

Original article

Effect of different segmentation algorithms on metabolic tumor volume measured on ^{18}F -FDG PET/CT of cervical primary squamous cell carcinomaWeina Xu^a, Shupeng Yu^a, Ying Ma^b, Changping Liu^a and Jun Xin^a

Background and purpose It is known that fluorine-18 fluorodeoxyglucose PET/computed tomography (CT) segmentation algorithms have an impact on the metabolic tumor volume (MTV). This leads to some uncertainties in PET/CT guidance of tumor radiotherapy. The aim of this study was to investigate the effect of segmentation algorithms on the PET/CT-based MTV and their correlations with the gross tumor volumes (GTVs) of cervical primary squamous cell carcinoma.

Materials and methods Fifty-five patients with International Federation of Gynecology and Obstetrics stage Ia ~ IIb and histologically proven cervical squamous cell carcinoma were enrolled. A fluorine-18 fluorodeoxyglucose PET/CT scan was performed before definitive surgery. GTV was measured on surgical specimens. MTVs were estimated on PET/CT scans using different segmentation algorithms, including a fixed percentage of the maximum standardized uptake value (20 ~ 60% SUV_{max}) threshold and iterative adaptive algorithm. We divided all patients into four different groups according to the SUV_{max} within target volume. The comparisons of absolute values and percentage differences between MTVs by segmentation and GTV were performed in different SUV_{max} subgroups. The optimal threshold percentage was determined from $\text{MTV}_{20\%} \sim \text{MTV}_{60\%}$, and was correlated with SUV_{max} . The correlation of $\text{MTV}_{\text{iterative adaptive}}$ with GTV was also investigated.

Results $\text{MTV}_{50\%}$ and $\text{MTV}_{60\%}$ were similar to GTV in the SUV_{max} up to 5 ($P > 0.05$). $\text{MTV}_{30\%} \sim \text{MTV}_{60\%}$ were similar to GTV ($P > 0.05$) in the $5 < \text{SUV}_{\text{max}} \leq 10$ group.

Introduction

Cervical cancer is one of the most common malignant tumors in women. Radiation therapy is a commonly used treatment for Ia–IVa stage cervical cancer. Accurate delineation of the tumor radiotherapy target is critical to maximize the dosage to tumor tissue and to minimize the dosage to the surrounding normal tissues [1].

Metabolic tumor volume (MTV), measured on fluorine-18 fluorodeoxyglucose (^{18}F -FDG) PET/computed tomography

$\text{MTV}_{20\%} \sim \text{MTV}_{60\%}$ were similar to GTV ($P > 0.05$) in the $10 < \text{SUV}_{\text{max}} \leq 15$ group. $\text{MTV}_{20\%}$ and $\text{MTV}_{30\%}$ were similar to GTV ($P > 0.05$) in the SUV_{max} of at least 15 group. $\text{MTV}_{\text{iterative adaptive}}$ was similar to GTV in both total and different SUV_{max} groups ($P > 0.05$). Significant differences were observed among the fixed percentage method and the optimal threshold percentage was inversely correlated with SUV_{max} . The iterative adaptive segmentation algorithm led to the highest accuracy ($6.66 \pm 50.83\%$). A significantly positive correlation was also observed between $\text{MTV}_{\text{iterative adaptive}}$ and GTV (Pearson's correlation $r = 0.87$, $P < 0.0001$).

Conclusion $\text{MTV}_{\text{iterative adaptive}}$ is independent of SUV_{max} , more accurate, and correlated with GTV. Iterative adaptive algorithm segmentation may be more suitable than the fixed percentage threshold method to estimate the tumor volume of cervical primary squamous cell carcinoma. *Nucl Med Commun* 38:259–265 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.

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Keywords: cervical cancer, metabolic tumor volume, positron emission tomography

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(CT) scan, represents the tumor biological target volume. It has the advantage of differentiating tumor tissue from surrounding normal tissues compared with conventional anatomic approaches [2–4]. PET/CT-based MTV segmentation algorithms are usually based on visual inspection [5], absolute standardized uptake value (SUV) threshold [6], fixed SUV_{max} or fixed percentage of maximum standardized uptake value (SUV_{max}) threshold [7], and gradient method [8,9]. At present, the fixed percentage of the SUV_{max} threshold algorithm is more popular, especially for target delineation of head and neck cancers, lung cancer, and cervical cancer [10].

