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Research article

Evaluation of parametrial infiltration in cervical cancer with voxel-based segmentation of integrated ^{18}F-FDG PET/MRI images: A preliminary study

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ABSTRACT

Purpose: To identify parametrial infiltration (PMI) in cervical cancer with voxel-based segmentation of integrated PET/MRI images.

Method: This retrospective study enrolled 79 cervical cancer patients confirmed by pathology (FIGO stage IB to IIB) who underwent ^{18}F-FDG PET/MRI prior to surgery. Region of interest (ROI) at the largest tumor level was delineated on the T2W-MR image, and the ROI was applied to PET image of the corresponding layer. Then, these images were postprocessed with segmentation and gray level calculations in the parauterine area.

Results: In total, 37 patients (46.8%) had postoperative pathology-confirmed PMI, and 42 patients (53.2%) showed no PMI. There was a moderate correlation between pathological results and the gray level values of each region ($rs > 0.5$, $P < 0.001$). According to FIGO stage, as the cervical lesions became more malignant, the gray level values gradually increased.

The diagnostic results of MRI and PET/MRI were in good agreement (kappa = 0.693, $P < 0.001$); the accuracy (78.5%), sensitivity (64.9%) and NPV (74.5%) of PET/MRI were slightly higher than those of MRI (74.7%,59.5%,71.2%, respectively), with no statistically significant difference ($P = 1.000$). The diagnostic results of MRI and PET/MRI + gray level values were generally consistent (kappa = 0.475, $P < 0.001$); the accuracy (87.3%), sensitivity(83.8%) and NPV(86.4%) of PET/MRI + gray level values were higher than those of MRI, with statistically significant differences (all P values < 0.05).

Conclusions: It is feasible to evaluate PMI based on PET/T2W-MRI voxel segmentation and to obtain quantitative and visual indicators. PET/MRI and gray level values considered together can also improve the accuracy, sensitivity and NPV of PMI diagnosis.

1. Introduction

Cervical cancer is the third most common gynecological cancer in the world, and its incidence has showed increasing trend in recent years, and it has trended to be younger [1], with approximately 85% of new cases occurring in developing countries. The treatment strategy for cervical cancer is based on clinical and histological examination results, and (in the main) using the 2018 International Federation of Gynecology and Obstetrics (FIGO) staging. However, clinical staging is subjective and can be affected by many factors. The accuracy of FIGO staging is in fact low, with an error rate of approximately 16%–65%, according to the literature [2].

A prospective, multicenter clinical study from the United States found that the FIGO stages IA to IIA were consistent with pathological findings in 76% of cases, and that stages ≥ IIB were only consistent with 21% of cases, leading to a poor detection sensitivity of only 29% [3]. The main difficulty of obtaining an accurate preoperative assessment is in assessing parametrial infiltration (PMI), and lymphatic and distant metastasis; PMI being of importance since it is a high-risk factor for cervical cancer recurrence [4]. In early-stage cervical cancer, 5-year survival rates as high as 95% can be achieved through surgery [5], but removal of parauterine tissue will generally increase the risks of the operation and the likelihood of complications, which may adversely affect the quality of life of patients.

Accurate preoperative judgement as to the depth and extent of PMI (including parametrial soft tissue involvement, parametrial lymph node metastasis and intravascular tumor thrombus) is therefore crucial in assessing indications for surgery, especially for those patients above stage IIB who did not undergo surgical treatment and were treated instead with radiotherapy and chemotherapy. While clinicians have

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Table 1
Main MR sequence parameters.

	Repetition time (ms)	Echo time (ms)	Field of view (mm)	Bandwidth (kHz)	Frequency	Slice thickness (mm)	Slice spacing (mm)	Matrix	NEX	Refocus angle (degrees)
ax/sag T1FSE	746	9.22/11.33	400/260	35.71	320	6	2/1.2	512 × 512	2	111
cor T2FSE	2919	85	300	41.67	288	6	1.2	512 × 512	2	111
ax T2 PROPELLER	4617	79	360	125	384	6	2	512 × 512	1.5	110
ax/sag T2 fs PROPELLER	4265/4014	64/65	400/240	125/112.4	384	6	2/1.2	512 × 512	4	110
Sag CUBE T2 B	2500	85	269	62.5	224	1.2	0	224 × 224	1	90

universally recognized the diagnostic value of MRI for PMI, the accuracy rate and NPV of MRI have been inconsistent in the literature, varying from 80% to 95% [6,7]. Certain clinical presentations are liable to cause false positive results, such as rich parauterine venous plexus, periuterine edema, inflammatory infiltration or short-term high signal formation after radiotherapy [8]; but false positives may also be due to differences in the scanning sequences and subjective experiences of the radiologists. In addition, although the accuracy of diagnosing PMI with MRI was shown to be higher (more than 75%) than with FIGO staging, the sensitivity and positive predictive value (PPV) were lower (less than 55%) [7].

