Advances in automatic delineation of target volume and cardiac substructure in breast cancer radiotherapy (Review)

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Abstract. Postoperative adjuvant radiotherapy plays an important role in the treatment of patients with breast cancer. With the continuous development of radiotherapeutic technologies, the requirements for radiotherapeutic accuracy are increasingly high. The accuracy of target volume and organ at risk delineation significantly affects the effect of radiotherapy. Automatic delineation software has been continuously developed for the automatic delineation of target areas and organs at risk. Automatic segmentation based on an atlas and deep learning is a hot topic in current clinical research. Automatic delineation can not only reduce the workload and delineation times, but also establish a uniform delineation standard and reduce inter-observer and intra-observer differences. In patients with breast cancer, especially in patients who undergo left breast radiotherapy, the protection of the heart is particularly important. Treating the whole heart as an organ at risk cannot meet the clinical needs, and it is necessary to limit the dose to specific cardiac substructures. The present review discusses the importance of automatic delineation of target volume and cardiac substructure in radiotherapy for patients with breast cancer.

Contents

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1. Introduction

The incidence of breast cancer in 2020 ranked first worldwide, and the disease was the main cause of death among women (1). Radiotherapy is an important treatment for breast cancer. Adjuvant radiotherapy after breast cancer surgery is beneficial to improve the local tumor control rate, reduce the recurrence and metastasis of breast tissue and surrounding lymph node tumors, and improve the survival rate of patients. The local control rate, distant metastasis rate and overall survival rate of radiotherapy after breast-conserving surgery for breast cancer can achieve comparable or even better results than those of traditional radical mastectomy (2-4). The core of a radiotherapy plan is the delineation of the therapeutic target area, so that the radiation can maximize the destruction of tumor tissue and minimize the irradiation of normal tissues and organs. The delineation accuracy of tumor contours and surrounding normal tissues and organs, namely the organ at risk (OAR), directly affects the therapeutic effect. The irradiation of the contralateral breast, the heart and lungs, and other OARs, will reduce the quality of life of patients, and even the heart-lung related radiotherapy complications caused by radiation will offset the gain brought by local radiotherapy for breast cancer (5,6). Manual delineation of target volume and OARs is tedious and time-consuming work, and the quality of contour delineation highly depends on the professional knowledge and experience of the clinicians, while the complexity of regional lymph node delineation is even more obvious (7-9). Automatic delineation techniques can avoid these deficiencies and provide more standardized identification of cardiac substructures.

2. Automatic delineation technology of target volume in radiotherapy for breast cancer

Atlas-based auto-segmentation (ABAS). The gold standard for target volume delineation is still manual delineation by radiologists, but there are differences in delineation results from individual physicians at different times and among different physicians, leading to differences in radiotherapy plans, which may affect the cure rate and treatment toxicity of patients (10). Studies have shown that the structural overlap between the target volume and OARs delineated by different treatment institutions and radiotherapy physicians is <10%, and the standard deviation of the volume change is as high as 60% (11). Automatic delineation can establish uniform standards, increase the consistency of contours and avoid major discrepancies. Automatic delineation of target volume and OARs in radiotherapy is via classical automatic image segmentation, which uses deformable image registration to propagate the segmentation structures from the atlas image of the patient image dataset. According to the number of the atlas, it can be divided into a single atlas and multi-atlas automatic segmentation (12). In the early studies of automatic delineation of breast cancer radiotherapy, the automatic segmentation method based on a single atlas could maintain good consistency when transforming the contour structure of the atlas to a new image, achieving 94% volume overlap and reducing the median clinical target volume (CTV) delineation time by 30%. However, when the body mass index (BMI) of the patient was quite different from that of the template patient, the effect of automatic segmentation was poor (P=0.02) (13). Fontanilla *et al* (14) studied the automatic delineation of the chest wall, heart and regional lymph nodes by single atlas automatic segmentation after a radical mastectomy. The results showed that the delineation effect of the chest wall and heart was good, with mean volume overlap rates of 91 and 93%, respectively; however, the delineation of the lymph nodes was poor. The mean volume overlap rate of supraclavicular nodes was 66% and that of internal mammary nodes was only 32%.

