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Original Article

CT, MRI, and PET imaging features in cervical cancer staging and lymph node metastasis

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Abstract: Objective: To assess the computerized tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) fusion imaging technique features in cervical cancer staging and lymph node metastasis. Methods: A total of 196 cervical cancer patients undergoing CT, MRI, PET/CT, and PET/MRI preoperatively were enrolled. The diagnostic accuracy and detection rates for paracervical invasion were evaluated on the basis of the International Federation of Gynecology and Obstetrics (FIGO) staging classification for cervical cancer. The diagnostic efficacy of each examination modality for determining lymph node metastasis was evaluated using surgical pathology as a reference. The CT and MRI imaging features of lymph node metastasis were compared. Results: PET/MRI had a higher diagnostic accuracy for cervical cancer (94.90%) than PET/CT, MRI, and CT (83.67%, 75.51%, and 69.39%) ($P < 0.05$). PET/MRI showed a higher detection rate of vaginal invasion, uterine invasion, bladder invasion, and cervical invasion than PET/CT, MRI, and CT ($P < 0.05$). The metastasis group showed higher maximum long and short axis diameters and axial ratios than the non-metastasis group ($P < 0.05$). The metastasis group had higher wash-in rates (WIR), maximum relative enhancements (MRE), wash-out ratios (WOR), and apparent diffusion coefficients (ADC), and lower times to peak (TTP) than the non-metastasis group ($P < 0.05$). The sensitivity (94.74%), specificity (93.33%), and accuracy (93.88%) of PET/MRI in the diagnosis of cervical cancer lymph node metastasis were higher than the sensitivity, specificity, and accuracy of PET/CT, MRI and CT ($P < 0.05$). Conclusion: CT, MRI, PET/CT and PET/MRI can be used effectively in the diagnosis of cervical cancer staging and lymph node metastasis, among which PET/MRI has a higher diagnostic sensitivity, specificity, and accuracy and is helpful in clinical diagnosis and treatment.

Keywords: Cervical cancer, staging, lymph node metastasis, CT, MRI, PET

Introduction

Cervical cancer is a common malignant tumor of the female reproductive system, with postcoital bleeding and postmenopausal bleeding as the main symptoms. The incidence rate of cervical cancer is on the rise, and the disease is more aggressive among younger patients [1, 2]. The disease's pathogenesis is complicated. It is associated with a persistent, high-risk human papillomavirus infection, and with sexually transmitted diseases and disorders, and early marriage and early childbirth, *etc.* may also induce cervical cancer [3]. Active and appropriate treatment can reduce mortality and improve prognosis, and the choice of treatment option is closely related to the stage of the disease. The FIGO staging of cervical cancer is often referred to, and the disease is classified using physical examinations, cystoscopies, intravenous pyelograms, and chest radiographies. Although it can effectively guide the diagnosis and treatment of the disease, it has the disadvantage of not involving lymphovascular space invasion or lymph node metastasis, and it cannot accurately determine the invasion of the bladder, rectum, and parametrium, so it is difficult to achieve objective and accurate

staging [4]. Therefore, an accurate and convenient diagnostic protocol is needed for diagnosing cervical cancer staging and lymph node metastasis.

Many imaging modalities, such as CT and MRI, are widely used in the diagnosis of cervical cancer, but they are less effective in determining distant lymph node metastasis and cervical invasion [5]. The advances in molecular imaging technology, PET/CT, PET/MRI, and other multimodal molecular imaging technologies have been highly valued clinically. PET/CT scans are a molecular medicine tool that integrates positron emission tomography (PET) scanning and x-ray computed tomography (CT) in a single gantry to determine the nature of the lesion through glucose uptake. PET/MRI scans are a two-in-one test combining images from positron emission tomography (PET) scans and magnetic resonance imaging (MRI) scans, which uses the strengths of PET and MRI to generate some of the most detailed images of the inside of the human body. Both are particularly crucial in the diagnosis, staging, and prognostic evaluation of malignant tumors [6, 7]. There are few comparative studies on the diagnosis of cervical cancer staging and lymph node metastasis using CT, MRI, PET/CT, and PET/MRI [8]. This study analyzed the characteristics of CT, MRI and PET fusion imaging techniques in cervical cancer staging and lymph node metastasis, providing more evidence for the clinical diagnosis and treatment of cervical cancer.

