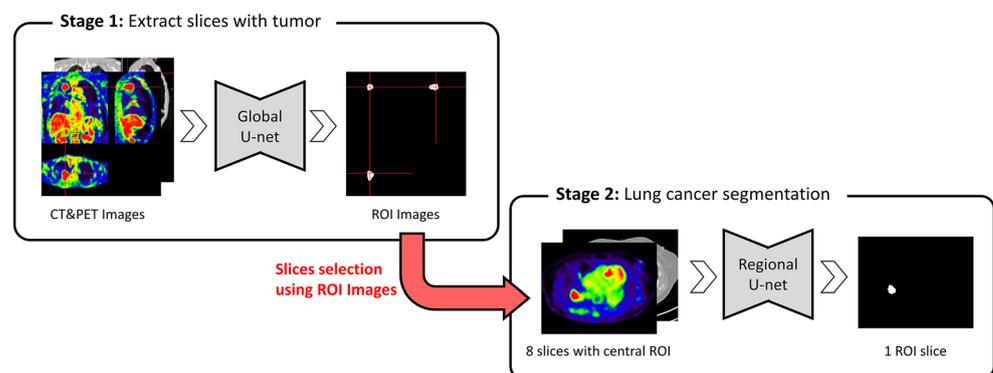
The whole-body [ $^{18}\text{F}$ ]FDG PET/CT scan data of 887 patients with lung cancer were retrospectively used for network training and evaluation. The retrospective use of the scan data and waiver of consent were approved by the institutional review board of our institution. The patients fasted for at least 6 h prior to image acquisition, resulting in blood glucose levels that were  $< 140$  mg/dL. [ $^{18}\text{F}$ ]FDG (5.18 MBq/kg) was injected intravenously into the patients, and PET scans were performed 60 min post injection using Biograph mCT40 or mCT64 PET/CT scanners (Siemens Healthineers, Knoxville, TN). The PET scan data were obtained from the base of the skull to the proximal thigh, followed by a CT scan obtained for attenuation correction and anatomical localization. PET images were reconstructed using an iterative algorithm (ordered-subset expectation maximization, iteration number 2 and 21 subsets) with an image matrix size of  $200 \times 200 \times \sim 200$  and voxel size of  $2.43 \times 2.43 \times 4.95$  mm $^3$ . The size of the reconstructed CT images was  $512 \times 512 \times \sim 490$  ( $0.98 \times 0.98 \times 2.0$  mm $^3$ ).

Ground-truth tumor volume-of-interests (VOIs) were drawn semi-automatically [31] using the LifeX software (<https://www.lifexsoft.org/>, version 4.0) [32]. Spherical VOIs were manually drawn on the PET images to include the primary tumor lesions; the metabolically active tumor regions in the spherical VOI were segmented by applying an adaptive threshold depending on the tumor and background intensities [33].

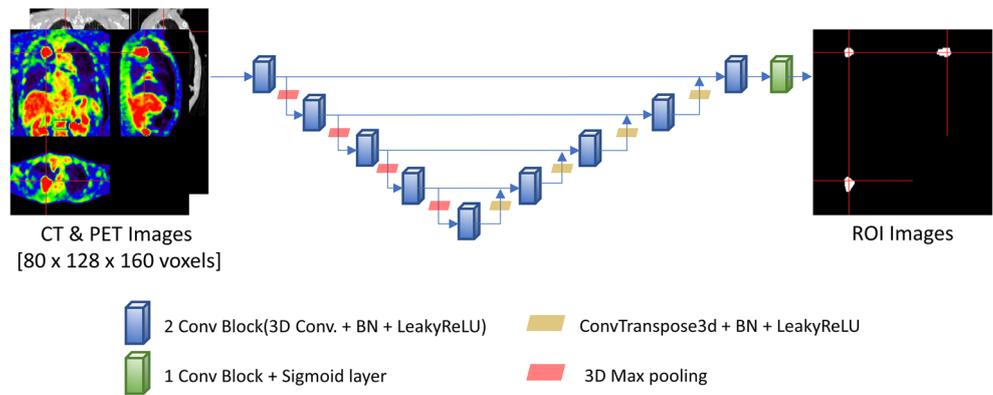
The dataset was randomly partitioned into training, validation, and test sets. Among the 887 PET/CT and VOI datasets, 730 were used to train the proposed models, 81 were used as the validation set, and the remaining 76 were used to evaluate the model.