Due to the differences between individual patients, the diversity of organs and the uncertainty of tumor morphology, the accuracy of image registration based on a single atlas is low. This problem can be solved by establishing a larger and more diversified patient atlas dataset. Bell *et al* (15) considered the differences between observers when applying the automatic segmentation of a multi-atlas. A total of 8 observers delineated the CTV and then verified the whole breast radiotherapy cohort containing 28 datasets. The results showed that using this method for automatic delineation, the dice similarity coefficient (DSC) was >0.7, the mean absolute surface distance (MASD) was <9.3 mm and the mean delineation time was <4 min. Eldesoky *et al* (16) evaluated the clinical effectiveness of CTV and OAR classification ABAS in local regional radiotherapy for early breast cancer, as well as the repeatability of another institutional atlas in the context of multi-institutional studies. Target volumes were delineated according to European Society for Radiation and Oncology (ESTRO) delineation guidelines (17), with 50 patients from local institutions for the internal validation cohort and 40 patients from other institutions for the external validation cohort. Review and correction were then performed by a researcher to form a new corrected contour. Compared with manual delineation, automatic delineation reduced the time taken by 93%, and automatic delineation plus correction reduced the time taken by 32% (P<0.01). The speed of automatic delineation of internal validation was faster than that of external validation (P<0.05). Automatic delineation had high consistency in the heart, lungs and breasts, general consistency in the chest wall and poor consistency in the lymph nodes, which was the same as the previous study results of Fontanilla *et al* (14) and Ciardo *et al* (18). In terms of delineation time, ABAS reduced the manual delineation time before and after correction by 93 and 32%, respectively. However, some structures still needed to be corrected manually before clinical application. This study demonstrated the repeatability, consistency and versatility of ABAS for multicenter applications (16).

Currently, the position used for radiation therapy for patients with breast cancer is generally the supine position due to the comfort and repeatability in this position. However, when patients with larger breast volumes are treated in the supine position, breast tissue stacking occurs, resulting in inhomogeneity of dose to the target area and increased dose to the endangered organs, and the use of prone position radiotherapy can effectively solve such problems (19). Dipasquale *et al* (20) studied the CTV structure and its dose volume effect in patients in the prone position during auto-segmentation, and was the first study to apply ABAS to patients treated with breast cancer radiotherapy in the prone position. Compared with previous studies using the supine position, ABAS in the prone position was more accurate and reduced inter-observer and intra-observer variability. The mean DSC was 0.91, which reduced the contouring time by 40% compared with manual contouring. Patients with a DSC of >0.97 and high breast draping had better target volume dosimetry results. Another study (21) also demonstrated the efficacy of ABAS in patients receiving radiotherapy in the prone position after breast-conserving surgery for breast cancer. In this study, OARs and CTV were automatically delineated, and the DSC of the heart, lungs and breasts was >0.91, which improved the efficiency without sacrificing the contour quality of the patients with early breast cancer, and saved 56.92% of time on average. This study also confirmed the inter-observer differences in the delineation of CTV and OARs (21). When automatic delineation based on a single atlas is performed in patients receiving radiotherapy in a prone position, the samples are stratified according to BMI and breast cup size, which can not only improve the automatic segmentation atlas, but can also improve the accuracy of CTV and OAR automatic segmentation. Among the improvements, the improvement effect to the heart was particularly obvious, DSC >0.9, and the automatic drawing time was reduced to 30-40% compared with the manual delineation time (22). ABAS can also provide reliable and high-quality automatic contour delineation of CTV and OARs for patients with breast cancer in the lateral position during radiotherapy (23).

Based on the aforementioned studies, it was found that ABAS was more accurate in segmentation of large-volume, well-defined structures such as the heart, lungs and breasts, with general consistency of the automatic delineation of the chest wall. The automatic delineation of the supraclavicular, internal mammary and axillary lymph nodes had the worst effect, as the lymph nodes are small in size, have unclear boundaries and change their position with the position of the arm (24). Automatic delineation results should be reviewed and corrected for preclinical use, especially if the target volume contains regional lymph nodes. The ABAS has been widely used in clinical practice, which solves the problems of the accuracy and reliability of manual delineation, reduces the delineation time and improves the efficiency of delineation. However, the selection of atlas stratification factors will also affect the segmentation results of ABAS, and more experiments are needed to determine the optimal stratification factors.