Materials and methods

General information

This study was approved by the medical ethics committee of Laizhou City People's Hospital. A total of 196 cervical cancer patients who underwent surgery in our hospital from July 2017 to April 2020 were enrolled. The patients ranged in age from 37 to 71 years old, with a mean age (51.37±5.58) years old. The patients' main symptoms were postmenopausal vaginal bleeding and postcoital bleeding.

Inclusion criteria: Patients who met the diagnostic criteria for cervical cancer according to the International Federation of Gynecology and Obstetrics 2012 Guidelines for the Diagnosis and Treatment of Cervical Cancer [9], patients who underwent lymph node dissections and radical hysterectomies, patients who did not undergo other treatments such as chemotherapy, radiotherapy, immunosuppressants, *etc*. before their surgeries, and patients who were informed about this study and who signed the consent form.

Exclusion criteria: Pregnant or lactating patients; patients with unconfirmed diagnoses using surgical pathology, those with an inability to cooperate with the various examinations used in the study, patients with concomitant severe hepatic or renal failure or impairment, and patients with other concomitant tumors.

Methods

CT examination: A Siemens 64-row spiral CT machine (model: Sensation n64) was used. 500 mL of 1% meglumine diatrizoate was administered orally about one hour before the examination, the urine was held, and the CT scan was performed. The CT scan was enhanced by using an intravenous injection of 80-100 mL of iopromide.

MRI examination: A Philips 1.5T magnetic resonance machine (model: Multiva 1.5T) was used. For the sagittal fat suppression, T2WI has a layer thickness of 4.0 mm, TR3840 ms, TE103 ms. The oblique cross-section of the uterine axis was perpendicular to the scan diameter. T2WI has a layer thickness of 4.0 mm, TR4890 ms, TE84 ms. MRI-enhanced scan. 20 mL of zapentine was injected intravenously, with the injection rate maintained between 8-12 ml/s. A T1WI-enhanced sagittal and cross-sectional scan was performed with a layer thickness of 4.0 mm, TR462ms, and TE8.8 ms.

PET/CT examination: A Siemens 64PET/CT machine (model: Biograph 64), 18F-FDG was used, with a radiochemical purity > 95%. The 18F-FDG was injected intravenously at a rate of 3.7-7.4 MBq/kg before the examination, with the whole body being visualized, and the PET/CT examination was performed from the base of the skull to the upper femur.

PET/MRI examination: A Philips Ingenuity TF PET/MRI machine was used and 18F-FDG 3.7-7.4 MBq/kg was injected intravenously into the elbow vein, and a pelvic PET/MRI scan was per-

formed 48-72 mins later, including pelvic PET image acquisition (1 bed for four minutes each), a rapid 3D T1WI gradient-echo MR sequence (atMR) scan, a and pelvic MR scan (axial DWI, multi-directional T1WI, and T2WI).

