Hyper-Connected Transformer Network for Co-Learning Multi-Modality PET-CT Features

Lei Bi, Xiaohang Fu, Qifang Liu, Shaoli Song, David Dagan Feng, Michael Fulham, Jinman Kim

Abstract—[18F]-Fluorodeoxyglucose (FDG) positron emission tomography – computed tomography (PET-CT) has become the imaging modality of choice for diagnosing many cancers. Co-learning complementary PET-CT imaging features is a fundamental requirement for automatic tumor segmentation and for developing computer aided cancer diagnosis systems. We propose a hyper-connected transformer (HCT) network that integrates a transformer network (TN) with a hyper connected fusion for multi-modality PET-CT images. The TN was leveraged for its ability to provide global dependencies in image feature learning, which was achieved by using image patch embeddings with a self-attention mechanism to capture image-wide contextual information. We extended the single-modality definition of TN with multiple TN based branches to separately extract image features. We introduced a hyper connected fusion to fuse the contextual and complementary image features across multiple transformers in an iterative manner. Our results with two non-small cell lung cancer and soft-tissue sarcoma datasets show that HCT achieved better performance in segmentation accuracy when compared to state-of-the-art methods. We also show that HCT produces consistent performance across various image fusion strategies and network backbones.

Index Terms—Positron Emission Tomography – Computed Tomography (PET-CT), Transformer Network

I. INTRODUCTION

Multi-modality [18F]-Fluorodeoxyglucose (FDG) positron emission tomography and computed tomography (PET-CT) has superseded CT as the preferred modality to assess a variety of cancers [1, 2]. This is because the integration of PET-CT in a single scanning device combines the higher sensitivity of PET in detecting sites of abnormal function and the underlying anatomical data from CT.

Computer aided diagnosis (CAD) is an emerging research area with the motivation to use the computer generated output as a ‘second opinion’ to aid physicians’ image interpretation, to improve diagnostic accuracy and reduce image interpretation time [3]. Automated PET-CT tumor segmentation is regarded as the first step in implementing CAD systems (CADs). The main aim

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of the segmentation is to co-learn available complementary features from the PET and CT images, and then use the derived image features to separate the tumors from background. Motivated by this need, various segmentation methods [4-6] have been developed for PET-CT.

Data-driven deep learning methods are leading to practical breakthroughs and research innovations in all fields of medical image analysis, e.g., disease classification, segmentation and retrieval. In segmentation, methods based on fully convolutional networks (FCNs) are the state-of-the-art [7]. FCN contains a convolutional neural network (CNN) to extract high-level abstract feature maps and then uses a CNN decoder to upsample the extracted feature maps to derive the segmentation results [8]. FCNs have also been applied to multi-modality PET-CT segmentation. Zhao et al. [9] reported a multi-view approach for pelvic bone and lymph node detection, where PET-CT images fused from axial, coronal and sagittal views were used as the input to a UNet architecture. Xu et al. [10] used two VNets (named WNets) to segment bone lesions, where the first VNet was applied to the input CT images and the segmentation results were refined with the second VNet together with PET and CT images as the input. Zhong et al. [11] proposed using two UNets for separate PET and CT segmentation with the results ensemble with a graph-cut approach. Guo et al. [12] used multiple FCNs with one for each of PET, CT and magnetic resonance (MR) images. The output segmentation results from three FCNs were ensemble to detect lesions from soft-tissue sarcomas. Kumar et al. [6] used a co-learning approach to segment the lungs, lung lesions and the mediastinum in non-small cell lung cancer patients, where a two branched UNet was implemented to extract and fuse PET and CT features across multiple UNet blocks. Bi et al. [4] proposed a recurrent fusion network (RFN), where cascaded FCNs were used for fusing the PET and CT features. More recently, Fu et al. [5] used the PET images as an attention map to guide the tumor segmentation on CT images. All these FCN based methods, however, usually suffer from the problem of relying on local convolutions (limited receptor field) and therefore fail to capture the long-range dependency that can capture image-wide contextual information. Specifically, the convolutional kernels within FCN can only operate on small kernels involving small sets of pixels of the image, which result in the FCN tending to dismiss global context and only focus on local patterns. Although there are attempts [13] to improve the long-range dependency by stacking convolutional layers and using attention modules, the receptive fields, however, are still limited with a conventional FCN architecture.