Automatic delineation based on deep learning. Atlas-based auto-segmentation depends on the accuracy of the image registration algorithm; it does not perform well in the delineation of structures with large anatomical changes and unclear edges, such as the tumor target volume and the lymph nodes. Moreover, the unpredictability of the tumor shape makes it difficult to ensure that all cases are included in the template library. The success rate of irregular structure segmentation based on the model of normal anatomical structure is insufficient (25). With the continuous development of computer technology, deep learning of artificial intelligence has been applied to medical image processing, and breakthroughs have been made. Automatic segmentation technology based on deep learning has great potential in the daily practice of radiotherapy, as it can not only speed up the contour drawing process, improve the accuracy and consistency of the contour, and promote compliance with the delineation guidelines, but it can also promote the application of online adaptive radiotherapy (26). Compared with traditional methods using manual features, deep learning-based methods can adaptively explore representative features in medical images and also have transfer learning ability, that is, features learned from one dataset can be effectively applied to other datasets (27,28). At present, deep learning algorithms commonly used in breast cancer radiotherapy include convolutional neural networks (CNN) (28), fully convolutional networks (FCN) (29,30), U-Net (31) and generative adversarial network (GAN) (25), among others.

CNN is a neural network composed of a convolutional layer, pooling layer and fully connected layer (28). The fully convolutional network (FCN) replaces the fully connected layer with the convolutional layer based on CNN. The ability of CNN to extract features can be improved by stacking layers (i.e., model depth). With the continuous increase in model depth, the features of input data can be extracted and the network can be trained repeatedly with input data to learn more complex functions, whose performance greatly benefits from the model depth (29,30). However, in the process of training a very deep convolutional network, gradient disappearance will occur, which makes it difficult to optimize the deep convolutional network, and feature disappearance will lead to the performance degradation of segmentation. However, the residual network (ResNet) solves this problem by adding the 'shortcut connection' with the output of the convolutional layer (31). Shortcut connection refers to the direct forwarding of the feature map computed at each encoding stage to each decoding stage, allowing the decoder at each stage to learn the features that will be lost when the encoder is pooled (32). Men *et al* (33) deployed an expanded convolution module network with four paths in front of the ResNet-101 network and developed a very deep dilated residual network (DD-ResNet). DD-ResNet is an end-to-end model, which can realize rapid training and testing, automatically delineate two-dimensional (2D) breast CTV of patients with breast cancer undergoing radiotherapy after breast-conserving surgery, and is compared with the performance of deep dilated convolution neural network (DDCNN) and deep deconvolution neural network (DDNN). DDCNN and DDNN were also developed by Men *et al* (34) for the automatic delineation of CTV and OARs for rectal and nasopharyngeal carcinoma. DDCNN adopted a multi-scale convolution architecture to extract multi-scale context features in early layers, expanded the receptive field of expanded convolution at the end of the network and then replaced the fully connected layer with the fully convolutional layer to achieve pixel-by-pixel segmentation (34). DDNN performed deconvolution based on VGG-16, reconstructed high-resolution feature maps from low resolution and then replaced the fully connected layer with the fully convolutional layer to realize pixel segmentation in CT images through self-adaptation (35). Among the three different models, the segmentation effect of left breast CTV was similar to that of right breast CTV, and the overall segmentation effect of DD-ResNet was better than that of DDCNN and DDNN. The mean DSC of CTV on the left and right sides of DD-ResNet, DDCNN and DDNN was 0.91/0.91, 0.85/0.85 and 0.87/0.88, respectively. The mean Hausdorff distance (HD) was 10.7/10.5, 15.6/15.1 and 14.1/13.5 mm, respectively. The DSC of the DD-ResNet model was comparable to or even better than that of manual delineation by radiologists. Manual delineation of each patient took 10-20 min, but the automatic delineation of the DD-ResNet, DDNN and DDCNN took only 15, 21 and 4 sec, respectively. Although the training time of the DD-ResNet model was longer than that of the other two models, the overall contouring effect was good and the consistency with the contours drawn manually by experts was the best.

U-Net is a neural network architecture mainly used for image segmentation. The basic structure consists of two paths: A contraction (contracting) path, also known as the encoder or the analysis path, to extract important features of the image and reduce the resolution of the image, and the extension path, also known as the decoder or synthesis path, which gradually restores the image details, locates the size of the lesion, and restores the image to the size of the input image. The overall network structure forms a 'U' shape, and shortcut connections are adopted between corresponding layers to allow the network to retrieve the spatial information lost due to pooling operations (32,36,37).

