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Automatic Segmentation of Clinical Target Volume and Organs-At-Risk for Breast Conservative Radiotherapy Using a Convolutional Neural Network

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Research Article

Keywords: Clinical target volume, Organ at risk, Auto-segmentation, Breast cancer radiotherapy, Clinical evaluation

Posted Date: June 2nd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-535967/v1

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Automatic segmentation of clinical target volume and organs-at-risk for breast conservative radiotherapy using a convolutional neural network

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Abbreviation: BC=breast cancer, BCS=breast conserving surgery, WBI=whole-breast irradiation, CTV=clinical target volume, OARs=organs at risk, ROIs=regions of interest, ABAS=atlas-based auto-segmentation, CNNs= convolutional neural networks, DIR=deformable image registration, GT=ground truth contouring, AI=artificial Intelligence, DICOM=digital imaging and communications in medicine, ESTRO=European Society for Radiotherapy and Oncology, RTOG= Radiation Therapy Oncology Group

Automatic segmentation of clinical target volume and organs-at-risk for breast conservative radiotherapy using a convolutional neural network

Abstract

Background and Objective: Delineation of the clinical target volume (CTV) and organs at risk (OARs) is very important for radiotherapy but is time-consuming and prone to inter- and intra-observer variation. We trained and evaluated a U-Net-based model to provide fast and consistent auto-segmentation for breast cancer radiotherapy.

Methods: We collected 160 patients' computed tomography (CT) scans with early-stage breast cancer who underwent breast-conserving surgery (BCS) and were treated with radiotherapy in our center. CTV and OARs (contralateral breast, heart, lungs and spinal cord) were delineated manually by two experienced radiation oncologists. The data were used for model training and testing. The dice similarity coefficient (DSC) and 95th Hausdorff distance (95HD) were used to assess the performance of our model. CTV and OARs were randomly selected as ground truth (GT) masks, and artificial intelligence (AI) masks were generated by the proposed model. The contours were randomly distributed to two clinicians to compare CTV score differences. The consistency between two clinicians was tested. We also evaluated time cost for auto-delineation.

Results: The mean DSC values of the proposed method were 0.94, 0.95, 0.94, 0.96, 0.96 and 0.93 for breast CTV, contralateral breast, heart, right lung, left lung and

spinal cord, respectively. The mean 95HD values were 4.31 mm, 3.59 mm, 4.86 mm, 3.18 mm, 2.79 mm and 4.37 mm for the above structures respectively. The average CTV scores for AI and GT were 2.92 versus 2.89 when evaluated by oncologist A (*P*=.612), and 2.75 versus 2.83 by oncologist B (*P*=.213), with no statistically significant differences. The consistency between two clinicians was poor (Kappa=0.282). The times for auto-segmentation of CTV and OARs were 3.88 s and 6.15 s.

Conclusions: Our proposed model can improve the speed and accuracy of delineation compared with U-Net, while it performed equally well with the segmentation generated by oncologists.

Key words: Clinical target volume, Organ at risk, Auto-segmentation, Breast cancer radiotherapy, Clinical evaluation

1. Introduction

Breast cancer (BC) is one of the most common cancers for women throughout the world[1]. Breast radiotherapy after breast-conserving surgery (BCS) is an essential treatment for early breast cancer patients[2; 3]. Radiotherapy of tumors requires accurate, individualized contouring of clinical target volume (CTV) and organs at risk (OARs) to deliver high radiation doses to the target and to spare healthy tissues[4]. Therefore, computer-assisted automatic segmentation techniques are highly desired and useful for relieving radiation oncologists from labor-intensive work as well as reducing considerable inter- and intra-observer variability in delineation of the regions

of interest (ROIs)[5; 6].

Current automatic approaches can be generally categorized into two groups: atlas-based auto-segmentation (ABAS) and convolutional neural network (CNN) based segmentation. Acceptable results have been reported using ABAS for OARs in head and neck cancer and prostate cancer[7-9]. However, CTV is not a region with clear boundaries but includes tissues of potential tumor or subclinical diseases that are barely detectable in CT images[10]. Moreover, the inconsistencies in body shape, organ size, and density of mammary glandular tissue remain large from person to person[11; 12]. Therefore, various kinds of CNN models[13-16] have been presented for different cancers[8; 16-20], showing better performance than ABAS.

A deep dilated residual network (DD-ResNet) was previously proposed by Men K et al[16] to perform automatic breast CTV contouring. A 0.91 DSC was reported for both the right and left breast CTV, but no clinical evaluation was performed. Moreover, this method was focused on CTV contouring; the OARs were not considered.

Here, we constructed a new CNN model based on the 2.5D U-Net model to solve the large inconsistencies between source and target image, even with a scarce amount of labelled training data. The proposed model was trained and then compared against U-Net. The accuracy and effectiveness were evaluated by both performance metrics and qualified radiation oncologists.

2. Materials and methods

2.1. Data acquisition

CT scans of patients with early-stage BC who underwent BCS in Peking Union Medical College Hospital were collected from January 2019 to December 2019. This study was approved by the Institutional Review Board of Peking Union Medical College Hospital. The inclusion criteria are as follows: (1) Patients who were diagnosed with early-stage BC and underwent breast conservative surgery. (2) All the patients met the indication for radiotherapy and received whole-breast irradiation. Patients who underwent axilla or supraclavicular lymph nodes radiotherapy were excluded.