Recently, a transformer network (TN), a deep learning model designed for handling sequence data, has become the state-of-the-art on various natural image analytics tasks e.g., image classification and object detection [14-16]. Such performance gains are from the use of image patch embeddings with self-attention mechanism to establish long-range dependency that is able to capture global context. Hence, TN based medical image segmentation methods have also been widely explored. Chen et al. [17] proposed a TransUNet architecture for medical image segmentation. TransUNet follows the classic U-shaped UNet architecture and replaced the encoder of the UNet with a TN based encoder operating on sequences of image patches. Zhang et al. [18]
proposed integrating the feature maps derived from FCN and TN for polyp segmentation from endoscopy images. Valanarasu et al. [19] integrated two TNs for segmenting ultrasound and histopathology images, where the first TN model was designed to encode image features at global (entire image) level while the second TN model was used to extract local level (image patches) features. Wang et al. [20], Karimi et al. [21] and Xie et al. [22] replaced the 2D patches used in the TN with 3D patches for medical image segmentation. However, all these TN based segmentation methods were designed for single modality image segmentation. A straightforward translation of single-modality TN to multi-modality TN is to conduct early-fusion, where multi-modality image features are fused prior to FCN, or late-fusion, where the learned resultant features are fused. However, early- and late-fusion methods have limited freedom to fuse multi-modality image features and tend to dismiss complementary correlations across different modalities.

A. Our Contribution

We propose a hyper-connected transformer (HCT) for automatic PET-CT tumor segmentation. HCT extends the definition of TN with multiple TN based branches to separately extract image features from PET-CT images. These complementary image features are then fused in a progressive manner across multiple transformers for segmentations. Our HCT adds the following contributions to the current knowledge by our proposition:

(i) to leverage TN for PET-CT tumor segmentation; our HCT provides the flexibility to learn complementary features in a long-range dependency and overcome the limitations that current FCN based methods have in segmenting PET-CT;

(ii) to separately extract features and fuse the extracted PET and CT image features with transformers; this allows continuous fusion of the complementary PET and CT image characteristics, and minimizes the loss of information during early- or late-fusion;

(iii) to propose a TN based decoder to embed the separately extracted PET and CT features; the decoder parses and prioritizes the segmentation relevant features across the PET and CT, and ensures that challenging tumors e.g., tumors with heterogeneous textures are detected.

II. MATERIALS AND METHODS

A. Overview of the Proposed Method

Our hyper-connected transformer (HCT), as shown in Fig. 1, consists of a CNN-TN encoder (CNN-TN-E) and a TN-CNN decoder (TN-CNN-D). CNN-TN-E has three branches to separately process PET, CT and concatenated PET-CT images. Each branch also employs a hybrid approach to encode image features with CNNs into embeddings \( E \). The encoded image
embeddings are then processed by the transformer encoders to learn complementary features in a long-range dependency between the PET, CT and concatenated PET-CT images (respectively of $E^{PET}$, $E^{CT}$, $E^{CON}$). The learned embeddings are fused by the transformer decoder to identify segmentation relevant features, which are then reshaped to a 2D feature map. Finally, a CNN is used to upsample the fused features and to output the segmentation results.

Fig. 1. Flow diagram of our hyper-connected transformer (HCT) architecture.

B. Materials

We used two non-small cell lung cancer (NSCLC) and one soft-tissue sarcoma (STS) datasets [23] for evaluation. The NSCLC datasets were acquired from the Department of Molecular Imaging at Royal Prince Alfred hospital, NSW, Australia (denoted as RPA dataset) and the Department of Nuclear Medicine at Fudan University Shanghai Cancer Center, Shanghai, China (denoted as FD dataset). The STS dataset was acquired from McGill University Health Centre, Quebec, Canada. All three datasets were pathologically confirmed. The datasets are shown in Table 1.