PET has high sensitivity and specificity in detecting small or concealed malignant lesions. Combining PET and MRI in the diagnosis of PMI has clear advantages, and previous studies have shown that, using fusion images acquired from PET/CT and MRI heterologous machines, the sensitivity and specificity of rediagnosing PMI could be significantly improved (by 85.7% and 82.4%, respectively) [9].

With the advent of combined positron emission tomography/magnetic resonance imaging (PET/MRI), a more precise diagnosis and staging of tumors in various parts of the body became possible, especially for women with cervical cancer. PET/MRI accurately obtains anatomical and functional imaging information in real time. Dual-modality imaging can share the same ROI, is more sensitive and accurate than conventional single-modality imaging, and can reduce the radiation dose and examination time required [10]. Existing studies have demonstrated that integrated PET/MRI not only offers great accuracy in the diagnosis and staging of primary cervical cancer but also provides two functional biomarkers i.e. standardized uptake values (SUVs) and apparent diffusion coefficients (ADCs) for evaluating tumor invasiveness and patient prognosis. Multimodality and multiparametric imaging is valuable in the pre-surgical evaluation of cervical cancer and assists in therapeutic decision-making [11].

In this study, a voxel-based segmentation method was used to quantitatively analyze the images, and we evaluated whether the combination of PET and T2W MRI could further improve the diagnostic accuracy of PMI.

2. Methods and materials

2.1. Patient enrollment

This retrospective study recruited cervical cancer patients treated in our hospital over the period December 2016–October 2018. All patients were staged according to FIGO guidelines and received PET/MRI scans according to a standardized protocol. The study was approved by the hospital's review committee, and patients gave informed consent. The inclusion criteria were as follows: (1) cervical cancers were confirmed by pathology and a FIGO stage of IB-IIB; (2) there was no radiotherapy and chemotherapy before surgery, and an ^{18}F-FDG PET/MRI examination was performed within 2 weeks prior to surgery; and (3) clinical, imaging, and postoperative pathology data were complete. The exclusion criteria were as follows: (1) a history of pelvic radiotherapy and chemotherapy or cervical surgery; (2) no consent given for radical hysterectomy; and (3) a large hemorrhage or necrotic area in the lesions, which may potentially affect lesion extraction and image segmentation. Finally, 79 patients with cervical cancer were included in the study.

2.2. PET/MRI protocols

PET/MRI scans were performed on an integrated PET/MRI scanner (Signa PET/MRI, GE Healthcare, WI, USA). All patients were fasted to reach a blood glucose level less than 150 mg/dL prior to the injection of ^{18}F-Fluorodeoxyglucose (^{18}F-F FDG) (0.08–0.15 mCi/kg). After 60 min of rest, PET images and MR data were obtained simultaneously. In addition to the following conventional diagnostic sequences (including T1-weighted and T2-weighted imaging), a three-dimensional high-resolution T2WI (Sag CUBE T2 B sequence) was added, giving a total scan time of approximately 40–50 min (Table 1). The scan ranged from the superior margin of the iliac bone to the proximal femur. PET reconstruction was performed with a TOF-PSF-OSEM algorithm (time-of-flight point spread function ordered subset expectation maximization; 3 iterations and 32 subsets, 5 mm cut-off filter) on a 192 × 192 matrix, 35 cm field of view, 2.78 mm slice thickness, with attenuation correction, scatter correction, random correction, and dead-time correction.