In 2006, Sebastian *et al.* [11] published the iterative adaptive segmentation algorithm. The iterative adaptive

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algorithm has an advantage over fixed threshold methods in accurate delineation of the target volume according to the individual metabolic activity. This method is usually based on the SUV_{max} uptake within the volume and the threshold defined according to the background uptake within the adjacent normal tissue using a mathematical algorithm. This is then used to define the threshold and thus the ^{18}F -FDG-avid volume of interest [12,13]. However, the investigations of MTV delineation for cervical cancer using an iterative adaptive algorithm are still limited [14,15]. This study compared the accuracy of MTV by the iterative adaptive algorithm ($MTV_{iterative\ adaptive}$) with that of the fixed percentage SUV_{max} threshold method using gross tumor volume (GTV) as the gold standard and investigated the correlation between them.

Materials and methods

Patients

The Institutional Research Ethic Committee of Shengji Hospital approved the present study. All patients signed the informed consent for this study. Fifty-five patients from November 2012 to May 2015 with International Federation of Gynecology and Obstetrics stage Ia~IIb were consecutively enrolled. ^{18}F -FDG PET/CT scans were performed for staging 1 week before definitive surgery. All patients had histologically proved cervical squamous cell carcinoma. Patients were excluded if they had received chemotherapy or radiotherapy before surgery.

^{18}F -FDG PET/CT imaging and analysis

All patients fasted for more than 6 h before ^{18}F -FDG PET/CT scans were performed on them. Their serum glucose level was controlled to lower than 7 mmol/l. ^{18}F -FDG (produced by MiniTrace II and TracerLab F_X -FDG purity > 99%; GE Healthcare, Waukesha, Wisconsin, USA) was injected at a dosage of 3.7 MBq/kg. Patients rested quietly for 60 min before PET/CT (Discovery PET/CT 690; GE Healthcare, USA) scanning. The wholebody CT and PET scans were all acquired with free breathing for attenuation correction and image fusion. First, low-dose non-enhanced CT images were scanned from the top of the skull to the mid-thigh, with bulb voltage 120 kV, Auto mA (30–210 mA; noise index 25), and slice thickness 3.27 mm, for attenuation correction of the PET images. Then, the PET data were acquired immediately after the CT scan using a three-dimensional acquisition mode at a speed of 1.5 min/bed (7~8 beds in total) and a matrix size of 192×192. Attenuation-corrected PET images were reconstructed using an ordered-subsets expectation maximization iterative reconstruction algorithm, with 24 subsets and two iterations. Time-of-flight and point-spread function techniques were also used in the reconstruction.

Images were interpreted in a blinded manner by two experienced nuclear medicine physicians on an AW4.6 workstation (GE Healthcare, USA). All patients were divided into four groups according to the SUV_{max} within the target volume: $SUV_{max} \leq 5$ group, $5 < SUV_{max} \leq 10$ group, $10 < SUV_{max} \leq 15$ group, and $SUV_{max} \geq 15$ group.

MTV was defined as the volume of hypermetabolic tissue with an SUV greater than a defined threshold. The threshold was defined by a fixed percentage of SUV_{max} and an iterative adaptive algorithm. For the fixed percentage of the SUV_{max} method, an SUV_{max} threshold ranging from 20 to 60% was used in increments of 10% ($MTV_{20\%} \sim MTV_{60\%}$). Volume Viewer (GE Healthcare, USA) was used to segment the fixed percentage of the SUV_{max} target. Volume computerized-assisted reporting (PET VCAR; GE Healthcare, USA) was used to segment MTV by the iterative adaptive algorithm ($MTV_{iterative\ adaptive}$) automatically. The PET and CT coregistration was first assessed once the images were loaded into the PET VCAR software. The primary PET gray scale and PET/CT fused images were then reviewed in the axial, sagittal, and coronal planes. Coregistration was assessed according to anatomical bony landmarks, for example, the base of the skull and vertebral pedicles. A boundary box, to autocontour and segment the region of interest, was placed over the image, reviewed, and adjusted to ensure that this three-dimensional cube contained the entire ^{18}F -FDG PET-positive area and excluded the ^{18}F -FDG PET-negative normal tissue. This process was repeated until each ^{18}F -FDG PET/CT-positive region had been selected and optimized. These volumes were then segmented automatically using an iterative adaptive algorithm to detect the threshold level that separated the target volume from the background tissue by weighting the SUV_{max} and the SUV_{mean} within the target volume with a weighting factor. This weighting factor was automatically set at 0.5 [11,12]. Percentage difference of segmentation MTVs and GTV was also calculated by $(MTV - GTV) \times 100\% / GTV$ and the optimal threshold percentage in the range 20~60% for each patient was defined by the smallest percentage difference between segmentations results and the GTV.