| Datasets | RPA | FD | STS |
|----------|-----|----|-----|
| Number of Studies | 50 | 70 | 51 |
| Cancer Types | Lung Cancer | Lung Cancer | Soft-tissue Sarcomas |
| PET Resolution (pixels) | 200×200 | 168×168 | 128×128 |
| PET Spacing (mm$^2$) | 4.07 | 4.06 | 3.91-5.47 |
| CT Resolution (pixels) | 512×512 | 512×512 | 512×512 |
| CT Spacing (mm$^2$) | 0.98 | 1.37 | 0.98 |
| Slice Thickness (mm) | 3 | 5 | 3.27 |
| Scanner | Siemens Biograph 128-slice mCT scanner | Siemens Biograph 16-slice TruePoint scanner | GE Discovery ST scanner |
| Regions of Interest | Tumors, Lungs and mediastinum | Tumors | Tumors |

For the RPA dataset [5][6], a scientist used the findings documented in the clinical reports to annotate the tumors, lungs and the mediastinum. The clinical reports were written by an experienced clinician who has read over 100K PET-CT scans. Initially, tumors were annotated from the PET images with 40% peak SUV connected thresholding; lungs were annotated with adaptive thresholding method; and mediastinum was annotated with a connected thresholding algorithm. Manual corrections were made.
to the annotations to adjust for over- and under-segmentations. We acknowledge that the contours were defined by a single observer. In addition, as with all manual adjustments, we accept that there may be a small number of misclassified regions of interest, however, the same data were used for all the comparison methods used in the study.

For the FD dataset and the data were analyzed anonymously, two radiologists annotated the tumor regions from the axial plane of the CT with the ITK-SNAP software (V3.6). PET images were used to assist in excluding conditions such as pneumonia.

For the STS dataset [23], an expert radiation oncologist annotated the tumor regions on the T2-weighted fat-suppression MRI images. After that, rigid registration algorithm was used to propagate the tumor annotations to PET-CT images.

In our pre-processing, we linearly upsampled the PET images to the same size as the CT images to avoid the loss of data.

C. CNN-Transformer Network Encoder (CNN-TN-E)

CNN-TN-E consists of a PET image branch, a CT image branch and a hyper-branch. The PET and CT image branches were used to derive feature encodings for PET and CT images. The hyper-branch was used to process the concatenated PET and CT images.

![Fig. 2. The transformer module used in the HCT.](image)

To prepare the input to the transformer encoder, we firstly projected the input image $I \in \mathbb{R}^{H \times W \times C}$ into a 1-dimensional (1D) feature vector, where $H$ represents the height of the input image, and $W$ represents the width and $C$ is the number of channels. $C$ was set to 1 for the input PET or CT images and was set to 2 for the concatenated input. To minimize the required computational complexity of the transformer encoder, we used CNN to produce 2D image feature maps at a size of $(\frac{H}{16}, \frac{W}{16}, C)$. We used the residual neural network (ResNet) [24] (ResNet-50) as the CNN backbone.

To encode the spatial information, a positional embedding was learned which was then added to the extracted image feature maps. We firstly flattened and projected the feature map into a $D$-dimensional embedding space $E_0 = \left(\frac{H \times W}{16 \times 16}, D\right) = \left(\frac{H}{16}, \frac{W}{16}, C\right)$.
(e_1, e_2, ..., e_D). After that, we calculated a positional embedding \( P = (p_1, p_2, ..., p_D) \) for every embeddings based on a truncated normal distribution. The final embedding was defined as \( E = (e_1 + p_1, e_2 + p_2, ..., e_D + p_D) \).

Our transformer encoder has multiple transformer modules, representing transformer encoder with different depths \( T \). Each transformer module, as shown in Fig. 2, has multi-head self-attention (MSA), multi-layer perceptron (MLP) and layer normalization (LN) [25] blocks to extract image features from the embeddings. Therefore, the overall process of the \( l \)-th transformer module can be written as:

\[
E'_l = MSA(LN(E_{l-1})) + E_{l-1} \\
E_l = MLP(LN(E'_l)) + E'_l
\]  

(1)  

(2)

MSA block comprises of multiple single attention (SA) layers. At each depth of \( l \), the input to self-attention layer is in a triplet of \((Q, K, V)\) computed from the input \( E_{l-1} \), calculated as:

\[
Q = E_{l-1}W_Q \\
K = E_{l-1}W_K \\
V = E_{l-1}W_V
\]  

(3)  

(4)  

(5)

where \( W_Q, W_K, W_V \) are the learnable parameters of three linear projection layers. SA can then be formulated as:

\[
SA(E_{l-1}) = \text{softmax}\left(\frac{E_{l-1}W_QE_{l-1}W_K}{\sqrt{d}}\right)(E_{l-1}W_V)
\]  

(6)

MSA is an extension of SA with \( m \) independent SA operations. The outputs of individual SAs are concatenated together and then linearly projected into a single output. \( s \) defines the ratio between the input feature channels to the number of SAs, which can be calculated as \( \frac{C}{m} \).