Prior to network training and evaluation, the image size was adjusted because the voxel sizes and dimensions of the

**Fig. 1** Two-stage U-Net architecture



**Fig. 2** Global 3D U-Net in Stage 1



PET and CT images were different. Because the VOIs for the primary tumor were segmented from the PET images, the images and voxel sizes of the CT images matched well with those of the PET images using trilinear interpolation.

**Model Architecture**

As described earlier, we designed a two-stage U-Net architecture to enhance the tumor segmentation performance (Fig. 1). In Stage 1, a global U-Net receives 3D PET/CT volume as the input and extracts the preliminary tumor area, thus generating a 3D binary volume as the output. In Stage 2, a regional U-Net receives eight consecutive PET/CT slices around the slice selected by the Global U-net in Stage 1 and generates a 2D binary image as the output.

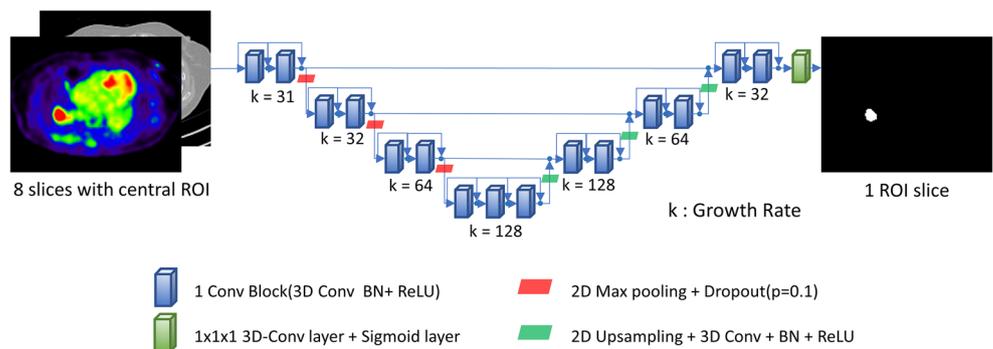
Figure 2 shows the detailed structure of the global U-Net used in Stage 1. We designed the detailed structure of Global U-Net based on a 3D U-Net [30] that demonstrated good performance in our previous works [23, 24, 34–36]. Rather than using the classification model, a segmentation model was used in stage 1. If a slice is included in the 3D tumor volume that Global U-Net produces, the index of slice is passed onto Stage 2, where the regional U-Net that will be described in the next section was applied for the final lung cancer segmentation.