Pathology

All patients underwent a radical hysterectomy and pelvic lymphadenectomy within a week after PET/CT scans. Once the fresh tumor specimen was collected after the surgery, the maximum vertical and horizontal tumor sizes were measured with a ruler. The specimens were subsequently fixed in 10% formalin for at least 24 h. The dimensions of the fixed tumor samples were also measured in the same way to determine the ratio of volume reduction because of fixation. Then, the fixed tumor specimens were sliced into consecutive tissue sections of 5 mm thick slices; the range of cutting included the entire tumor and surrounding normal tissues. Each slice

was numbered and stained with hematoxylin and eosin and photographed using a digital camera. The tumor area (A_i) was outlined by an experienced pathologist with Photoshop 7.01 (Adobe Systems, San Jose, California, USA). The tumor area for each slide was measured and the GTV for each specimen was calculated as $GTV = \sum A_i/R$, where R was defined as the change ratio of the sample dimensions before and after fixation, respectively.

Comparisons of absolute values and percentage difference between MTVs by segmentation and GTV were performed in different SUV_{max} subgroups. The optimal threshold percentage was determined from $MTV_{20\%} \sim MTV_{60\%}$, defined by the smallest percentage difference between segmentations results and the GTV. The optimal threshold percentage in different SUV_{max} groups was also compared and the relationship between them was analyzed. The correlation of MTV from iterative adaptive segmentation and GTV was also investigated.

Statistical analysis

Statistical analyses were carried out using SPSS 17.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were presented as mean and SD. Independent *t*-tests were performed for the comparisons of MTVs by different tumor segmentation algorithms in different groups. Two-tailed Pearson's correlations were used to assess the relationship between $MTV_{iterative\ adaptive}$ and GTV. *P* value less than 0.05 was considered statistically significant (Fig. 1).

Results

The mean age of 55 patients was 48.35 ± 9.23 years, ranging from 26 to 68 years (Table 1). $MTV_{20\%}$, $MTV_{30\%}$, $MTV_{40\%}$, $MTV_{50\%}$, $MTV_{60\%}$ and $MTV_{iterative\ adaptive}$ were 23.01 ± 16.99 , 14.86 ± 11.38 , 10.21 ± 8.76 , 7.12 ± 7.06 , 4.86 ± 5.26 , and 12.56 ± 10.60 cm³, respectively, and GTV was 12.35 ± 10.10 cm³. Absolute MTV (cm³) and the difference percentage between MTVs of different segmentations and GTV in all subgroups are shown in Table 2 and Fig. 2. $MTV_{50\%}$ and $MTV_{60\%}$ were similar to GTV ($P > 0.05$) in the $SUV_{max} \leq 5$ group. $MTV_{30\%} \sim MTV_{60\%}$ were similar to GTV ($P > 0.05$) in the $5 < SUV_{max} \leq 10$ group. $MTV_{20\%} \sim MTV_{60\%}$ were similar to GTV ($P > 0.05$) in the $10 < SUV_{max} \leq 15$ group. $MTV_{20\%}$ and $MTV_{30\%}$ were similar to GTV ($P > 0.05$) in the $SUV_{max} \geq 15$ group. $MTV_{iterative\ adaptive}$ were similar to GTV in both total and different SUV_{max} subgroups ($P > 0.05$). Significant differences were observed among the different segmentation groups (Fig. 2). Twenty percent and 30% threshold consistently overestimated the MTV (121.4 ± 111.5 and $41.9 \pm 66.31\%$), whereas 40, 50, and 60% thresholds led to underestimation of MTV (-8.34 ± 42.47 , -38.83 ± 30.39 , and $-59.38 \pm 27.89\%$). The iterative adaptive segmentation algorithm yielded the highest accuracy ($6.66 \pm 50.83\%$), although with a large SD 50.83%.