MLP consists of two fully connected layers (FC), which are interconnected with the Gaussian Error Linear Units function (GELU) [26] as:

\[
MLP(x) = FC\left(GELU(FC(x))\right)
\]  

(7)

D. Transformer Network-CNN Decoder (TN-CNN-D)

At the end of our CNN-TN-E, we generated three separate embeddings \( E^{PET}, E^{CT}, E^{CON} \) representing image features extracted from PET, CT and concatenated images. Similar to the transformer encoders, the transformer decoder also has multiple transformer modules representing transformer decoder with different depths. The transformer module was purposely designed to take concatenated embeddings and then to use the positional embedding to learn spatial information within the embeddings and across PET and CT images, which can be defined as:
The output embedding from the transformer decoder was reshaped into a feature map at a size of \( \left( \frac{H}{16}, \frac{W}{16} \right) \) and were further processed by two convolutional (Conv) layers, as shown in Fig. 3. We followed the design of the traditional FCN architecture and added the CNN produced feature map. Specifically, the feature map derived from the CNN encoder was processed by a Conv layer and fused to the linearly interpolated transformer produced feature map. The final segmentation was obtained by using a Conv layer and a pixel-wise softmax operation.

\[ E = \{ e^{PET}_1 + p_1, \ldots, e^{PET}_D + p_D, e^{CT}_1 + p_D, \ldots, e^{CT}_{2D} + p_{2D}, e^{CON}_{2D+1} + p_{2D+1}, \ldots, e^{CON}_{3D} + p_{3D} \} \]  \hspace{1cm} (8)

Fig. 3. Transformer-CNN decoder used in our HCT.

E. Implementation Details

PET images were converted to standardized uptake values (SUVs) and were then normalized to [0, 15]. CT images were converted to Hounsfield units and were then normalized to [-160, 240]. Our HCT was developed with PyTorch and the backbone ResNet was fine-tuned from a pre-trained ImageNet [27] model. At the training stage, we applied online data augmentation (random cropping, resizing and flipping) and used the pixel-wise cross-entropy loss to train HCT for 100 epochs on a NVIDIA 24GB 3090 GPU. The batch size was set to 2. The learning rate was set to \( 1 \times 10^{-4} \) and was decayed with a poly strategy [28]. The default of HCT depth was set to 4 and the embedding was set to 256. The Adam approach was used as the optimizer with an epsilon value of \( 1 \times 10^{-8} \) and weight decay was set to \( 1 \times 10^{-4} \).

F. Experimental Setup

A 5-fold cross-validation evaluation protocol was conducted for each dataset. For example, with our RPA dataset having 50 patient studies, image slices from 40 studies were used as the training set and image slices from the remaining 10 studies were used as the test set. For the RPA dataset, three classes including tumors, lungs and mediastinum were used for training and evaluation while only the tumor class was used for training and evaluating the FD and STS datasets. The experiments we conducted were as follows: We evaluated our HCT with different multi-modality fusion strategies with the use of FCN and TN.
We used ResNet-50 as the network backbone: (1) EF (early fusion) – multi-modality inputs fused at an early stage of the network; (2) LF (late fusion) – multi-modality inputs were separately processed by multiple networks with the output results being fused; and (3) HF (hyper fusion) – multi-modality image features fused within the network architecture. Supplementary Fig. S1 shows the different fusion methods used. We also investigated the segmentation performance of FCN and TN with PET or CT only to evaluate the contribution of PET and CT images.

We compared our HCT to current PET-CT segmentation methods and the included methods were: (1) Co-segmentation [11] – two UNets for separate PET and CT segmentation with the results ensembled with a graph-cut approach; (2) WNet [10] – two V Nets (named as WNet) for iterative segmentation, where the first VNet was applied to the input CT images and the segmentation results were refined with the second VNet together with PET and CT images as the input; (3) a co-learning [6] – a two branched UNet was implemented to extract and fuse PET and CT features across multiple UNet blocks; (4) UNet [29] with an early-fusion strategy; (5) RFN [4] – recurrent fusion network, where cascaded FCNs were used for fusing the PET and CT imaging features; (6) MSAM [5] – multi-modal spatial attention module, which uses the PET images as an attention map to guide the tumor segmentation on CT images; (7) TN [16] – a conventional transformer based segmentation with an early-fusion strategy; (8) PVT [30] – pyramid vision transformer where the concatenated PET and CT images were used as the input.