At present, a number of image segmentation networks are being further studied based on U-Net. Liu *et al* (38) constructed a new CNN network based on 2D U-Net known as the U-ResNet model; a deep network was added in U-Net and then ResNet was used as the decoder, and the network architecture was designed as 2.5D architecture. Compared with DD-ResNet, U-ResNet had a shortcut connection between the encoder and decoder, which could reduce the loss of information. The CT images of 160 patients after breast-conserving surgery were used for training, verification and testing, and compared with the U-Net model. In the automatic delineation of CTV, the mean DSC of U-ResNet and U-Net was 0.94 and 0.93 ($P<0.001$), respectively, while the mean 95th percentile HD (95% HD) was 4.31 and 4.88 mm ($P<0.03$), respectively. In all OARs, the accuracy of U-ResNet was better than that of U-Net, and the difference was statistically significant. Senior oncologists evaluated automatically delineated CTV and OARs, and found that most of the contours were directly applicable to the clinic and the scores were not statistically different from the manually delineated contours, indicating that the U-ResNet model proposed in this study showed good consistency with manually delineated contours. However, the consistency between the two oncologists was poor, which verified the large differences between the observers. The U-ResNet model automatically delineated CTV and OARs in 10.03 sec, while manual delineation took 20-30 min, showing that the model greatly reduced the delineation time (38). Another study combined U-Net with ResNet and added multi-resolution level processing to construct a fully convolutional neural network known as BibNet, which could not only adapt the size of the input image, but also process features with different resolution sizes (39). The DSC of BibNet multi-organ delineation of the left and right breast was >0.92, the DSC of the heart was as high as 0.95, and the HD values for the left breast, right breast and heart were 20.6, 20.0 and 8.5 mm, respectively. The results were better than those of U-Net. BibNet saved patients ~15.5 min of time compared with manual contouring. The data set of the training set patients was from three different institutions, and the patients were in the supine position with their arms raised. The robustness test set was from another different institution, where the patients were in the supine position with arms raised on the affected side. The results found that BibNet had good robustness.

During automatic segmentation, scanning 2D CT images slice by slice may cause the loss of three-dimensional (3D) anatomical structure information and reduce the segmentation accuracy. Studies have demonstrated that compared with 2D architectures, 3D architectures can extract features distributed across multiple slices, showing better performance in segmentation (40,41). Chung *et al* (42) used a 3D U-Net CNN, which was based on a U-Net structure, and combined it with the 3D version of EfficientNet-B0 as the backbone. The CTV (bilateral breast and regional lymph nodes) and OARs (heart, left and right lungs, esophagus, spinal cord and thyroid) of breast-conserving patients were automatically segmented. The CTV of the regional lymph nodes was delineated according to ESTRO guidelines, including axillary, internal mammary, supraclavicular and even interthoracic lymph nodes. For OARs, the mean DSC was >0.8, and the mean 95% HD was <5 mm. In CTV, the delineation effect of the breast was better, the mean DCS was >0.9 and the DS of regional lymph nodes was mostly >0.7. The dose distribution was also analyzed, and except for slight differences in the spinal cord and large differences in the regional lymph nodes, most of the automatic delineation showed good agreement with the manual delineation. Qualitative evaluation was performed in this study, and experts gave high scores for the differences and auxiliary scores of automatic delineations based on deep learning. However, all the contours of the study were drawn by one expert, ignoring the differences between observers. In the follow-up study, using network architecture based on the aforementioned study, the OARs of 10 patients with adjuvant radiotherapy after breast conservation were studied by 11 experts (attending physician, resident, clinical fellows and dosimetrist) from two institutions with different clinical backgrounds, and then the automatically delineated contours were corrected by these experts (43). The mean DSC of manual delineation, automatic delineation and correction after automatic delineation was 0.88, 0.90 and 0.90, respectively. The HD of breast and heart delineated by auto-delineation and subsequent correction were significantly lower than those delineated manually In the study of inter-observer variability, it was found that the automatic delineation system improved the quality of breast radiotherapy and reduced the inter-observer variability, and the time spent using the automatic delineation system was 84% lower than that spent on manual delineation, which was a significant reduction in the delineation time. At present, the research on 3D U-Net is extensive. Oya *et al* (44) used gradient-weighted class activation mapping 3D U-net CNN for CTV segmentation in whole breast radiotherapy, and the mean DSC was >0.85. Two radiotherapy centers in Norway used 3D U-Net CNN to automatically delineate CTV and OARs, and performed verification and dosimetric evaluation. The results showed that the model had good clinical applicability and has been put into clinical use (45). Patients with breast cancer require different clinical treatments, such as breast-conserving surgery or radical mastectomy, among other options. The aforementioned studies showed the advantages of automatic delineation based on deep learning in breast-conserving surgery. Liu *et al* (46) studied the delineation effect of CTV based on 2.5D CNN in modified radical mastectomy for breast cancer, with a mean DSC of 0.90. The 95% HD was 5.65 mm and it only took 3.45 sec to delineate the chest wall CTV using this model. In clinical evaluations, ~99% of automatic segmentation of the chest wall CTV slices can be directly applied to the clinic.