Figure 3 shows the relationship between the optimal threshold percentage and SUV_{max} ; the optimal percentage threshold was inversely correlated with SUV_{max} . The higher the SUV_{max} , the smaller the optimal threshold. In the $SUV_{max} \leq 5$ group, the optimal threshold percentage was $55 \pm 5.77\%$, whereas the optimal threshold percentage were 37.69 ± 8.32 , 35.88 ± 7.12 , and $30.48 \pm 8.65\%$ in the $5 < SUV_{max} \leq 10$, $10 < SUV_{max} \leq 15$, and $SUV_{max} > 15$ groups, respectively.

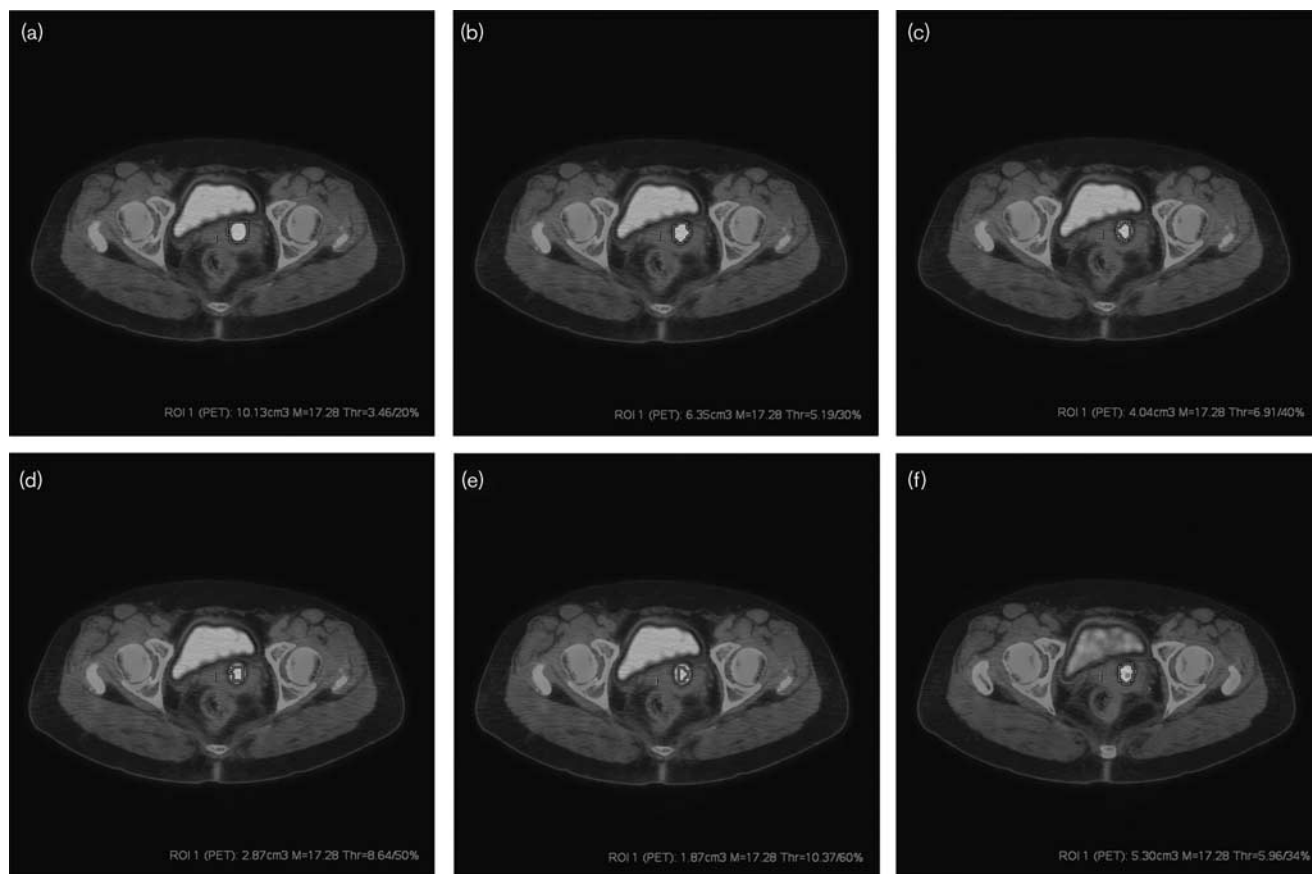
Also, a significant positive correlation ($r = 0.87$, $P < 0.0001$) was observed between $MTV_{iterative\ adaptive}$ and GTV (Fig. 4).