Observational indicators

Main outcomes: (1) Cervical cancer staging. The International Union of Obstetrics and Gynecology (FIGO) [10] staging classification for cervical cancer was used as the standard to assess the diagnostic accuracy of the cervical cancer staging using CT, MRI, PET/CT, and PET/MRI. FIGO staging criteria: Stage Ia: invasive carcinoma of the cervix with an infiltration depth of ≤5.0 mm and a horizontal infiltration ≤7.0 mm; preclinical lesions > stage I a or clinically visible lesions confined to the cervix is stage Ib; tumor b invades beyond the uterus but not to the pelvic wall and not to the lower third of the vagina, and without a parametrial tissue infiltration is stage IIa. Stage IIb: the cancer has grown beyond the cervix and the uterus and has spread into the tissues next to the cervix (the parametria). (2) Lymph node metastasis. With the pathological findings after surgery as the gold standard, the diagnostic efficacies of CT, MRI, PET/CT and PET/MRI for lymph node metastasis were evaluated, including their sensitivity, specificity, and accuracy. The criteria for determining the lymph node metastasis include: (i) Surgical pathology. There is more than one copy of the lymph node specimens where cancerous tissue can be observed microscopically in the lymph nodes. (ii) CT. Low-density areas are observed in the lymph nodes, and the enhancement scans of the lymph nodes show a mild or no enhancement in the central density area and circular enhancement of the margins. The shortest transverse diameter of the lymph nodes is ≥ 10 mm, the lymph nodes are clustered, the lymph node margins are blurred, and the envelope is incomplete. The diagnosis of lymph node metastasis can be confirmed if a patient has one of the above symptoms. (iii) MRI. 0 points: normal lymph node; 1 point: lymph node diameter < 0.5 cm; 2 points: lymph node diameter ranges from 0.5-1 cm, 3 points: lymph node diameter > 1 cm, and 4 points: fusion necrosis of lymph nodes. 0-2: no lymph node metastasis; 3-4: lymph node metastasis. (iv) PET/CT. The lymph nodes are scored according to the radioactive iodine uptake. 0 point indicates non-radioactive uptake, 1 point: microscopic lesions, the SUVmax of the tumor is equal to the surrounding tissues; 2 points: mild uptake, suspicious lesions, SUVmax higher than the surrounding tissues but < 2.5; 3 points: apparent uptake, metastatic lesions, SUVmax ≥ 2.5; 4 points: apparent metastasis. 0-2: no lymph node metastasis; 3-4: lymph node metastasis. (5) PET/MRI. Lymph node metastasis can be determined based on the abnormal signals on the diffusion images, the lymph node anatomy, and an abnormal increase in FDG uptake in the lymph nodes shown on PET images.

Secondary outcomes: (1) Paracervical invasion of the cervix. The CT, MRI, PET/CT, and PET/MRI examination detection rates for vaginal invasion, uterine invasion, bladder invasion, and cervical invasion were compared. (2) CT imaging. The maximal long-axis diameters, the maximal short-axis diameters, the axial ratios, and the lymph node distributions (intraskeletal, extraskeletal, total skeletal, occluded, and para-aortic) were compared among the patients with and without metastases. (3) MRI imaging. The WIR, MRE, WOR, ADC, and TTP were compared among the patients with and without metastases.

Statistical analysis

SPSS 22.0 software was used for the data processing. GraphPad Prism 8.0 software was used to plot the statistical charts. The measurement data were represented by ($\bar{x}$±S) and were compared among multiple groups using one-way ANOVA. The count data were represented as percentages and compared using χ^2 tests. $P < 0.05$ was considered statistically significant.

Results

Comparison of the clinical staging using CT, MRI, PET/CT, and PET/MRI

FIGO staging: there were 36 cases of Stage Ia, 60 cases of Stage Ib, 54 cases of Stage IIa, and 46 cases of Stage IIb. The CT, MRI, PET/CT, and PET/MRI had an accuracy rate of 69.39% (136/196), 75.51% (148/196), 83.67% (164/196), and 94.90% (186/196) for the diagnosis of cervical cancer, respectively. The

Table 1. Clinical staging using CT (n)

CT	FIGO staging				Total
	Ia	Ib	IIa	IIb	
Ia	24	2	0	4	30
Ib	4	42	4	6	56
IIa	6	0	40	6	52
IIb	2	16	10	30	58
Total	36	60	54	46	196

Table 2. Clinical staging using MRI (n)

MRI	FIGO staging				Total
	Ia	Ib	IIa	IIb	
Ia	28	4	0	2	34
Ib	4	44	4	6	58
IIa	4	0	44	6	54
IIb	0	12	6	32	50
Total	36	60	54	46	196

PET/MRI had a higher diagnostic accuracy for cervical cancer than the PET/CT, MRI, and CT (χ^2 = 23.133, P < 0.001), indicating that the PET/MRI is more effective at identifying the clinical stages of cervical cancer (**Tables 1**-**4**).