In total, 12,640 CT slices were collected from 160 patients; 79 patients had left-sided BC and the remainder had right-sided BC. All the CT scans followed the digital imaging and communications in medicine (DICOM) protocol and were scanned using a Philips Brilliance Big Bore CT scanner. CT images were reconstructed using a matrix size of 512 × 512 and a thickness of 5 mm. The pixel spacing of the data was 1.1543 mm × 1.1543 mm.

Contouring of the CTV and OARs (contralateral breast, lungs, heart, and spinal cord) were delineated manually by trained radiation oncologists following the European Society for Radiotherapy and Oncology (ESTRO)[21] and the Radiation Therapy Oncology Group (RTOG) [22]protocols. The specific sketching standards for CTV are shown in **Table 1**. All the contours were reviewed and approved by two professional radiation oncologists with more than 10 years' experience in our center.

Table 1. The standard delineation of CTV after BCS.

Borders	cranial	caudal	ventral	dorsal	lateral	medial
Residual breast CTV	Upper border of palpable/visible breast tissue; maximally up to the inferior edge of the sterno-clavicular joint	Most caudal CT slice with visible breast	5 mm below the skin surface	Major pectoral muscle or costae and intercostal muscles where no muscle	Lateral breast fold; anterior to the lateral thoracic artery	The edge of sternum

2.2. Network Architecture

Our model, called U-ResNet, is originated from the 2D U-Net model, which is composed of encoder and decoder paths. To conduct the segmentation task for BC radiotherapy, especially for the CTV segmentation, a deep network should be added to the U-Net to extract features as different abstraction levels. At the same time, the vanishing gradients of deep convolutional networks should be avoided. Therefore, ResNet is used as the encoder part. It encodes low-, middle- and high- level features and passes these features to the decoder part via four shortcut connections. In the decoder part, the upscaling is achieved using nearest neighbour interpolation, followed by a convolutional layer and a residual block. In this way, multiple-level features in the encoder and decoder parts are concatenated. The overall architectures of DD-ResNet and our proposed method are shown in **Fig. 1**. DD-ResNet has no shortcut connections between the encoder and the decoder. The output of the sum layer was interpolated to the original size with a factor of 8, which may result in information loss.

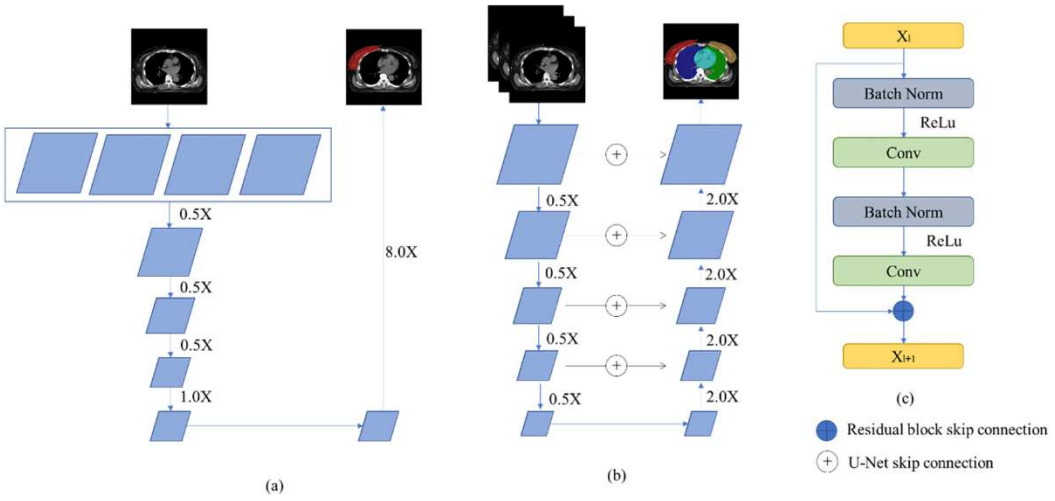

Fig.1 Architecture of (a) deep dilated convolutional neural network, (b) our proposed network, and (c) the residual block used in decoder part of our network.

The breast is a continuous and smooth surface. A 2D architectures may result in a rough segmentation result in a 3D view. To obtain the 3D information of CT scans, the network is designed as a 2.5D architecture by assigning three adjacent slices into three channels as the input.

2.3. Implementation details

The dataset, composed of 160 patients, was randomly assigned in 8:1:1 to three cohorts: (a) a training set of 128 patients was used to construct the segmentation model, (b) a validation set of 16 patients was used to optimize the parameters and (c) a testing set of 16 patients to was used obtain artificial intelligence-generated contouring for performance assessment. During the testing phase, all the CT slices of the 16 testing cases were tested individually.

We constructed our model using Python 3.6 and PyTorch 1.0. An Adam optimization

algorithm[23] was used for the optimization. The learning rate was 0.001. We trained and evaluated our model with a GTX 1080 GPU. The proposed model was trained over 50 circles to select the best model according to the lowest validation loss score. The convolutional layers are initialized using Xavier Uniform Initialization, and batch normalization layers were added after convolution layers to improve the training speed and to prevent over-fitting[24].

2.4. Performance measurement

Performance of the proposed method was evaluated using the dice similarity coefficient (DSC) and the 95th percentile Hausdorff distance (95HD) to quantify the results. The mean and standard deviation were also calculated.