As for the automatic segmentation algorithm based on deep learning in breast cancer radiotherapy, GAN was also combined with U-Net, the dilated fully convolutional network was combined with a phase-based active contour model, and a deep neural network was combined with dynamic stridden convolution, all obtaining relatively accurate segmentation results (25,47,48). With the continuous progress of computer technology, automatic segmentation algorithms are constantly improved and new automatic radiotherapy delineation systems are constantly emerging. The development of these systems can effectively save time and reduce inter-observer and intra-observer differences. However, most early studies only evaluated the performance of automatic delineation based on volume and surface-based geometric parameters, which could not necessarily reflect the actual clinical impact caused by geometric contour differences, whereas dosimetric analysis could evaluate the impact of contour on treatment planning (49). Dosimetric parameters are measures considered to be more clinically relevant than geometric consistency, and evaluation of the performance of automated delineation should include dose assessment for geometric differences, considering dose distribution to assess the clinical impact of local geometric differences (10,50). At present, the gold standard for the delineation of target volume and OARs is still manual delineation by radiologists, and the automatic delineation contour still needs to be reviewed by these experts. In the evaluation of the performance of the automatic delineation system, the qualitative score of radiologists should be added. In conclusion, the performance of the automatic delineation system should be evaluated in multiple fields.

3. Differences in the recognition of cardiac substructures by different automatic delineation techniques

In a large case-control study (5) of radiotherapy for breast cancer in women, the incidence of major coronary events was found to increase by 7.4% for every 1 Gy increase in the mean cardiac dose, while the cumulative incidence of acute coronary events was found to increase by 16.5% in another study (51), with radiation-related risks increasing linearly with the mean cardiac dose. Moreover, in women with and without cardiovascular risk factors, the increase in myocardial infarction rate per Gy was similar (52). Modern breast radiotherapy technology has been able to achieve a lower level of mean cardiac dose radiation, but some substructures of the heart such as the left anterior descending (LAD) artery or coronary artery may be exposed to higher doses of radiation, which may also cause cardiovascular-related adverse events, especially in patients with left breast cancer treated with radiotherapy. Several studies have shown that in addition to the mean heart dose, the dose to the cardiac substructures, such as the atrium, ventricle and LAD artery, should be limited in the radiotherapy for breast cancer (53-56). Several studies have also suggested that the left ventricle, LAD artery or coronary artery should be considered as separate OARs (57,58).