Comparison of the paracervical invasions using CT, MRI, PET/CT, and PET/MRI

The surgical pathology results showed 40 cases of vaginal invasion, 24 cases of uterine invasion, 6 cases of bladder invasion, and 10 cases of cervical invasion. The PET/MRI had a higher detection rate than the PET/CT, MRI, CT (P < 0.05), indicating that the PET/MRI is better at determining vaginal invasion, uterine invasion, bladder invasion, and cervical invasion (**Table 5**).

CT imaging features of the lymph nodes

The surgical pathology results showed 76 cases of lymph node metastasis and 120 cases of non-lymph node metastasis. The metastatic group had higher maximum long and short axis diameters and axial ratios than the non-metastatic group (P < 0.05). The two groups had no significant difference in their lymph node distributions (P > 0.05), indicating that the CT imaging characteristics of the patients with and without lymph node metastases were significantly different, but they had no connection with the distribution of the lymph nodes (**Figures 1** and **2**).

Table 3. Clinical staging using PET/CT (n)

PET/CT	FIGO staging				Total
	Ia	Ib	IIa	IIb	
Ia	30	2	0	2	34
Ib	4	50	4	2	60
IIa	2	2	46	4	54
IIb	0	6	4	38	48
Total	36	60	54	46	196

Table 4. Clinical staging diagnostic results using PET/MRI (n)

PET/MRI	FIGO staging				Total
	Ia	Ib	IIa	IIb	
Ia	34	0	0	0	34
Ib	2	56	2	0	60
IIa	0	2	52	2	56
IIb	0	2	0	44	46
Total	36	60	54	46	196

MRI imaging characteristics of the lymph nodes

The metastatic group had higher WIR, MRE, WOR and ADC, and significantly lower TTP than the non-metastatic group (P < 0.05), indicating a significant difference between the MRI imaging in patients with and without lymph node metastases (**Figures 3** and **4**).

Comparison of the efficacy of CT, MRI, PET/CT, and PET/MRI for determining lymph node metastasis

PET/MRI showed higher sensitivity, specificity, and accuracy of than PET/CT, MRI, and CT for the diagnosis of lymph node metastasis (P < 0.05), indicating that PET/MRI is more effective at determining lymph node metastasis in cervical cancer (**Tables 6**, **7**).

Discussion

Conventional CT density has a high spatial resolution and can display visceral organs and retroperitoneal lymph nodes and lymph nodes of the pelvis, which helps to assess the location, shape and size of the lymph nodes and the shortest transverse diameter of the lymph nodes ≥ 1 is a criterion to indicate lymph node metastasis using CT [11, 12]. Feng et al. [13] reported that the area under the ROC curve of spiral CT for determining the lymph node metas-

Table 5. Comparison of the paracervical invasion results using CT, MRI, PET/CT, and PET/MRI [n (%)]

Detection Methods	Vaginal invasion (n = 40)	Uterine invasion (n = 24)	Bladder invasion (n = 6)	Cervical invasion (n = 10)	Total (n = 80)
CT	22 (55.00)	10 (41.67)	4 (66.67)	2 (20.00)	38 (47.50)
MRI	28 (70.00)	18 (75.00)	4 (66.67)	6 (60.00)	56 (70.00)
PET/CT	34 (85.00)	20 (83.33)	6 (100.00)	10 (100.00)	70 (87.50)
PET/MRI	38 (95.00)	24 (100.00)	6 (100.00)	10 (100.00)	78 (97.50)
χ^2	17.229	11.710	4.800	18.333	51.401
P	0.001	0.008	0.187	< 0.001	< 0.001

