

Clinical Validation and Treatment Plan Evaluation Based on Auto-Delineation of the Clinical Target Volume for Prostate Cancer Radiotherapy

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Abstract

Purpose

Clinical target volumes (CTV) and organs at risk (OAR) could be auto-contoured to save workload. The goal of this study was to assess a convolutional neural network (CNN) for totally automatic and accurate CTV and OAR in prostate cancer, while also comparing anticipated treatment plans based on auto-contouring CTV to clinical plans.

Methods

From January 2013 to January 2019, 217 computed tomography (CT) scans of patients with locally advanced prostate cancer treated at our hospital were collected and analyzed. CTV and OAR were delineated with a deep learning based method, which named CUNet. The performance of this strategy was evaluated using the mean Dice similarity coefficient (DSC), 95th percentile Hausdorff distance (95HD), and subjective evaluation. Treatment plans were graded using predetermined evaluation criteria, and % errors for clinical doses to the planned target volume (PTV) and organs at risk(OARs) were calculated.

Results

The defined CTVs had mean DSC and 95HD values of 0.84 and 5.04 mm, respectively. For one patient's CT scans, the average delineation time was less than 15 seconds. When CTV outlines from CUNet were blindly chosen and compared to GT, the overall positive rate in clinicians A and B was 53.15% vs 46.85%, and 54.05% vs 45.95%, respectively ($P > 0.05$), demonstrating that our deep machine learning model performed as good as or better than human demarcation. Furthermore, 8 testing patients were chosen at random to design the predicted plan based on the auto-contouring CTV and OAR, demonstrating acceptable agreement with the clinical plan: average absolute dose differences of D2, D50, D98, Dmean for PTV are within 0.74%, and average absolute volume differences of V45, V50 for OARs are within 3.4%. Without statistical significance ($p > 0.05$), the projected findings are comparable to clinical truth.

Conclusion

The experimental results show that the CTV and OARs defined by CUNet for prostate cancer were quite close to the ground reality. CUNet has the potential to cut radiation oncologists' contouring time in half. When compared to clinical plans, the differences between estimated doses to CTV and OAR based on auto-contouring were small, with no statistical significance, indicating that treatment planning for prostate cancer based on auto-contouring has potential.

1. Introduction

Prostate cancer is the most common non-cutaneous cancer in males, and it is also the second highest cause of death from cancer[1]. Prostate cancer is expected to affect 1 out of every 9 men at some point in their lives[2]. For prostate cancer patients, intensity-modulated radiation therapy (IMRT) is an important aspect of current cancer care; with proper treatment, the 5-years survival rate is 98.2%[3]. Owing to the complex dose distributions in IMRT, radiation doses to clinical target volume (CTV) and organ-at-risk (OAR) can often be significantly and one of the essential steps for successful IMRT delivery. Such delineation is conventionally performed by radiotherapy oncologists through laborious manual delineation. The delineation is time-consuming[4]. Therefore, computational tools that can greatly reduce the radiotherapy oncologists' manual efforts, in an automatically and accurately way .

The hoppoint convolutional neural networks (CNNs) have demonstrated their advantages in performing medical segmentation tasks in recent years[5][6][7], having been commonly used in the CTV or OAR delineation of brain tumor[8], head and neck (H&N) cancer[9][10][11][12], breast cancer[13], esophageal cancer[14][15], rectal cancer [16][17] and cervical cancer[18]. As a well-known CNN architecture for medical image segmentation, U-Net was commonly used among all the CNN based contour delineation models[6][19]. These studies demonstrate that combining U-Net with an elegant feature extraction architecture would be an efficient way to get an effective CNN architecture for target region segmentation. On the other hand, attention has been proved to be an effective way to improve the network performance [20][21][22][23][24][25]. By using attention mechanism, the network could focus on important features and suppress unnecessary ones. In this work, we integrate Convolutional Block Attention Module (CBAM) module[26] that emphasize meaningful features along both channel and spatial dimensions into U-Net to facilitate automatic CTV and OAR delineation.