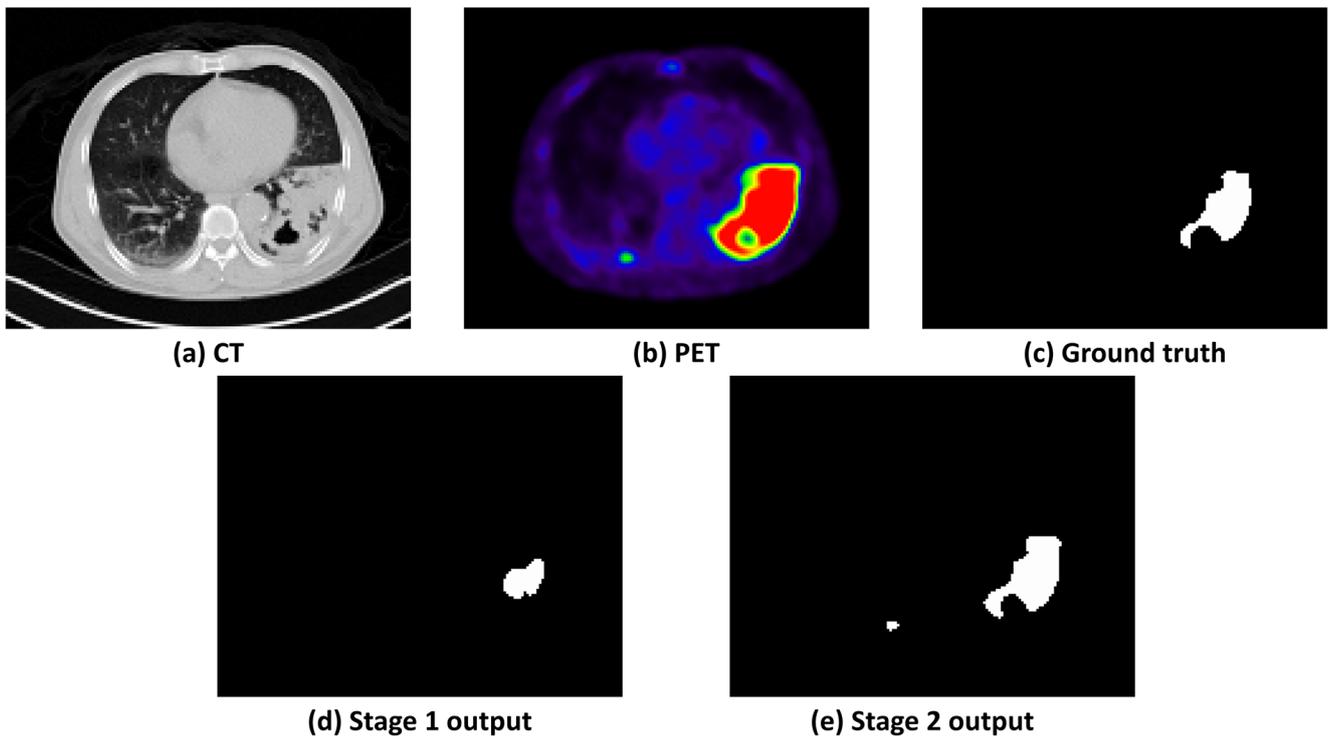
To reduce the learning time and memory consumption, the PET/CT images were cropped to have dimensions of  $80 \times 128 \times 160$  with a focus on the lungs. The initial convolution block comprised six channels, thus providing twice the number of channels for each down-sampling. The contracting path comprised two convolutional blocks. Each convolution block comprised  $3 \times 3 \times 3$  convolution layers, with batch normalization and leakyReLU with a negative slope of 0.2 as an activation function. In addition, a  $2 \times 2 \times 2$  max pooling operation with stride 2 was used for down-sampling. In the extracting path, the number of channels was reduced by 1/3 after concatenation.

Figure 3 shows the detailed structure of the regional U-Net used in Stage 2. The regional U-net receives eight consecutive slices centered on the slice predicted to have lung cancer in stage 1. Compared to the Global U-Net of Stage 1, the input size of the regional U-Net of Stage 2 is small. Therefore, in Stage 2, we designed a more sophisticated and complex network model, i.e., U-net, based on DenseNET [37].