The DSC was used to measure the spatial overlap between AI and GT contours, which is defined in Eq. (1).

$$DSC\ (A,B) = \frac{2|A \cap B|}{|A| + |B|} \qquad (1)$$

Where A represents the volume of the human-generated contour; B is the volume of an AI contour; and $A \cap B$ is the intersect volume that A and B have in common. The DSC value was between 0 and 1 (0 = no overlap, 1 = complete overlap).

The 95HD is defined as follows:

$$95HD\ (A,B) = \max\left(h(A,B), h(B,A), 95\text{th}\right) \qquad (2)$$

$$h(A,B) = \max_{a\in A}\ \min_{b\in B}\left||a-b|\right| \qquad (3)$$

$$h(B,A) = \max_{b\in B}\ \min_{a\in A}\left||b-a|\right| \qquad (4)$$

$\|\cdot\|$ means the Euclidean norm of the points of A and B. The 95HD means the maximum mismatch between A and B. When the HD value decreases, the overlap between A and B increases.

2.5. Oncologist evaluation

2.5.1. OARs evaluation

Considering that evaluation metrics cannot provide a comprehensive insight into whether the contours need to be modified in clinical practice, another 20 cases in clinical practice from our center were randomly collected. Each case was delineated with GT and AI contours for OARs and then distributed to two radiation oncologists with more than 10 years of clinical experience for further evaluation. Each slice was carefully evaluated, and the results were graded in four levels: 3 points (no need to be edited), 2 points (the number of layers need to be edited≤4), 1 point (the number of layers need to be edited≥4) and 0 point (not acceptable).

2.5.2. CTV evaluation

CTV segmentations generated by AI and GT were also evaluated blindly slice by slice. The test data contained 10 patients and 650 slices in total (AI: 327 slices vs. GT: 323 slices). The representative results were also graded on four levels: 3 points (acceptable for subsequent treatment), 2 points (Minor Revision), 1 point (Major Revision) and 0 point (Not Acceptable for treatment). When the score≥2, it was defined as suitable for clinical application.

Furthermore, to verify the consistency of the judgment of two oncologists, we collected the CTV score of each 650 slice evaluated by two oncologists, constituting a

total of 650 slices of data sets. The data were classified into the same group if the slice was evaluated by two oncologists with the same CTV score. We calculated the weighted Kappa coefficient to analyze for consistency.

2.6. Time cost

Processing time was measured for the AI tool and pre- and post-AI assistance in the delineation of CTV and OARs for BC radiotherapy.

2.7. Statistical analysis

The Wilcoxon matched-pairs signed-rank test was used to compare DSC and 95HD between our proposed model and U-Net and the differences between the two oncologists during the evaluation of CTV and OARs segmentation. McNemar test and Kappa test were used to assess the consistency of the two oncologists. Statistical significance was set at two-tailed $P<.05$.

3. Results

3.1. Performance of U-ResNet and comparison with U-Net

For CTV segmentation, the average DSC values of U-ResNet and U-Net were 0.94 vs.0.93 ($P=.001$), and the average 95HD value was 4.31 mm vs. 4.88 mm separately ($P=.030$). Both differences were statistically significant, implying better accuracy of CTV contouring by U-ResNet.

Among all OARs, significant differences between U-ResNet and U-Net were achieved for the spinal cord (DSC: 0.93 vs. 0.92 ($P=.015$), 95HD:4.37 mm vs. 5.07

mm (*P*=.003)) and the contralateral breast (DSC: 0.95 vs. 0.93 (*P*<.001), 95HD:3.59 mm vs. 4.15 mm (*P*=.010)). The right lung contouring also displayed a statistically significant difference in 95HD (3.18 mm vs. 2.98 mm (*P*=.041)).

The results of the comparison are summarized in **Table 2** and **Fig. 2**.

Table 2. DSC and 95HD for CTV and all OARs.

ROI	CTV	Contra-lateral Breast	Spinal cord	Heart	Right lung	Left lung
DSC±STD						
U-ResNet	0.94±0.019	0.94±0.016	0.93±0.024	0.94±0.023	0.96±0.017	0.96±0.025
U-Net	0.93±0.022	0.93±0.020	0.92±0.029	0.93±0.026	0.96±0.018	0.96±0.024
P value	**0.001**	**< 0.001**	**0.015**	0.066	0.257	0.942
95HD±STD						
（mm）						
U-ResNet	4.31±1.76	3.59±1.56	4.37±2.13	4.86±1.48	3.18±1.64	2.79±1.62
U-Net	4.88±1.64	4.15±1.28	5.07±2.26	5.17±2.32	2.89±1.26	2.76±1.52
P value	**0.030**	**0.010**	**0.003**	0.559	**0.041**	0.781