For the radiotherapy in prostate cancer, intra- and inter-observer variability is one of the major challenges in radiotherapy planning[27]. we further tried to designed the clinical plan on auto-contouring CTV and OAR, to compare its performance with clinical treatment plans, for exploring its feasibility and accuracy in clinical use. The auto-contouring CT-based dose prediction could reduce the time required for both the iterative optimization process and the structure contouring, allowing physicians and dosimetrists to focus their expertise on more challenging cases. To our knowledge, this is the first report to predict the dose distribution for IMRT using only auto-contouring deep learning CT images.

2. Materials And Methods

2.1 Patients database

The study was authorized by our hospital's Institutional Review Board. From January 2013 to January 2019, CT data from 217 patients with locally advanced prostate cancer were collected. Patients characteristics such as age, pathological type, were statistically examined. The patients were given a total dose of 70 Gy over 25 fraction, using 6-Mv X ray of intensity modulated radiation treatment (IMRT).

All of the data was taken with a Brilliance CT Big Bore with a size of 512512 pixels (pixel spacing: ranging from 0.770.77 to 1.951.95 millimeter) and a 5-millimeter thickness (Philips Healthcare, Best, the Netherlands). As the segmentation ground truth, qualified radiation oncologists manually drew the CTV and OAR contours prior to irradiation in clinical practice (GT). The CTV definition was created using a widely acknowledged consensus criteria [28] with certain modifications. The CTV was created by combining the prostate and seminal vesicle. To ensure the quality of the delineation, a professional radiation oncologist committee comprised of eight oncologists with more than 10 years of experience in radiotherapy for pelvic tumors reviewed and modified (only when necessary) all of the delineated contours together, as is the clinical routine in our department.

2.2 Machine learning models Data and preprocessing

The supplied CT slice intensity was thresholded between -1024 and 2048 HU. For each patient, zero-mean normalization was used to make the input picture data zero-centered and distributed in the same range, making training less sensitive to feature size and allowing for well-conditioned optimization. A training-validation set (195 patients) and a test set were chosen at random from the dataset (28 patients).

The architecture of CUNet is depicted in Fig. 1. 3D U-Net backbone architecture consisting of an encoding path and a decoding path is used. To concatenate the multilevel features thus to take advantage of both the low-level and high-level information, the encoding path and decoding path are combined together by a skip connection in the typical U-Net. As a result, the network learns to use the features equally. In CUNet, instead of combining the features directly, an attention center block is proposed to weight the features before being concatenated to the encoder part. As a result, the network will focus on a specific part of the features instead of the all the features. The attention center block is a Convolutional Block Attention Module (CBAM) module integrated with a ResBlock in ResNet [23]. CBAM infers attention maps along channel dimension and spatial dimension sequentially. Each attention maps are multiplied to the input feature map for adaptive feature refinement. The final feature map is then connected with the initial input feature map by a residual block skip connection. The channel attention map exploits the inter-channel relationship of features, showing 'what' is meaningful given an input image. The spatial attention map is generated by utilizing the inter-spatial relationship of features. Informative feature part will be emphasized while other part will be suppressed.

CUNet was used to train the contours of CTV,bladder, rectum, left femoral head, and right femoral head with 5 output channels.

2.3 Model Training

A total of 195 CT scans were used for training and validation, using a five-fold cross-validation technique. During training, patches with dimensions (64, 64, 64) were randomly generated on the fly and used to train the model from scratch. No augmentation was used. The model's output value was in the range of 0 to 1. The segmented mask's foreground was set to pixels with an output value greater than 0.5. After that, the foreground was given a contour extraction. The network was trained on an NVIDIA TITAN Xp with 12

GB of RAM. The Adam optimizer was used throughout the network, with an initial learning rate of 0.0001 and a decay rate of gamma 0.9 for each epoch. The total number of epochs was 50.