2.3. Image evaluation

All images were reconstructed on a workstation (Advantage Workstation VolumeShare 5, GE Healthcare) for analysis. Two physicians each with 10 years of experience and holding dual licenses in nuclear medicine and radiology, together delineated the ROIs (lesion and normal uterine boundary) at the largest tumor level on the T2W-MR image, and copied the ROI onto the corresponding PET image in a blinded manner. If/when the radiologists disagreed, a senior doctor made the final judgement. PMI was defined as when the cervical interstitial low signal fiber ring was damaged on the MR image [12]; and PMI on the PET/MRI image was mainly based on the MRI diagnostic criteria, with a simultaneous increase in focal FDG accumulation greater than that in the surrounding tissues [13]. Then, the ROIs of both the T2W-MR and PET images were exported to a personal computer for deep image processing (using self-developed in-house software that will be shared online with others for future research and validation once packaged); only anonymized data were transferred. The circular ROI was divided into 12 regions at intervals of 30 degrees (A1 135–105°, A2 105–75°, A3 75–45°, A4 45–15°, A5 15–345°, A6 345–315°, A7 315–285°, A8 285–255°, A9 255–225°, A10 225–195°, A11 195–165°, and A12 165–135°, as shown in Fig. 1). The mean of the gray level values was calculated between the sectorial regions 2 mm inside and outside the ROI boundary (since adjacent pixel spacing of the PET image is 1.6289 mm). A1–A3 was defined as the front zone, A4–A6 as the left zone, A7–A9 as the back zone, and A10–A12 as the right zone. As the anterior region was adjacent to bladder and affected by its hypermetabolism, we assumed that PMI was defined when the gray level of the left + right zone was greater than 2 times that of the back zone [24–26].