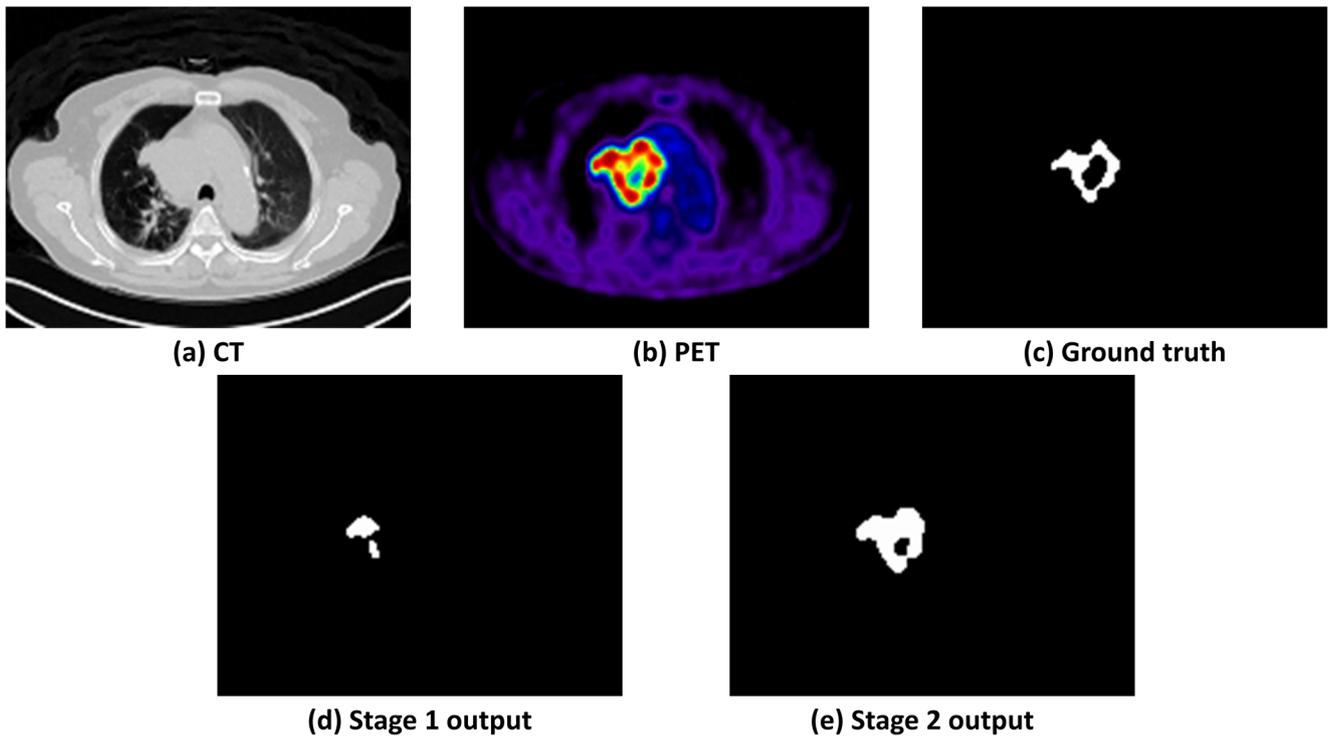
We used  $2 \times 2$  max pooling with stride 2 for down-sampling to preserve the features between slices and dropout layers of 0.1 to prevent overfitting. The bridge section connecting the contracting and expansion paths comprised three convolution blocks to supplement a small retractive field of a  $3 \times 3 \times 3$  convolution layer. After 2D up-sampling, a  $3 \times 3 \times 3$  convolution layer reduces the number of channels that are equal to the number of channels being skipped.

**Fig. 3** Reginal 2.5D U-Net in Stage 2





**Fig. 4** A case of a 66-year-old male patient with lung cancer. (a) CT, (b) PET, (c) Ground truth, (d) Stage 1 output, and (e) Stage 2 output



**Fig. 5** A case of a 77-year-old male patient with r/o lung cancer. (a) CT, (b) PET, (c) Ground truth, (d) Stage 1 output, and (e) Stage 2 output

**Table 1** Performance comparison between Stage 1 and Stage 2 U-Net approaches

Method	Mean Dice coefficient	Median Dice coefficient
1-Stage: Global U-Net only	0.74	0.86
2-Stage: Global + Regional U-Nets	0.78	0.90