2.4 Model evaluation

2.4.1 Quantitative evaluation metrics

The contouring accuracy was measured using the Dice similarity coefficient (DSC) and the 95th percentile Hausdorff distance (95HD). The DSC calculates the volumetric overlap ratio between segmented masks; a higher number indicates a higher overlap ratio. When two masks are totally identical, the value equals 1. The 95HD indicates how well two outlines agree; a higher value suggests a greater divergence.

2.4.2 Oncologist evaluation

The AI and GT outlines were randomly marked with red and green outline lines, respectively, in a clinically blinded assessment of drawing layers from 2237 layers of slices of 28 patients, sorting after creating 111 layers, and randomly marking the AI and GT outlines with red and green outline lines. Two clinicians with more than ten years of experience in prostate cancer radiation blindly chose which contour was superior for clinical use. It was recorded as a positive outcome if the AI group performed better, altogether how many layers AI had won were counted.

2.5 Plan evaluation

The accuracy of dose distribution prediction for OARs and PTV was further tested using a global 3D gamma analysis, which is used as a tool for IMRT plan dosage verification. Meanwhile, anticipated treatment plans based on auto-contouring CTV were compared to clinical plans.

The total DVH curves of PTV and distinct OARs were first exhibited between the prediction and clinical truth plans in terms of DVH parameters. Second, the clinically relevant dosimetric indexes (DI) were determined, including the mean dose (D_{mean}), D_2 , D_{50} , D_{98} for PTV (where D_i represents the dose received by i percent of PTV volume) and D_{mean} , V_{45} , V_{50} for OARs (where V_i represents the volume fraction of OARs irradiated by i Gy); homogeneity index (HI) and conformation index (CI) for PTV were further calculated as following formula: where V_{ptv} and V_{pres} are the volume of PTV and the prescription dose region, respectively, and V_{ref} is the irradiated PTV volume of the prescription dose.

$$HI = \frac{D_2 - D_{98}}{D_{50}}$$

$$CI = \frac{V_{ref} * V_{ref}}{V_{ptv} * V_{pres}}$$

2.6 Statistical analysis

The CTV and OAR contours predicted from CUNet were transferred to a treatment planning system (TPS) for radiotherapy plan designing. The time used for revising all the CTV and OARs' contours before radiotherapy planning were recorded as minutes per case. The performance of the models was further evaluated by a percent error relative to the prescribed dose, calculated as $(\text{predicted dose} - \text{clinical dose}) / \text{prescribed dose} \times 100\%$. Significance between the average and maximum doses of the clinical plan and the predicted and mimicked plans of each of the models were investigated and analysed, statistical significance was set at two-tailed $P < 0.05$.

3. Results

3.1 Quantitative analysis of CTV contour

The defined CTVs had mean DSC and 95HD values of 0.84 and 5.04 mm, respectively. For one patient's CT scans, the average delineation time was less than 15 seconds. See Table 1 for further information.

Table 1
The mean DSC and 95HD
values of selected 28 CT
scans

No.	Dice	HD 95
1	0.85	5.89
2	0.80	7.67
3	0.80	8.62
4	0.80	2.36
5	0.84	6.23
6	0.94	2.97
7	0.87	3.54
8	0.88	3.29
9	0.90	2.52
10	0.81	3.97
11	0.81	4.77
12	0.84	4.42
13	0.68	11.09
14	0.79	4.83
15	0.87	3.71
16	0.90	4.10
17	0.86	4.57
18	0.79	4.34
19	0.85	4.36
20	0.81	4.35
21	0.75	10.76
22	0.91	3.08
23	0.85	4.72
24	0.81	6.04
25	0.84	5.99
26	0.90	3.51

No.	Dice	HD 95
27	0.88	3.98
28	0.85	5.40
Mean	0.84	5.04
Std	0.05	2.15

3.2 The Turing imitation test

In the test dataset, 10% of the slices with GT masks were chosen at random to mark the contours of both AI and GT at the same time. CTV contours from AI and GT were shown for each slice, with the color of these two contours being assigned at random to red or green. A total of 112 slices were chosen from 28 CT images.