2.4. Statistical analysis

Statistical analysis was performed using SPSS software (version 23,

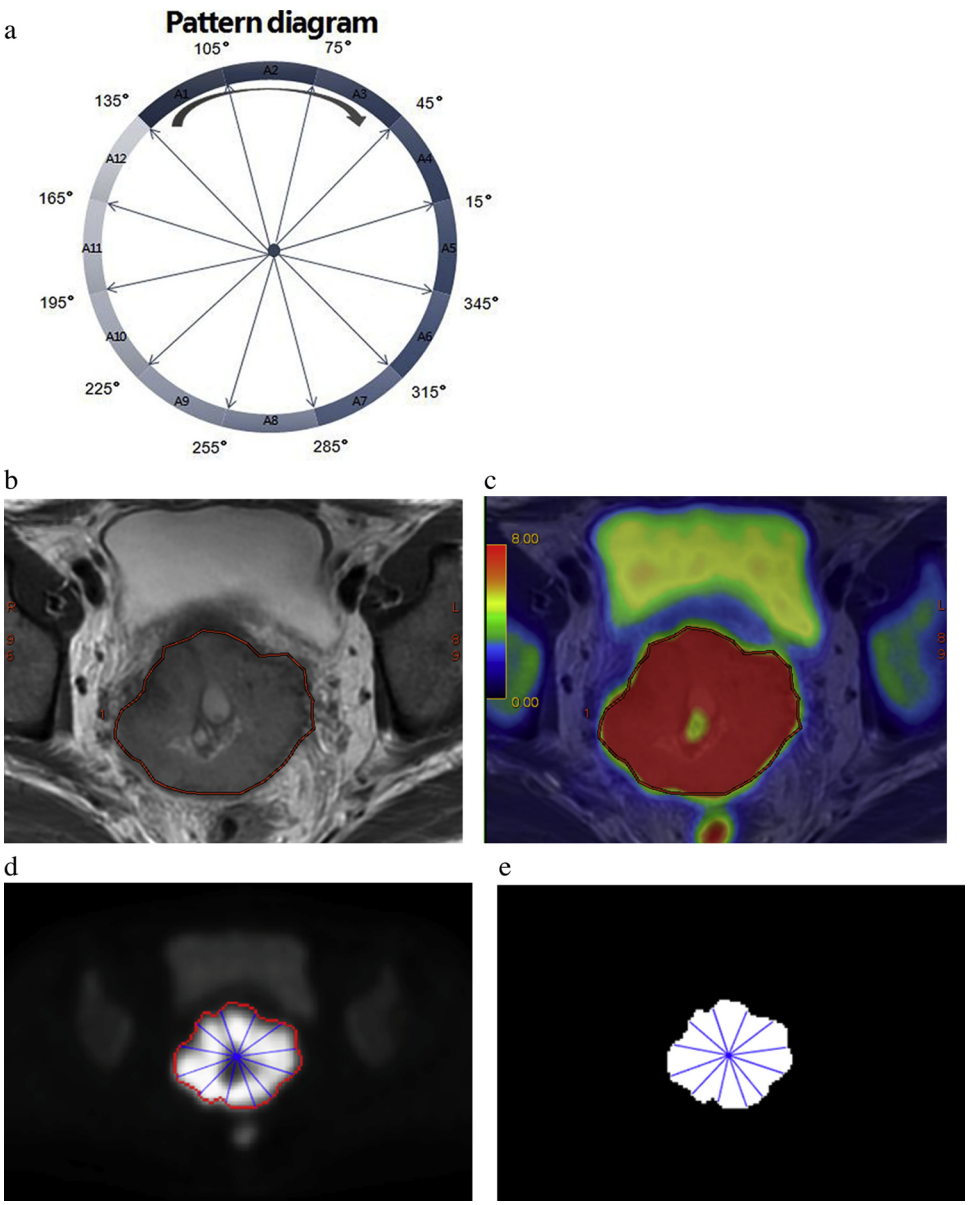

Fig. 1. (a) ROI was divided into 12 regions at an interval of 30 degrees (A1 135–105°, A2 105–75°, A3 75–45°, A4 45–15°, A5 15–345°, A6 345–315°, A7 315–285°, A8 285–255°, A9 255–225°, A10 225–195°, A11 195–165°, and A12 165–135°), and calculated gray level values between the sectorial regions 2 mm inside and outside the ROI boundary.
A 55-year-old patient with cervical cancer, FIGO stage IIB, had parametrial infiltration confirmed by postoperative pathology. (b) Axial T2WI showed a hybrid high-signal mass, and the low-signal fibrous rings in cervical interstitium were discontinuous, (c) PET/MRI fusion image showed hypermetabolic lesions, SUVmax = 7.82 (g/ml), and MRI and PET/MRI diagnosed the presence of PMI. (d, e) ROI extraction and segmentation on the PET image, and the calculated gray level values of each region are as follows: A1 7000.156, A2 9007.624, A3 9984.285, A4 11013.079, A5 10772.150, A6 10646.283, A7 10773.324, A8 10517.812, A9 11136.520, A10 11244.683, A11 11260.502, and A12 11172.035. A4-6 + A10-12 gray level values were 2 times larger than those of A7-9, suggesting that there was PMI.

IBM, USA). The normality of the gray level values of PET image was examined by the Kolmogorov-Smirnova test. The median (quartile range 25%, 75%) was used to describe non-normal data. The Wilcoxon, Mann-Whitney U and linear correlation tests were used to compare differences in gray level values between patients with or without PMI. The postoperative results were used as the gold standard to calculate the accuracy, sensitivity, specificity, PPV and NPV of the morphological MR image, PET/MRI image and combination of PET/MRI image with gray level values. The McNemar, chi-square and kappa concordance tests were employed to determine whether there were any differences between these methods. A kappa value greater than 0.81 indicated that the consistency was very good, a value between 0.61 and 0.80 indicated that the consistency was good, a value between 0.41 and 0.60 indicated that the consistency was average, and a value less than 0.40 indicated that the consistency was poor [14]. In this study, a P value < 0.05 was considered statistically significant.

3. Results

A total of 79 patients were included in the study, with a median age of 53 years (range, 23–78 years); of these patients, 37 patients (46.8%) had postoperative pathologically confirmed PMI, and 42 patients (53.2%) presented no PMI. The characteristics of these patients are shown in Table 2.

The gray level values of the PET image were not all normally distributed (A1–A10 $P < 0.05$, A11–A12 $P > 0.05$). The median gray level values (interquartile 25%, 75%) of the patients with and without PMI are shown in Table 3, with statistically significant differences between the groups ($P < 0.001$) and no statistically significant differences within the groups ($P > 0.05$). There was a moderate correlation between the pathological results and the gray level values of each region ($rs > 0.5$, $P < 0.001$) (Table 4). According to the FIGO stage, as the cervical lesions became more malignant, the gray level value gradually increased, with a statistically significant difference ($P < 0.05$) (Fig. 2). Of the 79 patients, 37 patients had postoperative pathologically-confirmed PMI. Morphological analysis of the MR and PET/MRI images found 27 and 28 cases of PMI, respectively, and the combination of PET/MRI image and gray level values identified 35 patients with PMI (Table 5).