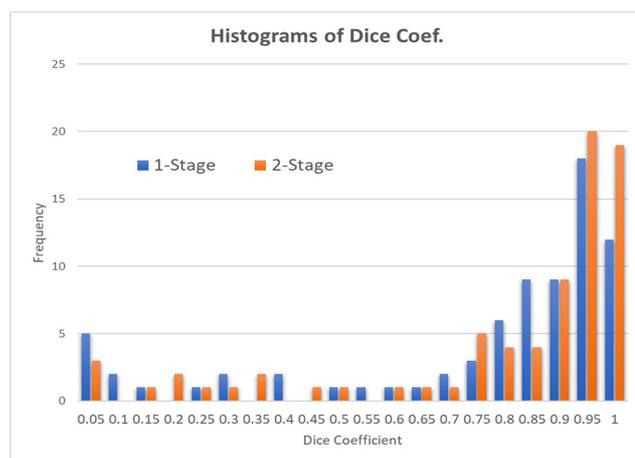
## Network Training and Evaluation

As a loss function for network training and performance indicator for network evaluation, we used the Dice similarity coefficient, which indicates the degree of overlap between the ground-truth and tumor regions segmented by deep neural networks.

Each model learns end-to-end mapping between the PET/CT images and VOI segmented by nuclear medicine physicians. Each layer was updated using error back-propagation with an adaptive moment estimation optimizer (ADAM), which is a stochastic optimization technique [38]. The exponential decay rates for the moment estimates  $\beta_1$  and  $\beta_2$  are 0.9 and 0.999, respectively, with  $\varepsilon = 10^{-8}$ .

The initial learning rate of the global U-Net was 0.1 and batch size was 6. The number of epochs was 45, and the learning rate was reduced by 0.1 times at 25 and 35 epochs. After the last sigmoid layer, we set the threshold to 0.6, which causes the validation set to lose its smallest value.

The initial learning rate of the regional U-Net was 0.001, and the batch size was 3. The number of epochs was 35, and the learning rate was reduced by half after every 5 epochs. After the last sigmoid layer, we set the threshold to 0.7, which causes the validation set to lose its smallest value.

**Fig. 6** Histograms of Dice coefficient for test set

## Results

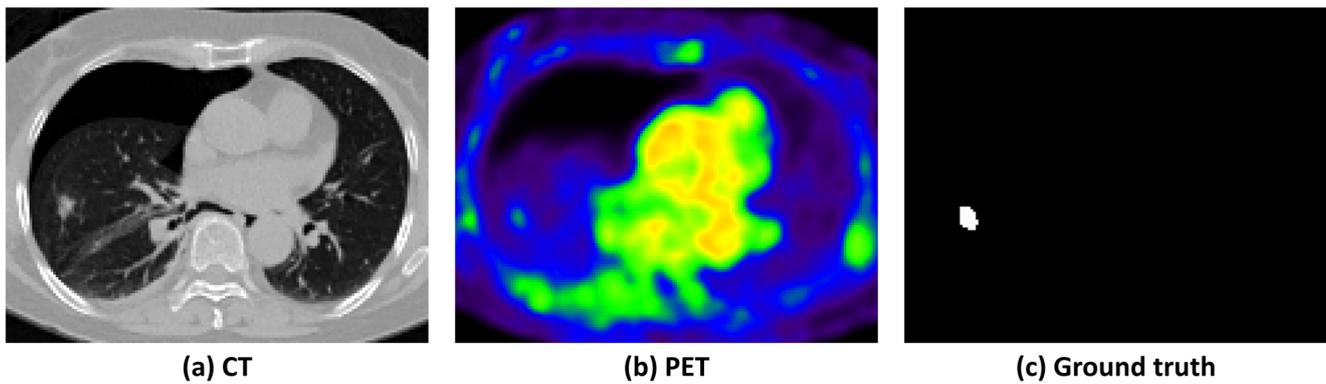
As shown in Figs. 4 and 5, the two-stage U-Net architecture proposed in this study outperformed the conventional one-stage 3D U-Net (Global U-Net in Stage 1) in primary lung cancer segmentation. The detailed margin of tumors, determined by manually drawing spherical VOIs and applying an adaptive threshold, was well predicted by the two-stage U-Net model.