Automatic segmentation of cardiac substructures based on the atlas. Patients with breast cancer are not usually administered intravenous contrast agents when performing routine scans. The lack of intravenous contrast enhancement and the presence of motion artifacts caused by the breathing and heartbeat of the patients in the CT scans of the radiotherapy planning system makes it challenging to manually sketch the substructure of the heart, and makes the method vulnerable to differences between and within observers (59,60). van den Bogaard *et al* (59) developed an automatic LAD artery segmentation tool in non-contrast planning CT based on anatomical landmarks. The whole heart (WH), right atrium, right ventricle, left ventricle and left atrium of each patient were delineated using an internally generated atlas, in which the WH and left and right ventricles were used as anatomical markers for automatic LAD artery segmentation. The average time for automatic LAD artery delineation was 57.2 sec, and the manual LAD artery delineation time was 20-30 min. The DSC of the LAD artery was only 0.15, and the maximum HD was 4.8 mm, showing poor geometric consistency. However, the dosimetric study showed that there was a high consistency between the manual and automatic delineation, and the maximum deviation of the average maximum dose to at least 5% of the volume and minimum dose to at least 95% of the volume of the LAD artery was 0.01 Gy. The contouring of the LAD artery depends on the anatomical landmarks defined in the ABAS. If the WH and ventricle are not delineated correctly, the automatic contouring of the LAD artery will also be biased. To improve the performance of automatic segmentation, Kaderka *et al* (60) established a diversified atlas, including patients with left and right breast cancer, those treated in the supine and prone positions, those with breast augmentation, and those with automatically delineated WH, left and right atria and ventricles, and LAD artery. The DSC of the WH was 0.93±0.02 and the mean HD was 18±6 mm. The DSC of the atrium and ventricle were ~0.8, and the DSC of the LAD artery was still very low, only 0.09±0.07, with a mean HD of 73±61 mm. However, when including the LAD artery, the manual and automatic delineation of dosimetric parameters had strong consistency. With the continuous deepening of research, the segmentation of cardiac substructures has been refined. Jung *et al* (61) automatically delineated the WH, the four heart chambers and the coronary arteries (left main coronary artery, LAD artery, left circumrotary artery and right coronary artery). A cardiac structure atlas library was created by using the CT of 30 groups of adult female patients, and for small structures such as arteries, the MASD was used for evaluation. The mean DSC of the WH was 0.97, and the mean DSC of the four chambers was 0.7. The MASD of the heart was the best at 1.0 mm. The MASD of the four compartments was ~4.5 mm. The consistency of the four coronary arteries was poor, and the mean MASD was <10.3 mm. According to the dosimetric comparison, the mean dose difference between the WH and the atrium was the smallest at <0.06 Gy, and the mean dose difference between the ventricle and the coronary arteries, with the exception of the LAD artery (mean difference, 2.3 Gy), was <0.3 Gy. Apart from the poor geometric consistency of the LAD artery translated into large differences in dosimetry, the method showed excellent performance in both geometry and dosimetry. The prerequisite for accurate segmentation of cardiac substructures in this study was the accuracy of WH contouring. Subsequently, a new automated segmentation heart atlas library was created using patient data from the RadComp clinical trial (62). The patient images were non-contrast radiotherapy plan CT images, and the same automatic segmentation method was used to automatically segment the WH, the four heart chambers and the LAD artery (63). The DSC and MASD of the WH and the heart cavities were similar to those in previous studies, while the MASD of the LAD artery was 6.4 mm, which was better than the 7.3 mm found in a previous study (61). The mean difference in LAD dose was 1.8 Gy, and the dose difference of the left breast was significantly higher than that of the right breast. This method can be directly applied to the CT images of breast cancer radiotherapy planning. Although the automatic LAD artery segmentation and manual LAD artery segmentation had great differences, they had a high consistency in dosimetry. Milo *et al* (64) segmented the cardiac substructures of patients with breast cancer undergoing radiotherapy based on non-contrast enhanced CT into 22 substructures: 18 cardiac substructures and the ascending aorta, pulmonary trunk, and the superior and inferior vena cava. The results of this study were similar to those of the aforementioned studies. ABAS showed excellent geometric consistency and dose correlation in the WH and for atrial and ventricular segmentation, but still showed great differences in smaller structures such as the coronary arteries.

Through the aforementioned studies, it can be observed that although the delineation effect of the WH and heart cavity was good, the manual delineation of small structures such as the coronary arteries was poor in terms of repeatability, and the results of automatic delineation were not reliable. The difficulty of delineation of coronary arteries and other structures can be avoided by constructing geometric alternative volumes. Tan *et al* (65) proposed to extend and improve the anterior myocardial region containing the LAD artery as an OAR. Stockinger *et al* (66) defined six cardiac structures and geometric alternative volumes (aortic value, pulmonary value, deep structures, right anterior myocardium, left anterior myocardium and complete myocardium), and developed a cardiac atlas. Munshi *et al* (58) proposed the 'coronary strip' (spatial arc of spread of coronary vessels) as a new

OAR. Loap *et al* (67) defined the high-risk heart region as a substitute for the LAD artery, and the maximum dose limit of the high-risk heart regions effectively reduced the radiation exposure to the LAD artery. A number of scholars have proposed high-risk regions of different cardiac substructures, but none of them have been integrated into the cardiac atlas. Loap *et al* (68) proposed a simplified functional cardiac atlas, defined the cardiac high-risk regions of LAD substitutes and evaluated the automatic segmentation of cardiac conduction system substructures for the first time. Validation results showed that the performance of the cardiac atlas was acceptable and could save a lot of delineation time.