The accuracy, sensitivity, specificity, PPV and NPV of MRI and PET/MRI in the diagnosis of early-stage cervical cancer with PMI were: 74.7% and 78.5%, 59.5% and 64.9%, 88.1% and 90.5%, 81.5% and

Table 2
Characteristics of the patients included.

Variable	Value n = 79(%)
Age (year)	53 (23-78)
FIGO stage	
IB1	4 (5.1%)
IB2	7 (8.9%)
IB3	9 (11.4%)
IIA1	17 (21.5%)
IIA2	19 (24.1%)
IIB	23 (29.1%)
Histological type	
Squamous cell carcinoma	63 (79.7%)
Adenocarcinoma	10 (12.7%)
Adenosquamous carcinoma	6 (7.6%)
Degree of differentiation	
1 (well differentiated)	19 (24.1%)
2 (moderately differentiated)	35 (44.3%)
3 (poorly differentiated or undifferentiated)	25 (31.6%)
Postoperative pathology	
PMI	37 (46.8%)
without PMI	42 (53.2%)

Age median(range); FIGO International Federation of Gynecology and Obstetrics; PMI parametrial invasion.

Table 3
Gray level values in the different districts of patients with or without parametrial infiltration.

Group	Without PMI	PMI
A1	4595.556 (3860.222, 5591.685)	6743.463 (4965.423, 9999.032)
A2	5059.37 (4214.81, 5807.456)	7379.972 (5614.729, 10603.059)
A3	4741.091 (4050.333, 5822.843)	8057.854 (6113.732, 10282.753)
A4	4620.093 (3997.872, 5891.259)	8270.874 (6627.58, 10325.539)
A5	4857.028 (4226.636, 6065.264)	8552.377 (6877.483, 10897.918)
A6	5445.264 (4486.414, 6463.919)	8794.902 (7597.65, 12162.784)
A7	5972.028 (4949.563, 6799.486)	8540.334 (7470.609, 11769.839)
A8	6855.704 (5867.435, 7868.7)	9675.096 (8345.32, 12315.209)
A9	7325.227 (6080.948, 8398.575)	10374.043 (9126.436, 12589.655)
A10	7530.754 (6145.066, 8350.458)	11319.709 (9570.23, 12651.84)
A11	7348.229 (6259.618, 8300.944)	11065.201 (9681.335, 12611.416)
A12	7148.395 (5960.578, 8195.775)	10713.049 (9350.683, 12218.278)

Median (interquartile 25%,75%) [M(P_{25},P_{75})].

85.7% and 71.2% and 74.5%, respectively, and the corresponding values for the PET/MRI + gray level values were 87.3%, 83.8%, 90.5%, 88.6% and 86.4%. The diagnostic results of MRI and PET/MRI were consistent (kappa = 0.693, $P < 0.001$); the accuracy, sensitivity and NPV of PET/MRI were slightly higher than those of MRI, and the differences were not statistically significant ($P = 1.000$). The diagnostic results of MRI and PET/MRI + gray level values were generally consistent (kappa = 0.475, $P < 0.001$); the accuracy, sensitivity and NPV of the PET/MRI + gray level values were significantly higher than those of MRI, and the differences were statistically significant (all P values < 0.05).

4. Discussion

Due to its unique advantages, such as high soft tissue resolution, MRI has been widely used in the preoperative diagnosis and staging of cervical cancer. Many experimental studies have shown MRI to be highly accuracy in tumor localization, evaluation of PMI, and confirmation of myometrial or endometrial infiltration [15,16].

However, the sensitivity and PPV of MRI in the diagnosis of PMI have been shown to be low. Kim M et al. reported that the sensitivity of preoperative MRI in the diagnosis of stage IB1 to IIA2 cervical cancer patients was 53.3%, and the PPV was 50.0% [7]. Moloney F et al. compared the diagnostic value of MRI and transvaginal sonography (TVS) for the local staging of cervical cancer and found that the sensitivity of MRI for the detection of PMI was only 40% [17]. Similarly, we found that, among these three diagnostic methods, MRI had the lowest diagnostic efficiency for PMI, with an accuracy, sensitivity and NPV of 74.7%, 59.5% and 71.2%, respectively.