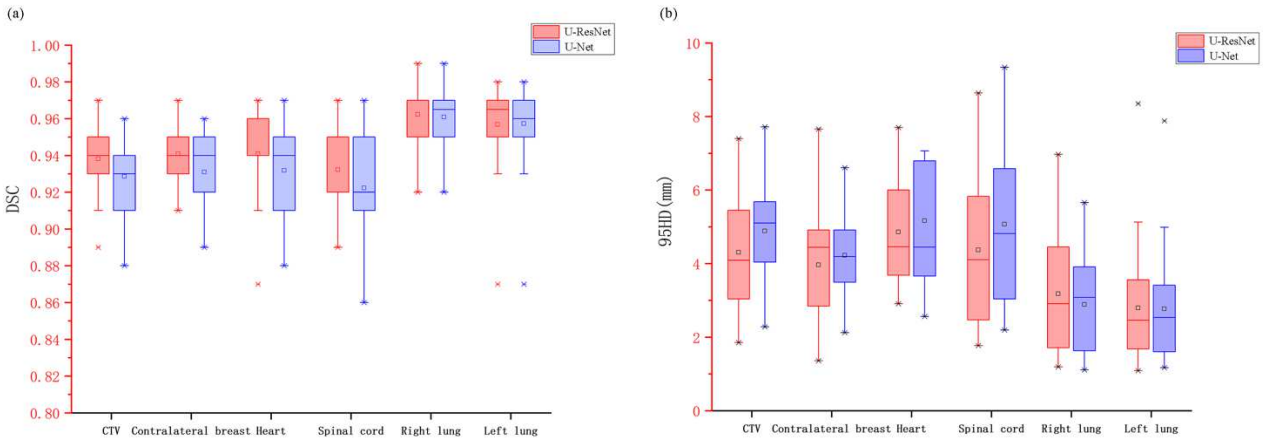

Fig. 2 Boxplots obtained for (a) DSC and (b) 95HD analyses of U-ResNet and U-Net.

Fig. 3 shows the visualization segmentation samples in different cases. The auto-segmented contours with U-ResNet were in good concordance with the GT contours.

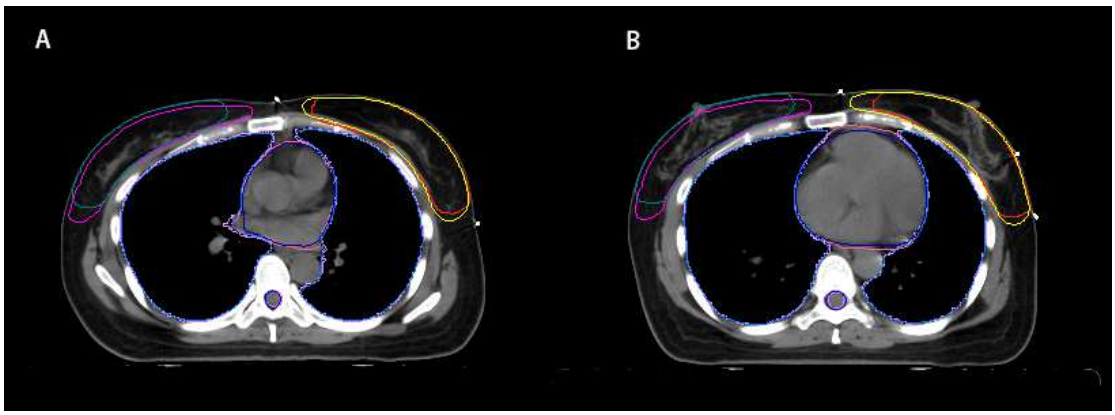

Fig. 3 CTV and OARs contours generated by GT and AI after breast conservative surgery. Yellow lines are CTV contours generated by AI, red lines are CTV contours by GT. Blue lines are OARs contours by AI, while pink lines are OARs generated by GT.

3.2. Oncologist evaluation

Tables 3 and **4** show the oncologist evaluation results of OARs and CTV contours. Scores ≥2 were defined as suitable for clinical application. When using our grading criteria for contour evaluation, the majority of AI- and GT-generated OARs contours were deemed acceptable by the experts. Only 1 contour (5%) of the heart was assessed to require major revision by oncologist A.

Table 3. Evaluation for CTV and OARs by oncologist A.

	CTV		Contra-lateral Breast		Spinal cord		Heart		Right lung		Left lung	
Scores	**AI**	**GT**	**AI**	**GT**	**AI**	**GT**	**AI**	**GT**	**AI**	**GT**	**AI**	**GT**
0	0	0	0	0	0	0	0	0	0	0	0	0
1	0.6%	1.9%	0	0	0	0	0	5%	0	0	0	0
2	7%	7.4%	30%	35%	5%	20%	20%	20%	20%	20%	10%	0
3	92.4%	90.7%	70%	65%	95%	80%	80%	75%	80%	80%	90%	100%
P value	0.612		0.414		0.083		0.527		1.00		0.157	

Table 4. Evaluation for CTV and OARs by oncologist B.

	CTV		Contra-lateral Breast		Spinal cord		Heart		Right lung		Left lung	
Scores	**AI**	**GT**	**AI**	**GT**	**AI**	**GT**	**AI**	**GT**	**AI**	**GT**	**AI**	**GT**
0	0	0	0	0	0	0	0	0	0	0	0	0
1	0.6%	0.6%	0	0	0	0	0	0	0	0	0	0
2	23.5%	14.9%	10%	15%	0	0	0	0	0	0	0	0
3	75.9%	85.5%	90%	85%	100%	100%	100%	100%	100%	100%	100%	100%
P value	0.612		0.655		1.00		1.00		1.00		1.00	

Regarding CTV contours, 99.4% of those generated by AI were clinically acceptable by oncologist A, compared with 98.1% of GT segmentations. For oncologist B, the results were 99.4% for both methods. The average CTV scores for AI and GT were 2.92 vs. 2.89 when evaluated by oncologist A (*P*=.612) and 2.75 vs. 2.83 by oncologist B (*P*=.213), with no statistical differences.