Quantitative analysis using the Dice similarity coefficient confirmed the advantages of the two-stage U-Net. The mean and median Dice similarity coefficients obtained by applying the one-stage and two-stage U-Net architectures are summarized in Table 1: The two-stage U-Net showed higher mean and median Dice similarity coefficients than those of the one-stage U-Net. It was observed that there is a difference  $> 0.1$  in mean and median Dice similarity coefficients. As shown in Fig. 6, in most cases, the proposed two-stage U-Net yielded a Dice similarity coefficient of 0.75 or greater. The Dice coefficient of 1-stage and 2-stage was significantly different with  $P$  value of 0.028 ( $< 0.05$ ) when paired  $t$ -test was performed.

Both methods take less than 1.5 s for data loading and segmentation. The difference in computation time was not significant.

## Discussion

Low standard uptake value (SUV) in lung cancer is the main cause of segmentation failure. Figure 7 shows an example of an unsuccessful lung cancer segmentation by the network. In this case, the maximum and mean SUVs in the lung cancer were only 1.00 and 0.75, respectively, and the global U-Net in Stage 1 could not detect the cancer. Table 2 shows the maximum and mean SUVs of three missed cases (Dice similarity coefficient = 0) by the two-stage U-Net, which are compared with the average maximum and mean SUVs of all cases in the test set. SUV level seems to mainly affect stage 1 (actually, zero output was obtained in five cases with low SUV), and stage 2 seems to contribute to finding more detailed



**Fig. 7** A false negative case. (a) CT, (b) PET, and (c) Ground truth

boundaries for tumor. The number of missed cases in 1-stage and 2-stage were five and three. In three cases, neither 1-stage nor 2-stage detected the tumors. In other two cases, 1-stage missed the tumor (Dice coefficient = 0), but 2-stage successfully segmented the tumors from the output slices of 1-stage.

Occasionally, the two-stage U-Net detected lymph nodes and distant metastases, although they were not included in the training set. Training networks with additional data with ground-truth segmentation of lymph nodes and distant metastasis are likely to enhance the usefulness of the proposed method.

One of the limitations of this study is that the final output of the proposed method a 2D slice rather than a 3D volume. This can lead to discontinuity of binary segments in coronal and sagittal slices.

There is room for further improvement in segmentation performance. In this study, only the usefulness of a 2-stage network was investigated. Further investigation to improve and optimize the network architecture will be necessary. Because lung cancer occupies a very small part of the body, small errors cause large degradation in DSC. Therefore, lung segmentation shows lower DSC compared to other segmentation tasks.

**Table 2** SUV means and standard deviations (STDs) of the cases with zero Dice coefficients

	Test set	Case 1	Case 2	Case 3
SUV mean	4.23	1.25	1.28	0.76
SUV STD	1.08	0.16	0.13	0.09

## Conclusion

In this study, we developed an automatic deep-learning-based [ $^{18}\text{F}$ ]FDG PET/CT lung cancer segmentation method. The proposed 2-Stage U-Net model achieves a Dice similarity coefficient of 0.78 for the test set. The proposed method will be useful for reducing the time and effort required for accurate lung cancer segmentation in [ $^{18}\text{F}$ ]FDG PET/CT.

**Author Contribution** The study was designed by Jun Young Park, Seung Kwan Kang, Donghwi Hwang, Jae Seon Eo, and Jae Sung Lee. Material preparation and data collection were performed by Hongyoon Choi, Seunggyun Ha, and Jae Seon Eo. The first draft of the manuscript was written by Jun Young Park, and Jae Sung Lee and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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**Data Availability** Contact the corresponding author for data requests.

## Declarations

**Competing Interests** Jun Young Park, Seung Kwan Kang, Donghwi Hwang, Hongyoon Choi, Seunggyun Ha, Jong Mo Seo, Jae Seon Eo, and Jae Sung Lee declare no competing interests.

**Ethics Approval and Consent to Participate** The study was approved by the institutional review board of Seoul National University Hospital (H-2106-027-1225), and the requirement for written consent was waived by the institutional review board. All procedures performed in studies involving human participants were in accordance with the Helsinki Declaration as revised in 2013 and its later amendments.

**Consent for Publication** Not applicable.

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