Automatic segmentation of cardiac substructures based on deep learning. Compared with automatic segmentation methods based on the atlas, deep learning has strong ability in term of learning complex and low-contrast anatomical features, and has more advantages in the automatic segmentation of cardiac substructures, which can provide more robust and reliable automatic segmentation results (69). van den Oever *et al* (70) developed a two-stage depth algorithm based on a small data set for the automatic segmentation of cardiac substructures in non-contrast planning CT. In the first stage, the InceptionResNetV2 network was used to identify the slice containing the heart structure. In the second stage, a deep learning model composed of three U-Net3+ neural networks was used to train and segment the left and right atria, and the ventricles, as well as the WH. The volume change between the automatic delineation of the WH and the heart chamber and the real value was very small. The median DSC of the WH was 0.96, the DSC of the four heart chambers was >0.80, among which the DSC of the left and right ventricles was >0.88, and the DSC of the atrium was lower. The automatic delineation could be completed within 30 sec. The WH and heart chamber could be delineated with high accuracy, but the manual delineation of the blood vessels and valves of the heart was extremely difficult, and the effect of automatic segmentation was also poor. Jin *et al* (71) used the 3D deep neural network combined with ResNet and U-Net to achieve fast and accurate automatic segmentation of the left and right atrium, left and right ventricle, aortic valve, LAD valve, tricuspid valve, mitral valve and pulmonary valve, and increased the DSC of the LAD valve to 0.39±0.10. The mean segmentation time per patient was only 2.1 sec, which was a significant time saving. The study also evaluated the impact of image artifacts caused by implants such as tissue expanders on the performance of automatic segmentation for the first time and found that images with artifacts can reduce the accuracy and robustness of image segmentation. Harms *et al* (72) used the mask scoring regional convolutional neural network (RCCN) composed of five subnetworks to automatically segment the heart cavity, valves and major blood vessels. The backbone network ResNet50 learned multi-scale features from CT images, and then the regional proposal network detected the location of all substructures through these feature atlases. Finally, the structure information was extracted from the three subnetworks. The model innovatively included two modules: Attention gate (AG), a simple convolutional layer sequence that could make the whole network better by detecting the tissue boundary with low contrast and enhancing the robustness to noise and uninformative features, and mask scoring (MS), where multiple maskers could be generated in each cardiac substructure type for each patient and then scored to select the best segmentation structure. The mean DSC of large vessels, coronary arteries and heart valves was 0.93, 0.66 and 0.77, respectively, and the 95% HD was 4.44±5.91, 7.19±7.58 and 5.38±3.45 mm, respectively. The mean surface distance and the mean centroid distance were significantly better than those of 3D U-Net and RCNN without AG and MS, and all substructures could be delineated within 5 sec (72). Another study used mutually reinforcing deep learning to automatically delineate coronary arteries and heart valves. The model was composed of the retinal U-Net, a classification module and a segmentation module, and compared with 3D U-Net, Mask-RCNN, MS-RCNN and the proposed network without a classification model. It was found that the new proposed network had the same effect as mask scoring RCCN in the automatic delineation of large structures such as the heart cavity, which was significantly better than the other three networks, and was significantly better than the other four networks in the segmentation of small structures such as the coronary arteries (73).

Although coronary CT angiography and MRI have high recognition of cardiac substructures, they are not used in the routine clinical nursing process of patients with breast cancer undergoing radiotherapy. The aforementioned automatic segmentation algorithms are all based on non-contrast enhanced CT images to segment cardiac substructures. Deep learning algorithms can be used to train enhanced CT or even MRI, and then the model can be applied to the automatic segmentation of non-contrast enhanced CT images used in conventional treatment. Morris *et al* (74) used 3D U-Net to train the multi-channel input data of MRI and CT, and then used U-Net to segment cardiac substructures on non-contrast CT images. The DSC of the coronary arteries was >0.5, and the DSC of the LAD artery reached 0.53. Automatic delineate of each patient too ~14 sec. Bruns *et al* (75) reconstructed the coronary CT angiography image and the fully aligned virtual non-contrast CT image at the same time through contrast enhancement acquisition on a dual-layer detector CT scanner, manually segmented the coronary CT angiography image and then propagated it to the virtual non-contrast CT image. The reference segmentation with voxel accuracy was used to train the automatic segmentation of deep learning and then applied to the non-contrast enhanced CT, which showed excellent performance in heart and large artery segmentation. The method had good generality for images obtained from single energy CT scanners from different institutions and images with different layer thicknesses, and could accurately segment the heart cavity and large vessels in 74% of cases in the multicenter evaluation. Based on the study by Bruns *et al* (75), van Velzen *et al* (76) developed a deep learning method for the segmentation of ventricles and large arteries, and for planning the trajectory localization of three major coronary arteries in CT scans. The median DSC was 0.76 to 0.88 in the cardiac cavity and aorta evaluated in 2D images, and 0.87 to 0.93 in 3D images. This method not only had good consistency in geometry but the dosimetry analysis results also showed that automatic delineation could accurately predict the results. The deep convolutional neural network could also generate synthetic contrast-enhanced CT images from non-enhanced contrast CT images, and then be used to contour cardiac substructures. Chun *et al* (77) applied this method to the automatic segmentation of cardiac substructures in patients with breast cancer undergoing radiotherapy and proved the feasibility of this method.