Wilcoxon matched-pairs test was performed for the evaluation of the two oncologists for AI and GT contours separately. The results indicated that the average score of

oncologist A was higher than that of oncologist B in AI contours, with a significantly statistical difference (*P*=.009 for AI contours and *P*=.314 for GT contours). The comparison of the average CTV scores evaluated by two oncologists is shown in **Fig. 4**.

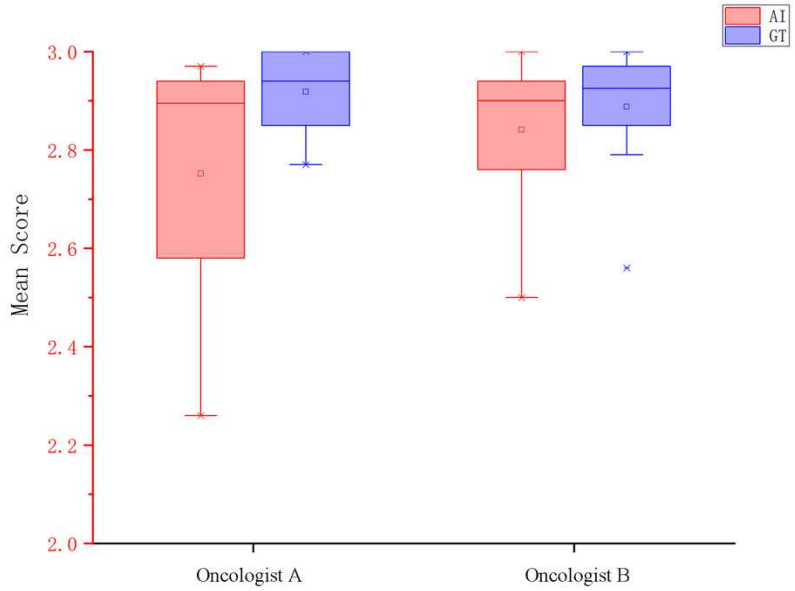

Fig. 4 The average CTV scores evaluated by two oncologists.

The evaluation results of the two oncologists were further analyzed for consistency. We independently collected the CTV scores of all the 650 slices generated by both AI and GT segmentations, and used the data to calculate weighted Kappa coefficient. The results are shown in **Table 5**. Of all the 650 slices, 532(81.8%) were evaluated with the same CTV score. The consistency between two oncologists were not good (Kappa=0.282).

Table 5. The consistency test between two oncologists.

CTV score		Doctor A				
		0	**1**	**2**	**3**	**Total**
Doctor B	**0**	0	0	0	0	**0**
	1	0	2	4	17	**23**
	2	0	5	26	75	**106**
	3	0	0	17	504	**521**
	Total	**0**	**7**	**47**	**596**	**650**

3.3. Time cost

Time for auto-segmentation of CTV and OARs with U-ResNet were 3.88 s and 6.15 s, compared with 20 minutes and 30 minutes by experienced oncologists. With AI assistance, the delineation time can be reduced to 10 minutes and 5 minutes for CTV contouring and OARs contouring, separately.

4. Discussion

Accurate and consistent delineation of CTV and OARs is a basic requirement for contemporary radiotherapy planning, while it is also the most burdensome step in the radiotherapy workflow[25; 26]. Manual delineation is a time-consuming process and has considerable inter- and intra-observer variability in anatomical contouring[27; 28]. In recent years, computer-assisted automatic segmentation techniques have made great breakthroughs in increasing reliability and accuracy as well as in relieving radiation oncologists from time-intensive contouring.

Among these automatic methods, CNNs are the most advanced method available for medical images and have shown better performance than atlas-based methods[29]. As a completely end-to-end network, only a limited amount of data is required. Among all the CNN-based models, U-Net has been a remarkable and the most popular deep network. However, it may lose some abstract information with relatively lower level convolutional layers. To alleviate the disparity between the encoder-decoder features, we have trained and evaluated a new model based on the 2D U-Net model.

Our model was based on U-Net architecture. Therefore, the performance of the proposed model was also compared with U-Net. During the training stage, U-Net had the same training configuration as that of the proposed model. This was the first study assessing the performance of both CTV and OARs segmentation for breast-conservative radiotherapy. The analysis revealed that U-ResNet algorithm outperformed the U-Net algorithms. Moreover, U-ResNet performed well, with good agreement to the segmentations contoured manually by oncologists.

The DSC and HD are used as quantitative evaluation metrics to assess the proposed method. DSC values are used more commonly than HD values in the literature. Numerous studies have reported DSC values of CTV ranges from 0.88~0.93[16; 30-32]. The average DSC of our proposed model was 0.94, which was higher than those in historical reports. The result indicated a strong concordance between our automatic model and human experts for CTV contouring. The corresponding average DSC of U-Net was 0.93. For our model, we also used the 95HD to exclude the unreasonable distances caused by outliers, and the value was 4.31 mm for CTV.

According to HD values, our model performed better than DDCNN (15.6 mm), DDNN (14.1 mm), and DD-ResNet (10.7 mm) in left breast CTV, as reported by Men K et al[16]. Moreover, we also evaluated the 95HD for OARs. Among all OARs, the best values were achieved for both lungs (95HD=3.18 mm, DSC=0.96). This is mainly because the lung has good low-contrast visibility and a relatively regular shape. Both of the above metrics are statistically significant. Based on the results stated above, we can demonstrate that U-ResNet is superior to the U-Net architecture for this task.