The evaluation on the state-of-the-art methods were conducted on all three datasets. In addition, we conducted ablation study and generalizability analysis on the FD dataset.

We evaluated our HCT with various backbones and decoder architectures. The backbones were MobileNet (MobileNetV2) [31] and Xception (Xception65) [32], and they are commonly used for evaluating the generalizability of different segmentation methods. We further extended HCT to include the decoder architecture used in RefineNet [33] to evaluate if the HCT can benefit from using additional decoders. RefineNet uses an efficient multi-path refinement network to linearly interpolates the extracted image features for high-resolution image segmentation.

In addition, we evaluated the performance of HCT with different setup: (i) depths – we referred depth to the number of transformer modules used in the transformer encoder, an equal number of transformer modules were used in the transformer decoder; (ii) embeddings – the different sized embeddings used in the transformer encoder; and (ii) heads – the number of single attentions used in the multi-head self-attention (MSA) block.

The included evaluation metrics [6] are: Dice score, precision (Pre.), sensitivity (Sen.), specificity (Spe.), accuracy (Acc.) and precision-recall (PR) curves.
III. RESULTS

A. Segmentation with Various Fusion Strategies

Table 2 shows the segmentation results with different fusion strategies. Fig. 4(a) shows the precision-recall (PR) curves. Fig. 5 shows the example segmentation results. The results indicate that TN based methods consistently improved the FCN based counterparts with a margin of >3% in DSC. In addition, HCT achieved better performance compared to the TN based methods e.g., EF-TN and LF-TN methods. Fig. 5 shows that the comparison methods were unable to segment tumors with heterogeneous textures. HCT, in contrast, was able to accurately segment these challenging studies.

Table 2. Segmentation results for the FD dataset with different fusion methods. Bold represents the best results.

| FD Dataset | DSC  | Pre.  | Sen.  | Spec.  | Acc.  |
|------------|------|-------|-------|--------|-------|
| EF-FCN     | 65.71 ± 24.24 | 68.89 ± 27.90 | 74.11 ± 28.30 | 99.42 ± 0.91 | 99.03 ± 0.99 |
| EF-TN      | 69.57 ± 25.63 | 76.20 ± 26.90 | 70.58 ± 28.56 | 99.71 ± 0.52 | 99.30 ± 0.75 |
| LF-FCN     | 62.43 ± 26.80 | 67.66 ± 30.75 | 67.84 ± 31.41 | 99.43 ± 0.47 | 99.05 ± 0.82 |
| LF-TN      | 68.47 ± 25.18 | 75.20 ± 26.59 | 70.68 ± 29.05 | 99.71 ± 0.38 | 99.26 ± 0.68 |
| HF-FCN     | 64.03 ± 26.11 | 67.11 ± 29.85 | 70.86 ± 30.51 | 99.45 ± 0.74 | 99.06 ± 0.84 |
| HCT        | 72.25 ± 22.77 | 77.83 ± 24.33 | 73.48 ± 26.04 | 99.74 ± 0.36 | 99.36 ± 0.63 |

Fig. 4. Precision-recall (PR) curves on the FD dataset with: (a) different fusion methods, (b) only using CT, PET and PET-CT images, and (c) HCT using MobileNet, Xception backbones and RefineNet decoder.
Fig. 5. Three selected studies of parenchymal lung lesions (i-iii) shown on transaxial image slices with (a) PET in first column and (b) CT in second column. The segmentation results, enlarged, from the different methods are shown in columns (c) to (h). The red contour outlines the ‘ground truth’ segmentation and the cyan contour outlines results from the comparison methods. The black bounding box indicates the region that has been enlarged (scale factor of ~3).