Discussion

It is known that accurate tumor target volume delineation is critical for the effectiveness of radiotherapy. As PET/CT shows the tumor metabolism activity, it is increasingly being accepted as an effective way for tumor biological target volume delineation [16–19]. The aim of this study was to compare the MTVs from a PET/CT-based iterative adaptive algorithm and from the fixed percentage (20~60%) of the SUV_{max} method to determine whether the $MTV_{iterative\ adaptive}$ algorithm is better estimated to GTV of primary cervical cancer.

Our results showed that the dynamic threshold percentage correlated inversely with SUV_{max} , similar to a previous report on esophageal tumor [20]. However, the related trend between optimal percentage threshold and SUV_{max} was not obviously identical to that of Hyun *et al.* [21] study, in which the ideal threshold was defined when the maximum metabolic tumor length was exactly the same as the length of the known maximum pathologic tumor length. In our study, the optimal percentage threshold was relatively determined to be within 20~60%, which was defined by the smallest percentage difference between MTVs by segmentations and the GTV; this was the main reason for the differences in the results. In addition, some authors applied a fixed percentage threshold to measure MTVs of cervical cancer and head and neck cancer [22–27]. Kim *et al.* [22] compared MTV of 40% SUV_{max} threshold in 45 patients with invasive cervical cancer to their pathological and prognostic outcomes. The results showed that the patients with MTV larger than 20 cm³ had a significantly reduced disease-free survival compared with those with MTV less than 20 cm³ ($P = 0.029$), and the MTVs were significantly different among the groups according to the status of lymph node metastasis, parametrial invasion, tumor differentiation, and International Federation of Gynecology and Obstetrics stage ($P < 0.05$). In addition, a feasibility study by Ciernik and colleagues [25,26] evaluated the use of PET/CT in radiation therapy planning, and 50% SUV_{max} was found to be a reliable correlate to CT tumor volume. Showalter *et al.* [28] and Lee *et al.* [29] used the 40% SUV_{max} threshold to define the primary tumor diameter of early-stage cervical cancer and a significant

Fig. 1



A 54-year-old woman with moderately differentiated cervical squamous cell carcinoma and FIGO stage IIb1. MTVs of primary tumor were 10.13 cm³ (a), 6.35 cm³ (b), 4.04 cm³ (c), 2.87 cm³ (d), and 1.87 cm³ (e) by the 20~60% SUV_{max} threshold, and 5.30 cm³ (f) by the iterative adaptive algorithm. GTV is 5.23 cm³. FIGO, International Federation of Gynecology and Obstetrics; GTV, gross tumor volume; MTVs, metabolic tumor volumes; SUV_{max}, maximum standardized uptake value.

Table 1 Characteristics of all patients

| Characteristics | n (%) |
|----------------------------|---------|
| Age (median) (years) | 48 |
| Age (range) (years) | 26–68 |
| FIGO stage | |
| Ib1 | 20 (36) |
| Ib2 | 12 (22) |
| IIa1 | 18 (33) |
| IIa2 | 5 (9) |
| Tumor differentiated grade | |
| Well | 9 (16) |
| Moderate | 37 (68) |
| Poor | 9 (16) |

FIGO, International Federation of Gynecology and Obstetrics.

positive correlation was found with the pathologic tumor diameter ($r=0.757$, $P<0.0001$). Also, a few other radiation therapy planning and treatment evaluation studies on cervical cancer used thresholds between 40 and 60% [22,30–31]. Kidd *et al.* [30] found an MTV of 40% SUV_{max} threshold in cervical cancer decreased at weeks 2 and 4 after radiation therapy compared with the baseline

($P<0.05$). Yu *et al.* [31] evaluated the percentage SUV_{max} for non-small-cell lung cancer target volume delineation using pathologic GTV as the gold standard, they found that the optimal thresholds ranged from 20 to 42% ($31\pm 11\%$) SUV_{max}, and there was no certain optimal threshold. These findings suggest that different biological properties and metabolic levels of the primary tumor yield different percentages of the SUV_{max} threshold. Thus, the fixed percentage SUV_{max} threshold method is not suitable for different types of malignancy, tumor characteristics, and different metabolic levels [32], especially when SUV_{max} of at least 15. The volumes of the gross tumor are strongly dependent on the segmentation tools [13].