Table 2
The results of the Turing-like imitation test.

	Clinician A		Clinician B	
	Slice	Ratio	Slice	Ratio
Positive	59	53.15%	60	54.05%
Negative	53	46.85%	52	45.95%
Total	112	P>0.05	112	P>0.05

Subclass analysis was performed to evaluate individual oncologist and CT slices, as shown in Table 3. Sample CTV delineations are presented in Figure 2.

Table 3
The subclass analysis results of the Turing-like imitation test.

Clinician A	Clinician B		
	Negative	Positive	Total
Negative	28	25	53
Positive	24	35	59
Total	52	60	112

3.3 Statistics of DVH dosimetric index

Overall DVH comparisons of PTV and OARs between clinical and predicted results for eight randomly selected testing subjects, revealing that clinical and anticipated DVHs of PTV and OARs have an acceptable agreement for each patient.

The mean and standard deviation of the clinically relevant DI for PTV and OARs in 8 testing patients are shown in Table 4. The average absolute dose differences of D2, D50, D98, and Dmean for PTV are found to be within 0.74 percent, and the average absolute volume differences of V45, V50 for OARs are found to be within 3.4 percent. Without statistical significance ($P > 0.05$), the projected findings are comparable to clinical truth.

Table 4
Mean and standard deviation of dosimetric index for planned target volume(PTV) and organs at risks(OARs).

DI	Clinical	Prediction	P-value
PTV			
D98(Gy)	68.20±0.98	67.93±1.48	0.65
D50(Gy)	71.96±0.62	71.81±0.62	0.62
D2(Gy)	73.32±0.75	73.08±0.68	0.51
Dmean(Gy)	71.78±0.52	71.59±0.55	0.50
Dmax(Gy)	75.46±1.32	74.72±0.72	0.18
HI	1.05±0.02	1.05±0.02	0.96
CI	0.20±0.33	0.03±0.06	0.17
Rectum			
V50(%)	14.75±5.71	14.95±5.70	0.94
V45(%)	16.86±6.07	17.03±5.83	0.95
D25(Gy)	30.36±14.01	29.39±12.43	0.88
D50(Gy)	8.76±3.82	7.92±3.14	0.63
Dmean(Gy)	19.34±5.07	19.00±4.04	0.88
Bladder			
V50(%)	13.25±7.39	14.99±7.82	0.64
V45(%)	15.01±8.17	16.77±8.53	0.67
D25(Gy)	25.29±15.76	28.68±16.89	0.67
D50(Gy)	8.82±6.77	9.96±6.55	0.73
Dmean(Gy)	17.98±7.20	19.40±7.50	0.70
left femoral head			
D5(Gy)	16.20±2.34	16.72±2.39	0.65
Dmean(Gy)	11.20±2.43	11.17±2.57	0.98
Right femoral head			
D5(Gy)	16.64±2.67	17.31±2.99	0.63
Dmean(Gy)	11.27±1.99	11.65±2.37	0.72

4. Discussion

Radiation oncology for prostate cancer is important as it can decrease the mortality associated with this disease. CTV and OAR contouring for treatment is still fundamental, time-consuming and prone to human-errors, leading to potentially avoidable delays in start of treatment. Many current CNNs have paid attention to auto-segmenting prostate CTV contouring by CNN-based method, although the performance of the models have achieved satisfactory results, there is still room for improvement, and there is arguably a long way before these models can be used safely and effectively in clinical practice. Hence, we collected and standardized CT images from 237 patients in our department and proposed a new deep learning network named CUNet to automatically segment the CTV and OARs in prostate cancer.