B. FCN and TN based Segmentation with PET or CT Images

PR curves of the segmentation results with individual modalities (either PET or CT) using FCN or TN, together with our HCT (modality PET-CT) results, are shown in Fig. 4(b). Two segmentation results are exemplified in Fig. 6. The PET based methods resulted in higher segmentation accuracy compared to the CT counterpart. Similarly, to the fused results in Section III.A, TN based methods achieved higher segmentation performances than FCN counterparts. The results suggest that the multi-modality transformer based methods performed better compared to only using PET or CT.

Fig. 6. Two examples of parenchymal lung lesions (i, ii) are shown on transaxial image slices with PET (a) and CT (b). The segmentation results from the different methods are enlarged (scale factor of ~3) and presented in columns in (c) to (h).

C. Segmentation with MobileNet, Xception Backbones and RefineNet Decoder

Segmentation results of FD datasets with different backbones and decoders are shown in Fig. 4(c) and Supplementary Table S1. HCT consistently achieved the best performance among different backbones and decoders (2.23% to 8.97% improvements in DSC).
D. Comparing to the State-of-the-art

Table 3, Table 4, Fig. 7 and Fig. 8 show the comparison results of our HCT to the state-of-the-art multi-modality segmentation methods. TN achieved 1.82% better in DSC on the FD dataset and 2.04% improvement in DSC on the STS dataset when compared to the second-best performing FCN based method of RFN. Our HCT further improved the TN, measured in DSC, by an average of 2.68%, with FD, 1.4% with STS, and 3.91% with RPA datasets.

Table 3. Comparison with the state-of-the-art segmentation methods on the RPA and FD datasets. Co-seg. = Co-segmentation; Med. = Mediastinum.

|       | RPA   |        |       | FD    |
|-------|-------|--------|-------|-------|
|       | Tumors| Lungs  | Med.  | Average| Tumors|
| UNet [29]| 50.77 | 91.01  | 65.50 | 69.09 | 49.78 |
| WNet [10]| 53.40 | 92.24  | 74.01 | 73.22 | 50.84 |
| Co-seg. [11]| 63.09 | -      | -     | -     | -     |
| Co-learning [6]| 63.85 | 91.73  | 75.25 | 76.94 | 52.49 |
| RFN [4]| 65.80 | 93.61  | 79.91 | 79.77 | 67.75 |

|       | PVT [30]|       |       |       |       |       |
|-------|---------|--------|-------|-------|-------|-------|
|       | 66.79   | 91.50  | 81.51 | 79.97 | 66.87 |
| TN [16, 34]| 60.51 | 94.19  | 79.10 | 78.12 | 69.57 |
| HCT   | 67.11   | 94.54  | 84.01 | 82.03 | 72.25 |

Table 4. Comparison with the state-of-the-art segmentation methods on the STS dataset.

|       | DSC   | Pre.  | Sen.  | Spec. |
|-------|-------|-------|-------|-------|
| UNet [29]| 59.63 | 64.50 | 64.49 | 99.65 |
| Co-seg. [6]| 59.07 | 68.95 | 60.06 | 99.65 |
| RFN [4]| 62.92 | 69.27 | 66.07 | 99.69 |
| MSAM [5]| 62.26 | 69.00 | 64.74 | 99.74 |

|       | PVT [30]|       |       |       |       |       |
|-------|---------|--------|-------|-------|-------|-------|
|       | 65.83   | 72.92  | 67.65 | 99.69 |
| TN [16]| 64.96   | 71.57  | 66.37 | 99.74 |
| HCT   | 66.36   | 71.45  | 69.93 | 99.69 |

Fig. 7. Two examples of soft-tissue sarcomas (i – in the chest wall; ii – in the right buttock) are shown on transaxial image slices with PET (a) and CT (b). The segmentation results are shown in columns (c) to (h). Note that UNet (c) and TN (h) failed to segment the tumor on the first example.

Fig. 8. Example segmentation results on the RPA dataset, where transaxial image slices of PET and CT are shown in (a) and (b). The ground truth (GT) annotation is shown in (c) and the segmentation results are shown in the following columns in (d) to (g). The colors represent tumor (red), mediastinum (yellow) and lungs (green).
E. HCT Segmentation Results at Different Depths, Embeddings and Heads

The results with different depths, embeddings and heads were relatively stable (shown in Supplementary Fig. S2) across the different setup, where in DSC the depths’ range is 1.49%, the embeddings’ range is 1% and the heads’ range is 1.23%. The relatively lower performance at Depths = 8, Embeddings = 512 and Heads = 16 is expected; these three models have much greater number of additional parameters, which is usually more difficult to be trained with limited number of medical imaging data.