Except for performance metrics, we randomly distributed the AI and GT contours to experienced oncologists for further evaluation to verify their significance in clinical practice. The results showed that the majority of the AI contours can be accepted for subsequent treatment. There are no significant differences in scores grading between AI and GT contours for CTV and all OARs, meaning that the U-ResNet model performed well, with good agreement for the manual contours. However, a Wilcoxon matched-pairs test indicated the significant difference between the evaluation of two oncologists. The inter-observer variability of the delineation standard is also one of the limitations of our study.

In addition, the consistency between the two radiation oncologists did not seem to be good. Among all the 650 slices of CTV marked with AI and GT contours, 532 slices(81.8%) were evaluated with the same CTV score, and The weighted Kappa test (*Kappa* = .282) showed the poor consistency between the oncologists. The results proved the considerable inter- and intra-observer variability, resulting in different

judgment criteria. This may illustrate the fact that the acceptance of AI contouring methods is still impacted by the opinion and expertise of the treating radiation oncologists. We also evaluated the time needed for segmentation. The proposed model can significantly reduce the time cost.

Several limitations of our study should be noted. First, the study is a single-center study, and the ground truth contours were approved by only two oncologists. Therefore, the proposed model cannot meet the contouring preferences of other centers and all clinicians. In the future, multi-center research should be conducted to obtain larger datasets to improve the generalization ability of the auto-segmentation model. Second, studies have suggested that 3D architecture showed better performance on segmentation compared with 2D[33]. We may consider extending our model to 3D U-Net in the future.

5. Conclusion

Accurate and consistent segmentation is important for improving radiotherapy outcomes. Our study implemented a U-ResNet model to auto-delineate the CTV and OARs for breast conservative radiotherapy on planning CT images. The results showed that AI assistance can effectively improve consistency in contouring and streamlining radiotherapy workflows. In the future, with the assistance of AI, we may be able to obtain an initial standard segmentation to reduce the bias caused by observer preferences. However, for different patients and diseases, the contouring details should still be delineated specifically according to the principle of

individualization.

Declarations

Funding

This work was supported by the Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (grant numbers 2019XK320014).

Conflicts of interest

Author Shaobin Wang, Qi Chen and Yu Chen were employed by the company MedMind Technology Co. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Availability of data and material

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Code availability

The code used or analysed during the current study are available from the corresponding author on reasonable request.

Author's contributions

Zhikai Liu and Fangjie Liu contributed to the conception of the study; Fangjie Liu and Xia Liu delineated CTV and OARs; Zhikai Liu and Jing Shen evaluated the result of GT and AI delineation; Fangjie Liu and Yinjie Tao performed the data analyses and wrote the manuscript; Other authors helped perform the analysis with constructive discussions. All authors read and approved the final manuscript.

Ethics approval

This study was approved by the Institutional Review Board of Peking Union Medical College Hospital.

Consent to participate

Written informed consent was obtained from individual or guardian participants.

Consent for publication

Written informed consent for publication was obtained from all participants.