The performance of CUNet for prostate CTV contouring was comprehensively evaluated with the mean DSC and 95HD values were 0.84 and 5.04 mm for the delineated CTVs, showing the high quantitative of CTV contour. Moreover in the turing imitation test, two clinicians with more than 10 years of experience in radiotherapy for prostate tumors blindly selected which one contour was better for clinical application, the overall positive rate in clinician A and B were 53.15% vs 46.85%, and 54.05% vs 45.95%($P>0.05$), demonstrating our deep machine learning model performed equally well or even better than human delineation. The mean DSC and 95HD values of the CTV contours predicted from CUNet were 0.86 ± 0.04 and 5.34 ± 1.56 mm

An inherent product of the auto-contouring of the CTV is a reduction in the radiation oncologists' contouring time. The average manual CTV contouring time for one prostate cancer patient was 10-20 minutes[31], while the corresponding time was 15 seconds for CUNet. Afterwards, each case required an average of 2 minutes to be further manually revised. In total, it took approximately 8 minutes for the whole process including 5 minutes for manually data transferring.

Treatment plans were further scored and compared between clinical and predicted(auto-contouring) CTV, The overall DVH comparisons of PTV and OARs for four randomly selected 8 testing patients showed that the average absolute dose differences of D2, D50, D98, Dmean for PTV are within 0.74%, and the average absolute volume differences of V45, V50 for OARs are <3.4%. The predicted results are comparable to clinical truth without statistical significance ($P > 0.05$). see the compare in **Figure 3** below. All these results show that dose distributions prediction using auto-contouring CTV are accurate. Differences between predicted doses to OARs of the models were small when compared to clinical plans, and not found to be clinically relevant, showing a potential in automated treatment planning for prostate cancer. The predicted dose distribution can be taken as a quality control tool for clinical treatment plan, by which the planners can know whether or where the dose distributions can be improved, and the physicians can immediately view 3D dose distributions to adjust OARs dose constraint requirements. Meanwhile, the planners can take advantage of these OARs DVH from dose distributions to define

optimization objective function which may improve the quality and consistency of treatment plans, and reduce planning time.

Currently, all the datasets have been collected from a single institution, on the other hand, the current results in prostate CTV and OAR contouring demonstrate that CUNet is able to learn high-level semantic features well, and this method may also have the potential to be used for volume delineations in other cancers. It would also be a good exploring direction to further collecting more data from multiple manufacturers and multiple institutions for validating, we will explore this possibility in future studies.

5. Conclusions

Accurate and consistent delineation of CTV and OAR is of significant importance in radiotherapy. This study presents a novel CNN (CUNet) for fully automatic and accurate CTV and OAR segmentation in prostate cancer. Performance of CUNet was evaluated quantitatively and subjectively for 28 patients. Accurate delineation results were provided by CUNet and high clinical acceptability was achieved. The results demonstrate that CUNet can be used to improve efficiency and reduce adverse effects with random errors in delineating CTV and OARs in cervical cancer patients.

Abbreviations

CTV: Clinical target volumes;

OAR: organs at risk;

CNN: convolutional neural network

IMRT: intensity modulated radiation therapy;

Declarations

Ethical approval and Consent to participate

The Institutional Review Board (IRB) of Peking Union Medical College Hospital (PUMCH) reviewed the protocol. This is retrospective study. The protocol is rational and scientific. The study accords with principle of ethics. The IRB thus approve the protocol. This is a retrospective study and written human subject consent was unnecessary.

Consent for publication

Not applicable

Availability of data and materials:

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

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

SJ and TJY were responsible for data collection and drafted the manuscript;

GQ, ZHN, DTT, HL participated in the design of the study;

SJ performed statistic analysis and data interpretation;

SJ and LZK designed the study and revised the manuscript;

All authors read and approved the manuscript.