IV. DISCUSSION

Our main findings are that: (i) fusing multi-modality image features through our hyper-connected transformer architecture enabled accurate segmentation of challenging studies e.g., tumors with heterogenous (inhomogeneous) textures; (ii) learning through multi-modality PET-CT images through a transformer can produce better segmentation results when compared to only using PET or CT images alone, or when compared to using FCN; (iii) HCT consistently outperformed the state-of-the-art multi-modality segmentation methods across various datasets and, (iv) HCT is generalizable across various backbones and decoders.

A. Analysis of Different Fusion Methods

TN based methods can achieve higher segmentation accuracy more consistently than the FCN based counterpart across different fusion strategies. We attribute this to the use of the transformer for leveraging image patch embeddings with self-attention mechanism to establish a long-range dependency which is able to capture global context, and thus aid in the removal of the false positive regions. This is exemplified in Fig. 5(ii) where FCN based methods (EF-FCN, LF-FCN and HF-FCN) tend to over-segment the heart and include it as part of the tumor regions.

Compared to the EF-TN, the LF-TN separately processed the multi-modality inputs with the output results being fused just prior to the output. This resulted in the complementary image features not being learnt in a joint manner. With the second-best performing EF-TN, segmentation results tended to focus on the PET image features while dismissing the complementary CT features; in this process, the complementary CT features could already be lost during early fusion. Fig. 5(iii) shows the segmentation results on a challenging study, where the tumor has heterogeneous textures. EF-TN and LF-TN appear to under-segment the tumor sites. In contrast, our HCT separately processed and then co-learned PET and CT image features, and minimized the loss of information during the early-fusion process. In addition, our transformer based decoder allows for the fusion of the separately extracted PET and CT image features and prioritizes the segmentation relevant image features. Therefore, compared to LF-TN method, which fused image features just prior to the final output, our HCT exhibited flexibility in
retaining important PET and CT image features for segmentation.

B. Comparison of Single and Multi-Modality Segmentation

The improvement of using PET based methods over CT based methods is as expected; in most of time, PET enables the characterization of tumoral glucose metabolism which makes tumor structures more visible when compared to the CT image. The improvement of PET-TN to PET-FCN illustrates the advantages of using the transformer for tumor segmentation.

Our HCT based on PET-CT imaging and transformer further improved PET-TN method. PET-TN only used PET images for the segmentation, which resulted in focusing on segmenting high uptake regions only. Consequently, tumor segmentation results tend to be under-segmented, as shown in Fig. 6(i). In contrast, the proposed HCT method leverages the accessible global context information from the transformer and the complementary information from PET and CT images, ensured better tumor detection capability as well as accurate segmentation of the tumor boundaries.

C. Comparison to Existing PET-CT Segmentation Methods

The improvement of Co-learning method over UNet is attributed to the use of relationship of multiple structures e.g., the tumor, lungs and mediastinum, where Co-learning leverages the training annotation of different structures to constrain the searching space. Its performance, therefore, was not retained with FD and STS datasets where the training dataset only comprised annotated tumors. The improvement of MSAM over Co-learning is likely attributed using the multi-modality spatial attention module, which allows it to leverage the PET images as an attention map to guide the tumor segmentation on CT images. RFN further improved MSAM by using an iterative approach to progressively refine the segmentation results. Consistent with our ablation results, these FCN based methods are inherently restricted by the limited receptive field, which prohibited these methods from learning the global context.