In addition, MRI technology alone has certain limitations in assessing lymph node involvement. Furthermore PET/MRI has emerged as the favorable modality in terms of scan time required since PET/MRI can simultaneously acquire MR and PET data, which reduces scanning time. PET/MRI has clear advantages in gynecological tumor evaluation, staging, and individualized diagnosis and treatment planning, especially where there is lymph node metastasis and extrapelvic infiltration [18]. Grueneisen J et al. found that integrated PET/MRI could provide the correct T staging for 85% of patients with primary cervical cancer and correctly identify 80% of patients with regional metastases (N1) and 100% of patients with nonregional lymph node metastasis [11]. The sensitivity and specificity of PET/MRI in the diagnosis of parametrial tissue invasion were as high as 90% (9/10) and 94% (16/17), respectively. Other recent prospective studies have compared the diagnostic value of PET/MRI and PET/CT in patients with primary gynecologic malignancies (i.e. cervical and endometrial cancer). Schwartz M et al. reported that hybrid PET/MRI detected seven cases of parametrial soft tissue invasion of primary tumors, leading to escalated staging for five patients, and eventually changing the diagnosis and treatment plans for two of these patients [19].

However, a retrospective study of 30 patients with cervical cancer conducted by Kitajima K et al. [20]. showed that the accuracy of fusion PET/MRI in T staging was 83.3% (25/30), which is comparable to that of MRI alone. Our study also showed that diagnostic accuracy, sensitivity, and NPV of conventional PET/MRI (78.5%, 64.9%, and 74.5%, respectively) were only slightly higher than those of MRI, although the values were in good agreement (kappa = 0.693, $P < 0.001$); this finding may be due to the small number of patients who met the inclusion criteria in this study, nevertheless these results do not argue for the advantages of PET/MRI.

The diagnosis of PMI with MRI or PET/MRI is mainly based on morphological observations without actual quantification, which is not optimal. Therefore, we sought to increase the diagnostic accuracy by calculating the gray level values of the parametrial area of PET images. (To the best of our knowledge, we are the first to describe this technique.) Our calculation of gray level values was within the same predefined SUV (42% SUVmax) contour threshold (usually approximately 40%) [21]. The gray level values (pixel differences) of the para-region on the PET images were analyzed, which could be used as a substitute for signal intensity. In a study of 66 patients with cervical cancer, Nakamura K et al. found that there was a significant correlation between SUVmax and FIGO stage ($P = 0.036$) [22], and our results also confirmed that with higher FIGO stages, gray level values gradually increased ($P < 0.05$), indicating that this is a practical diagnostic technique for PMI.

Voxel segmentation is a routinely used and well-established method

Table 4
The correlation coefficients between the postoperative pathology and gray level values.

	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12
Spearman's rho	0.586	0.560	0.654	0.713	0.718	0.741	0.707	0.692	0.741	0.777	0.771	0.782
P	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