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No

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Figures

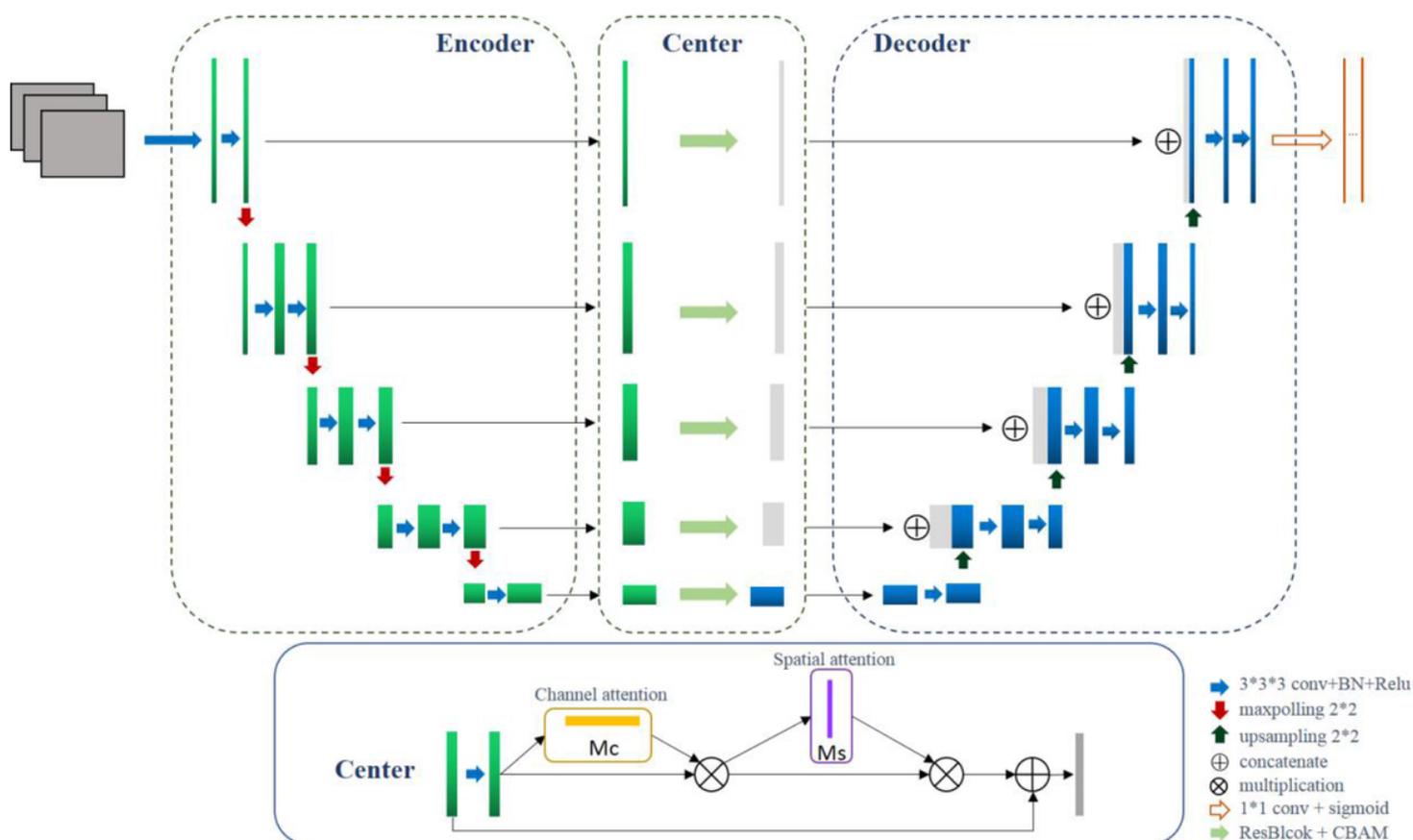


Figure 1

The architecture of the proposed CUNet.