The better performance of TN and PVT over RFN we suggest relates to the use of the transformer to capture the global context. TN shows competitive segmentation performance to our HCT method on the FD and STS datasets. However, the segmentation results for TN are imbalanced when there are multiple structures that need to be segmented and this leads to overfitting to the structures that are easier to segment e.g., lungs. This is evidenced from Table 3, where TN was 0.35% lower when compared to our method in segmenting the relatively easy lung structures and was 6.6% lower and 4.91% lower compared to our method in segmenting the more challenging tumor and mediastinum structures. PVT also showed imbalanced segmentation accuracy across different datasets, where PVT was 2.06% lower in average DSC on the RPA dataset and 0.53% lower to our method on the STS dataset, and achieved a large margin of 5.38% lower on the FD dataset. In addition, as both the
TN and the PVT are designed for single modality image segmentation, early fusion (concatenation) was applied for PET-CT image segmentation. Consequently, the useful complementary information could be lost during early fusion and resulted in limited segmentation performance in segmenting challenging tumors e.g., tumors with low-contrast to the background (Fig. 7(i)) and tumors with heterogeneous textures (Fig. 7(ii)). In contrary, our HCT fused the PET, CT and concatenated PET-CT image features across multiple transformer modules; the fusion of various image features enabled the appearance of the results to be in an agreement with different imaging modalities. Furthermore, the fusion of multi-modality image features across multiple transformer modules allowed for the HCT to continuously leverage the PET and CT image features in iteratively segmenting the challenging tumors.

D. Generalizability Analysis

The adoption of ResNet backbone in our HCT had better performance compared to MobileNet and Xception backbones. As expected, HCT with Xception backbone was better than with MobileNet backbone, where Xception has greater number of learned parameters compared to MobileNet. The number of learned parameters improves the discriminability of the extracted PET and CT image features. The addition of RefineNet decoder lowered the overall segmentation accuracy. We attribute this to the fact that the outputs from the transformer decoder have sufficient number of image features for segmentation and the additional RefineNet decoder, which is designed for the low-receptive field FCN architecture, influenced the learned transformer based image features. Nevertheless, the consistent improvement with different backbones and decoder architecture suggests that our HCT is more generalizable to the baseline TN method.

V. Conclusion

We introduced a hyper-connected fusion network to fuse the contextual and complementary image features from PET-CT through multiple transformer networks. This approach which minimized the risk of losing information during early- and late-fusion. Our results with three clinical PET-CT datasets showed that the HCT outperformed comparative state-of-the-art methods across different PET-CT datasets and network architectures and suggest that our method is more generalizable than the existing methods.

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SUPPLEMENTARY MATERIALS

Fig. S1. Different fusion methods based on fully convolutional network (FCN) and transformer network (TN) for PET-CT segmentation. (1) EF (early fusion) – multi-modality inputs fused at an early stage of the network; (2) LF (late fusion) – multi-modality inputs were separately processed by multiple networks with the output results been fused; and (3) HF (hyper fusion) – multi-modality image features fused within the network architecture.

Table S1. Segmentation results for the FD dataset with MobileNet, Xception backbones and RefineNet decoder.

| FD Dataset | DSC      | Prec.    | Sen.      | Spec.    | Acc.      |
|------------|----------|----------|-----------|----------|-----------|
| TN (MobileNet) | 62.66 ± 30.93 | 67.67 ± 33.20 | 65.36 ± 34.03 | 99.67 ± 0.57 | 99.12 ± 1.15 |
| HCT (MobileNet) | 66.30 ± 26.71 | 74.35 ± 26.97 | 69.28 ± 30.84 | 99.68 ± 0.47 | 99.21 ± 0.81 |
| TN (Xception) | 71.24 ± 23.10 | 77.16 ± 23.96 | 73.17 ± 25.95 | 99.72 ± 0.44 | 99.31 ± 0.66 |
| HCT (Xception) | 73.47 ± 21.49 | 77.26 ± 23.33 | 75.97 ± 25.23 | 99.72 ± 0.40 | 99.35 ± 0.65 |
| TN (RefineNet) | 60.69 ± 30.84 | 69.63 ± 33.49 | 65.53 ± 34.53 | 99.58 ± 0.82 | 99.09 ± 1.02 |
| HCT (RefineNet) | 69.66 ± 25.59 | 76.67 ± 26.88 | 70.42 ± 28.38 | 99.75 ± 0.36 | 99.28 ± 0.77 |
Fig. S2. PR curves of the HCT method with different (i) depths, (ii) embeddings, and (iii) heads on the FD dataset.

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**Figures:**

- **(i)** Precision vs. Recall for different depths: Depths = 2, Depths = 4, Depths = 8.
- **(ii)** Precision vs. Recall for different embeddings: Embeddings = 128, Embeddings = 256, Embeddings = 512.
- **(iii)** Precision vs. Recall for different heads: Heads = 4, Heads = 8, Heads = 16.