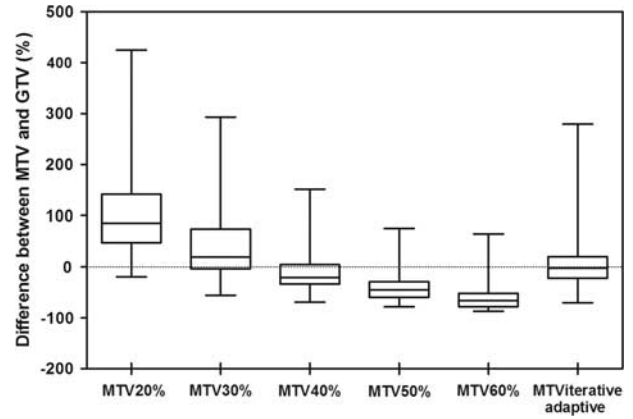
Our study confirmed that the MTV by fixed percentage threshold and the optimal threshold percentage are SUV_{max} dependent. Thus, fixed percentage SUV_{max} threshold was not the ideal method for MTV delineation, despite its simplicity of measurement for practical clinical use. It is obvious that an accuracy and maneuverable

Table 2 MTVs with different segmentation algorithms (mean ± SD) and percentage difference in different SUV_{max} groups

| Groups | n | MTV _{20%} | MTV _{30%} | MTV _{40%} | MTV _{50%} | MTV _{60%} | MTV _{iterative adaptive} | GTV |
|------------------------------|----|--------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-----------------------------------|--------------|
| SUV _{max} ≤ 5 | 4 | 13.02 ± 3.50 (244.9 ± 120.7) | 8.56 ± 1.42 (125.6 ± 59.28) | 6.94 ± 0.29 (81.75 ± 31.22) | 4.84 ± 1.08 (27.65 ± 39.77)* | 3.88 ± 1.81 (4.10 ± 56.02)* | 4.37 ± 2.34 (13.47 ± 57.25)* | 3.89 ± 0.56 |
| 5 < SUV _{max} ≤ 10 | 13 | 18.44 ± 9.7 (165.3 ± 123.7) | 10.77 ± 3.90 (63.61 ± 87.51)* | 6.11 ± 3.00 (-1.21 ± 49.75)* | 3.78 ± 1.88 (-40.44 ± 27.99)* | 2.08 ± 1.18 (-66.73 ± 19.00)* | 6.14 ± 5.12 (3.48 ± 38.68)* | 6.16 ± 4.42 |
| 10 < SUV _{max} ≤ 15 | 17 | 36.5 ± 27.1 (140.4 ± 116.6)* | 19.8 ± 16.7 (92.58 ± 44.50)* | 13.6 ± 13.4 (-15.97 ± 27.43)* | 9.50 ± 3.60 (-45.30 ± 20.22)* | 6.63 ± 2.80 (-63.63 ± 16.35)* | 14.4 ± 13.80 (-10.58 ± 23.17)* | 16.0 ± 15.90 |
| SUV _{max} > 15 | 21 | 23.20 ± 14.78 (55.32 ± 46.28)* | 16.57 ± 11.65 (7.69 ± 36.5)* | 12.03 ± 8.76 (-23.74 ± 26.10) | 8.79 ± 6.82 (-45.25 ± 22.24) | 6.06 ± 5.11 (-63.48 ± 18.03) | 16.95 ± 10.81 (21.3 ± 68.29)* | 15.51 ± 9.19 |

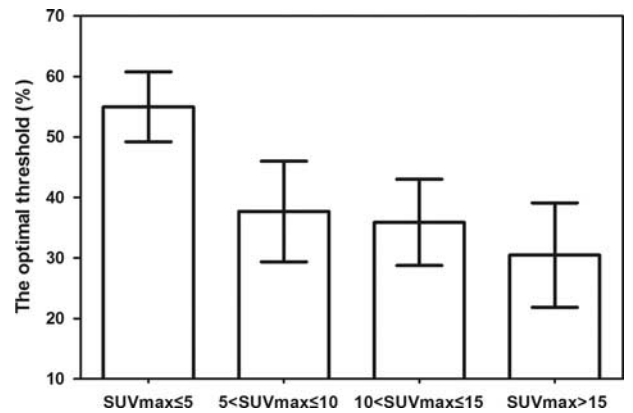
The differences between MTV_{50%}, ~MTV_{60%} and MTV_{iterative adaptive} were analyzed using a t-test; *P* < 0.05 was assumed to be statistically significant. GTV, gross tumor volume; MTVs, metabolic tumor volumes; SUV_{max}, maximum standardized uptake value. **P* > 0.05, no significant differences between MTV and GTV.