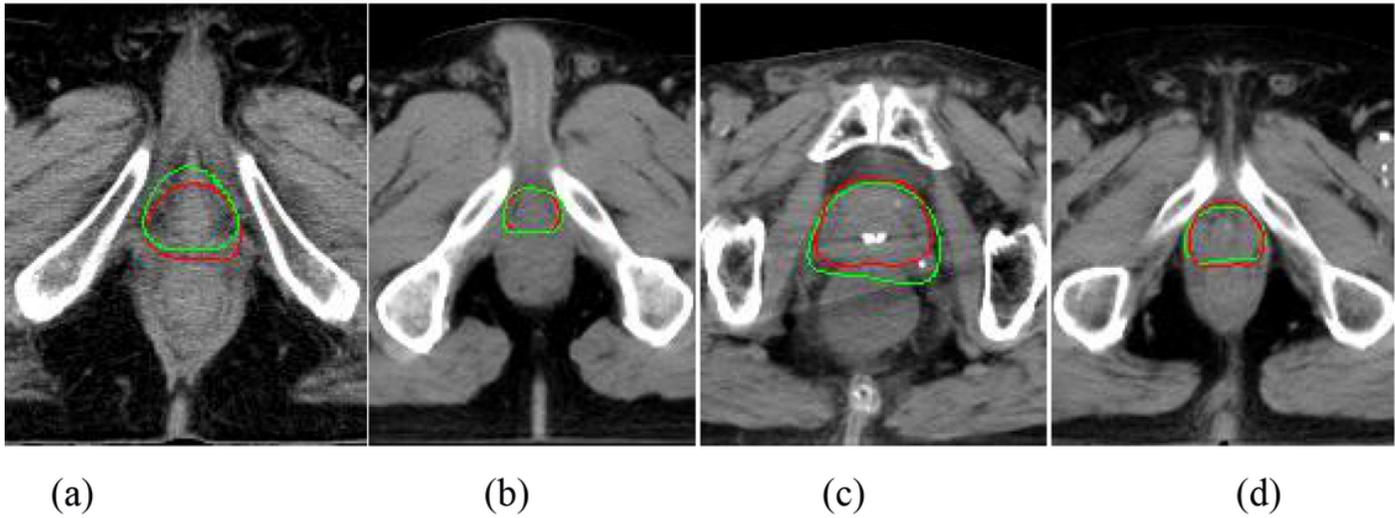
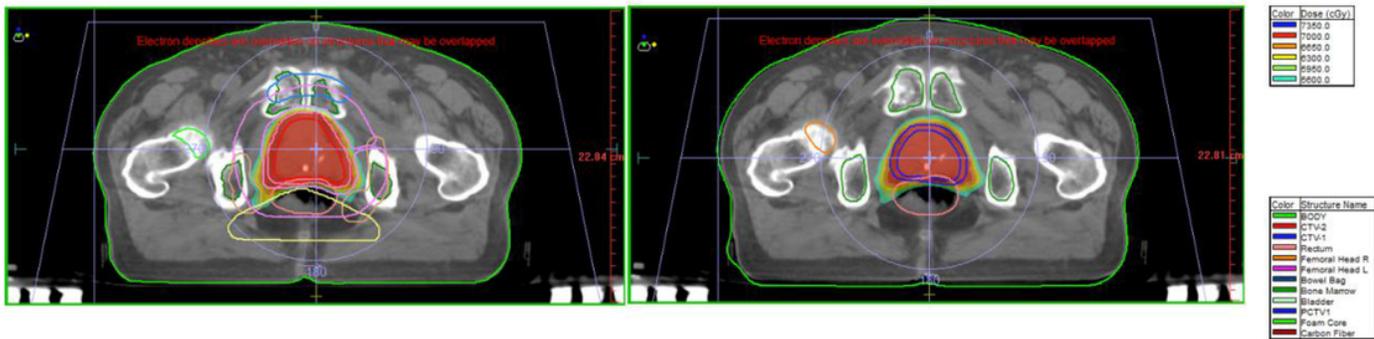


Figure 2

The distribution map of the positive results.

(a) A sample slice where GT contour was approved by both the oncologist. GT contours in green line. AI contours in red. (b) A sample slice where AI contour was approved by both the oncologist. AI contours in red line. GT contours in green. (c) A sample slice where AI contour was only approved by oncologist A. AI contours in green line. GT contours in red. (d) A sample slice where AI contour was only approved by oncologist B. AI contours in green line. GT contours in red.



(A) clinical plan

(B) predicted plan

Figure 3

Example of the clinical and predicted plans

(a) showed the clinical plan and (b) the predicted plan based on auto-contouring CTV in the same patient.