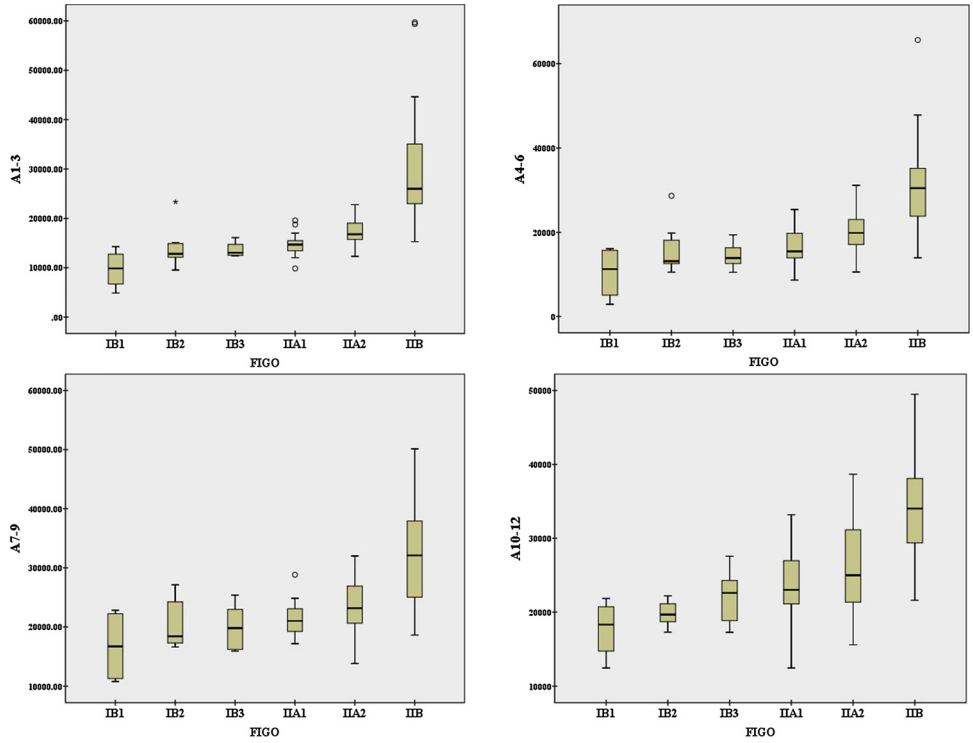

Fig. 2. According to FIGO staging, as the cervical lesions became more malignant, the gray level values of the different regions gradually increased.

for computer-aided diagnosis and artificial intelligence. In the past, Voxel segmentation has been applied in the diagnosis of nasopharyngeal carcinoma [23], and cervical cancer [24]. Torheim T et al. used Fisher's linear discriminant analysis (LDA) to obtain intensity and spatial information from MR images of cervical cancer patients based on the tumor segmentation of multiparameter MR image voxels (including T2W, T1W and DCE sequences) [24]. We applied it to integrated PET/MRI images for cervical cancer, and made full use of the two modalities sharing one ROI—an advantage of scanning and image postprocessing, along with the combined advantages of MR structural and PET functional imaging. Our results also showed that the accuracy, sensitivity, and NPV (87.3%, 83.8%, and 86.4%, respectively) of the combined PET/MRI + gray level values for PMI were higher than those for MRI or PET/MRI alone, and the differences were statistically significant (all P values < 0.05).

However, our research has several limitations. One is that a retrospective analysis such as ours may result in selection bias. Another is that our total sample size was small; most patients will undergo radiotherapy and chemotherapy instead of surgery, but only patients with PMI confirmed by postoperative pathology were included in our study, hence the small sample size. Therefore, more large-scale, prospective research is needed. Furthermore, no evaluation between multiple observers was performed. In our study, the images needed to be exported to a personal computer for gray level analysis. With the development of computer-aided diagnosis techniques, embedding commercial software into workstations may solve this problem.

5. Conclusions

In conclusion, it is feasible to evaluate parametrial infiltration of cervical cancer based on the PET/T2W-MRI voxel segmentation method with quantitative and visual indicators. The synergistic value of PET/MRI and gray level values can also improve the accuracy, sensitivity and NPV of PMI diagnosis, which may be accumulated for future artificial intelligence image analysis.

Compliance with ethical standards

All procedures performed in the studies involving human participants were in accordance with the ethical standards and Helsinki Declaration.

Declaration of Competing Interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled, "Evaluation of parametrial infiltration in cervical cancer with voxel-based segmentation of integrated ^{18}F-FDG PET/MRI images: A preliminary study".

Table 5
Diagnostic value of MRI, PET/MRI, and the combination of PET/MRI and gray level values in detecting parametrial invasion of cervical cancers.

Method	PMI (withoutPMI)	Accuracy (%(n))	Sensitivity (%(n))	Specificity (%(n))	PPV (%(n))	NPV (%(n))	*kappa Value*
MRI	27 (52)	74.7 (59/79)	59.5 (22/37)	88.1 (37/42)	81.5 (22/27)	71.2 (37/52)	0.693 *(P < 0.001)*
PET/MRI	28 (51)	78.5 (62/79)	64.9 (24/37)	90.5 (38/42)	85.7 (24/28)	74.5 (38/51)	0.607 *(P < 0.001)*
PET/MRI + gray level values	35 (44)	87.3 (69/79)	83.8 (31/37)	90.5 (38/42)	88.6 (31/35)	86.4 (38/44)	0.475 * *(P < 0.001)*

* Comparison between MRI and PET/MRI + gray level values.

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