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Figures

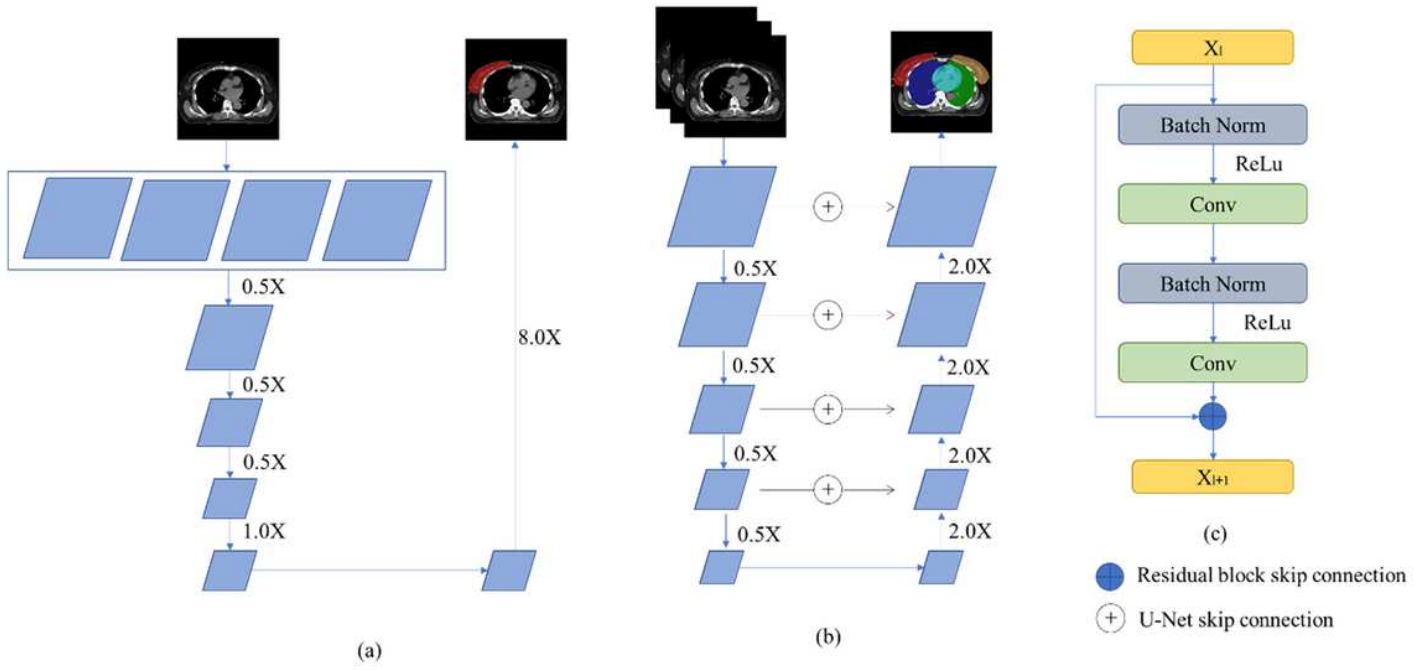

Figure 1

Architercture of (a) deep dilated convolutional neural network (DDCNN), (b) our proposed network, and (c) the residual block used in decoder part of our network.

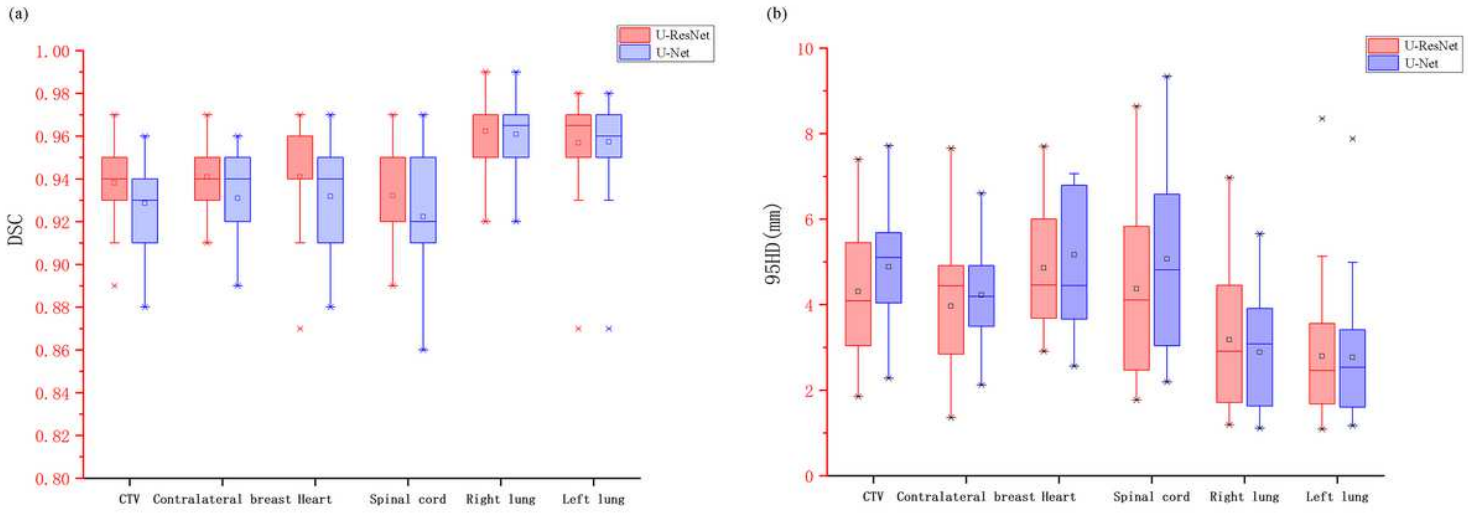

Figure 2

Boxplots obtained for DSC and 95HD analyses of RTD-Net and U-Net. (a) DSC analyse, (b). 95HD analyse.