In high-risk patients with early and locally advanced breast cancer, irradiation of the regional lymph nodes in addition to whole breast radiation should be required to reduce the risk of local recurrence and distant metastasis. From the aforementioned research, it can be seen that, compared with that in other organs or tissues with clear and regular boundaries, the consistency of automatic delineation of the regional lymph nodes was poor and the delineation effect was not good. However, in general, the deep learning-based automatic delineation algorithm was significantly better than the atlas-based automatic delineation algorithm for the regional lymph nodes. Chung *et al* (42) used the 3D U-Net CNN method to automatically delineate regional lymph nodes with a DSC >0.7 in most patients with breast cancer. In other tumors, the automatic delineation algorithm based on deep learning could generate high-quality automatic delineation results of the lymph nodes, with a median DSC >0.7 and a maximum DSC of 0.91 (78,79). The improved algorithm model can also be applied to the automatic delineation of radiation therapy for breast cancer. The aforementioned studies show that deep learning also provides excellent performance in the automatic delineation of regional lymph nodes. However, the overall delineation effect of the regional lymph nodes was relatively poor compared with that of other OARs with a large volume and clear boundary. At present, the regional lymph nodes are still the main obstacle to the automatic delineation of radiotherapy. In the future, it is necessary to improve the accuracy of automatic delineation through further technological improvement, the design of advanced detection and the use of segmentation technology combined with deep learning (80). On the other hand, the automatic delineation effect of regional lymph node structures with small volumes can be improved by reducing the scanning layer thickness during CT positioning (81).

4. Conclusions

In the automatic delineation of radiotherapy for patients with breast cancer, the segmentation effect of automatic segmentation based on a multi-atlas is better than that based on a single atlas. However, it is not true that the greater the number of atlases the better. A large number of atlases will not only reduce the segmentation accuracy, but also increase the cost of calculation. The selection of an appropriate atlas for different patients is also a problem to be solved. The deep learning algorithm achieves better results than the atlas-based algorithm in the research. In non-contrast-enhanced CT images of patients with breast cancer for automatic delineation of OARs and target volume, both methods show a superior performance in large-volume tissues and organs with a clear boundary. However, the delineation effect is poor in small-volume structures with unclear boundaries, such as the regional lymph nodes and coronary arteries. The effect of automatic contouring based on deep learning was better than that based on the atlas, and the deep learning algorithm could train multi-modal images. To solve the problem of the poor delineation effect of the regional lymph nodes, the automatic delineation algorithm based on deep learning can be adopted in practical application. On the other hand, the scanning layer thickness during CT positioning can be reduced to improve the automatic delineation effect of these small regional lymph nodes. As the tumor boundary does not have significant imaging features, tumors of different stages are very different, and there are potentially undetectable tumor areas, so the overall automatic delineation effect of target volume is not as good as that of OARs. Although enhanced CT and MRI can enhance image contrast, the use of multimodality approaches and a better understanding of the association between imaging and biology/pathology will result in better accuracy of definition. However, in the routine nursing process of radiotherapy for patients with breast cancer, only non-contrast CT is generally used, and most of the automatic drawing software are based on non-contrast CT images. Deep learning can realize the transmembrane state segmentation task without additional image acquisition. Only on non-contrast CT images can parameters trained on enhanced CT or MRI images be used for automatic delineation, which can effectively improve the accuracy. At the same time, it can also improve the regional lymph node delineation effect. At present, delineation of cardiac substructure in radiotherapy for breast cancer is not a routine clinical task, as manual delineation is difficult, and automatic delineation of the cardiac substructure is still in the research stage. However, with the continuous progress of precision medicine, the prolongation of patient survival time and the improvement of the requirements for quality of life after treatment, the requirements for radiotherapy will become more stringent in the future, and the delineation of cardiac substructure may become a routine clinical task. In addition to the advances in algorithms, it is necessary to develop standards for image acquisition and structure delineation within radiotherapy institutions. The quality of images presented to image processing algorithms is a very important factor in the reliability of algorithms. Standardization will facilitate the wider use and acceptance of automated segmentation tools in routine clinical practice. At present, the regional lymph nodes are still the main obstacle to the automatic delineation of radiotherapy. In the future, it is necessary to improve the accuracy of automatic delineation through further technological improvement, the design of advanced detection and the use of segmentation technology combined with deep learning.

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Authors' contributions

JS and PG performed the literature search and selection and were major contributors in the writing of the manuscript. YW and ZW were responsible for the conception and design of the study, and reviewed the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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