Fig. 2



Relative percentage errors between GTV and MTVs of different segmentation methods. GTV, gross tumor volume; MTVs, metabolic tumor volumes.

Fig. 3

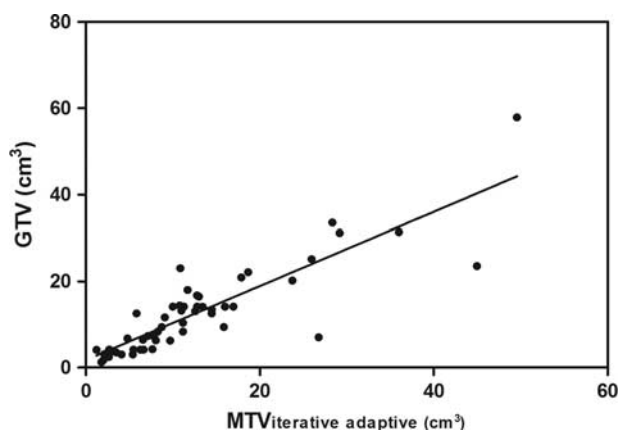


Relationship between the optimal threshold percentage and SUV_{max}. SUV_{max}, maximum standardized uptake value.

MTV segmentation algorithm is necessary for the planning of radiotherapy and accurate quantification of cervical cancer. This study adopted an iterative adaptive algorithm in the PET VCAR from GE Healthcare for automatic and accurate delineation of MTV in cervical cancer. Our results showed that MTV_{iterative adaptive} was similar to GTV in all SUV_{max} groups (*t* test, *P* > 0.05), and yielded satisfactory results with the smallest bias (6.66%), although there was a large SD (50.83%) as MTVs by fixed percentage threshold were either largely overestimated or underestimated. Overall, MTV_{iterative adaptive} correlated strongly with GTV (*r* = 0.87).

Some studies have reported a comparison of different methods for segmentation of ¹⁸F-FDG PET-positive tissue for target volume definition, but there are not many studies on iterative adaptive algorithm segmentation

Fig. 4



Correlation between $MTV_{iterative\ adaptive}$ and GTV (cm^3). MTV , metabolic tumor volume; GTV , total glycolytic volume.

methods using SUV_{max} and SUV_{mean} in tumor uptake. The iterative adaptive segmentation technique has some advantages compared with the traditional threshold algorithms. First, $MTV_{iterative\ adaptive}$ is dependent on both the SUV_{max} and the SUV_{mean} of the tumor uptake. Second, the accuracy of the iterations was assessed in the software by comparing the achieved and expected volumes [11,12]. MTV from the iteration adaptive algorithm in our study showed a much better correlation with pathologic tumor volume compared with the fixed percentage SUV_{max} threshold method.

Yu *et al.* [33] used PET image X , Y , and Z axis maximum diameters compared with three corresponding directions of the maximum tumor pathological diameter to determine the optimal segmentation threshold. But, in this approach it is difficult to ensure that the PET image slice and gross specimens slice match well. The GTV measurement method in our study was more accurate because the entire tumor pathological volume estimation did not depend on the degree of pathological and corresponding PET imaging matching. In addition, we compared two volumes before and after fixing, and eliminated specimens for which the shrinkage rate was in excess of 5% of the first volume of the specimen to ensure the reliability of GTV measurement. There are some limitations in this study. First, our clinical samples are still limited. Second, although the change ratio of the sample dimensions before and after fixation was considered, manual measurement errors could not be avoided and we failed to overlap the volumes from PET imaging and histopathology because of the lack of reliable markers in pathologic sections. Third, the influence of tumor volume itself on the accuracy of the MTV estimation (i.e. the partial volume effect) was not analyzed. Thus, a large cohort study of MTV estimated by the iterative adaptive algorithm for cervical cancer

radiotherapy target delineation or tumor growth/response is needed in the future to investigate its accuracy and repeatability.

Conclusion

$MTV_{iterative\ adaptive}$ is independent of the SUV_{max} , and is more accurate and correlated with GTV . Iterative adaptive algorithm segmentation may be more suitable than the fixed percentage threshold method to estimate the tumor volume of cervical primary squamous cell carcinoma.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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