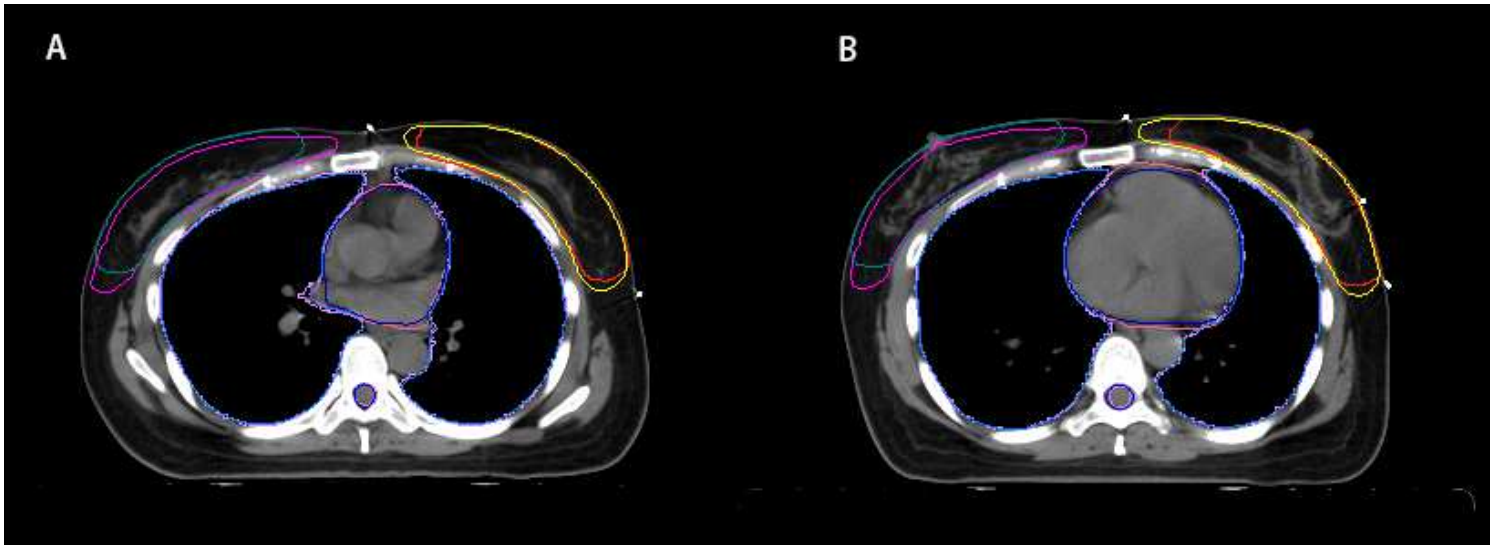

Figure 3

CTV and OARs contours generated by GT and AI after breast conservative surgery. Yellow lines are CTV contours generated by AI, red lines are CTV contours by GT. Blue lines are OARs contours by AI, while pink lines are OARs generated by GT.

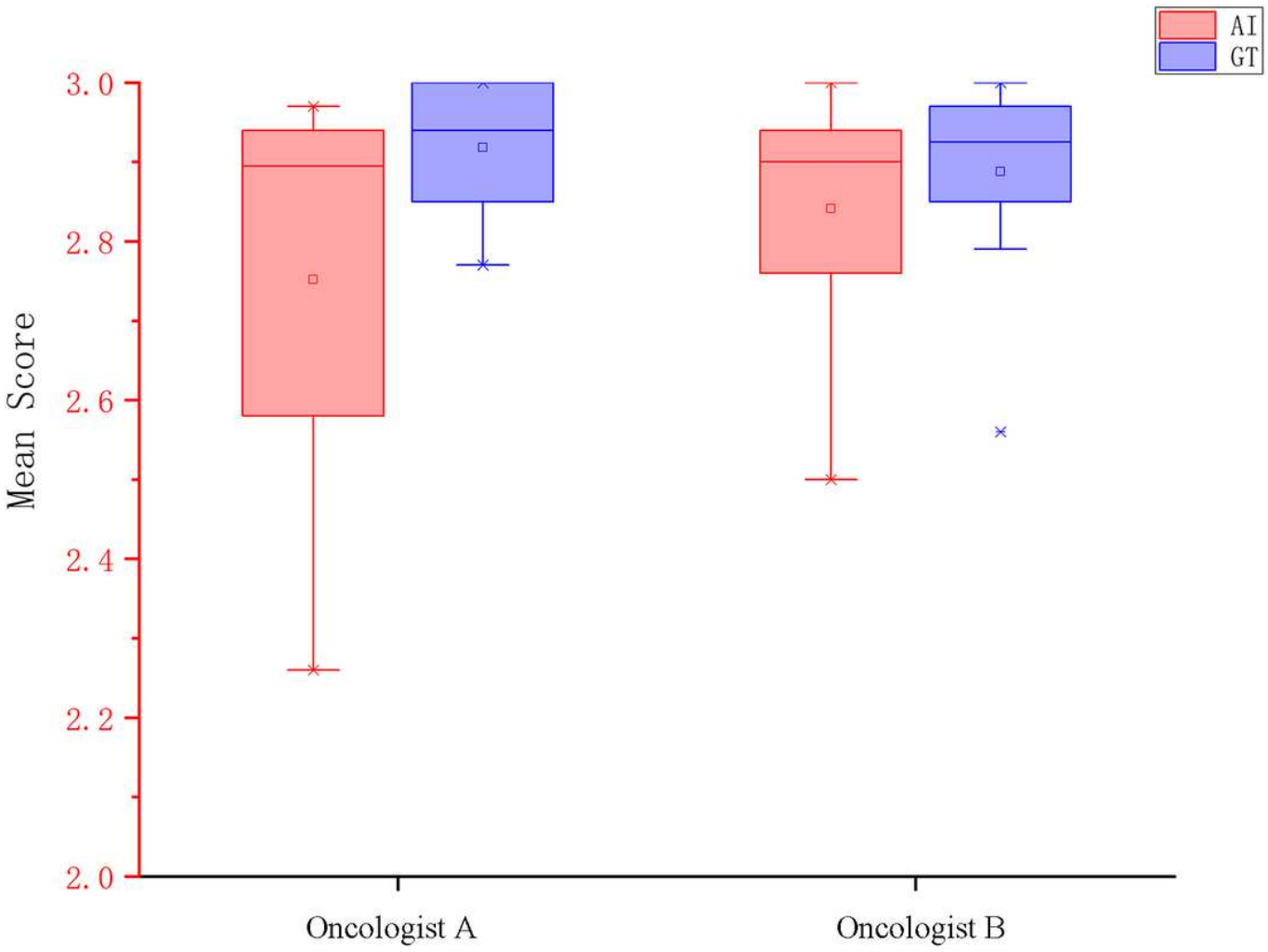

Figure 4

The average CTV scores evaluated by two oncologists.