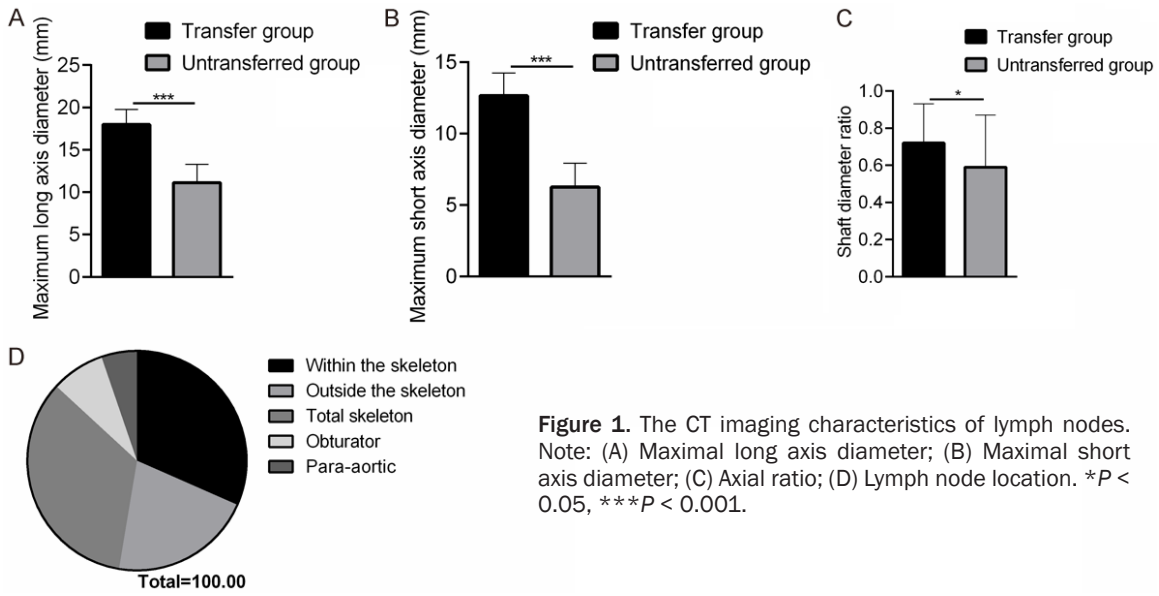

Figure 1. The CT imaging characteristics of lymph nodes. Note: (A) Maximal long axis diameter; (B) Maximal short axis diameter; (C) Axial ratio; (D) Lymph node location. **P* < 0.05, ****P* < 0.001.

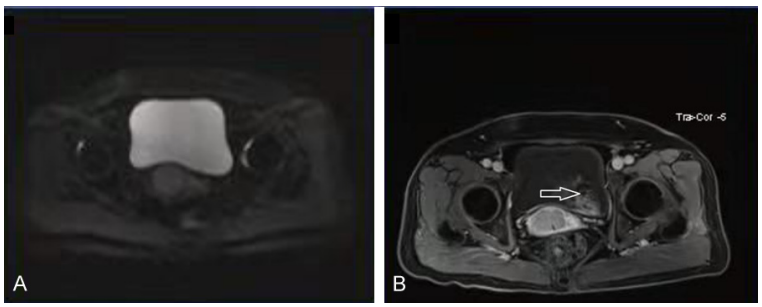

Figure 2. Typical CT images from a cervical cancer patient. Note: (A) Dispersion image shows a slightly high signal with a clear boundary and a size of about 2.6*2.2 cm; (B) T1-weighted image of the pelvic cavity, dynamic contrast-enhanced scanning, with the lesions showing heterogeneous enhancement.

tasis of cervical cancer was 0.816 (95% CI: 0.769-0.903), and the sensitivity, specificity, and accuracy was 86.9%, 71.4%, and 78.9%, respectively. In this study, CT had a low sensitivity for diagnosing cervical cancer lymph node metastasis, which is inconsistent with the above research results. The possible reasons were related to the small sample size and the operational performance in this study. For clinical diagnoses, CT is still inadequate. For example, the diagnosis is confirmed only when there is parametrial invasion, irregular outer edges and an enlargement of the cervix. It is hard to distinguish the tumor tissue from the nerves, inflammation, lymphatic tissues, blood vessels, and fibrotic tissues, especially in the early stages, so it is impossible to determine the depth of the tumor invasion [14]. In addition, plain CT cannot identify blood vessels or lymph nodes, so it is difficult for it to show the internal structure of the lymph nodes, but enhanced scanning can identify the blood vessels, but it only shows a ring-

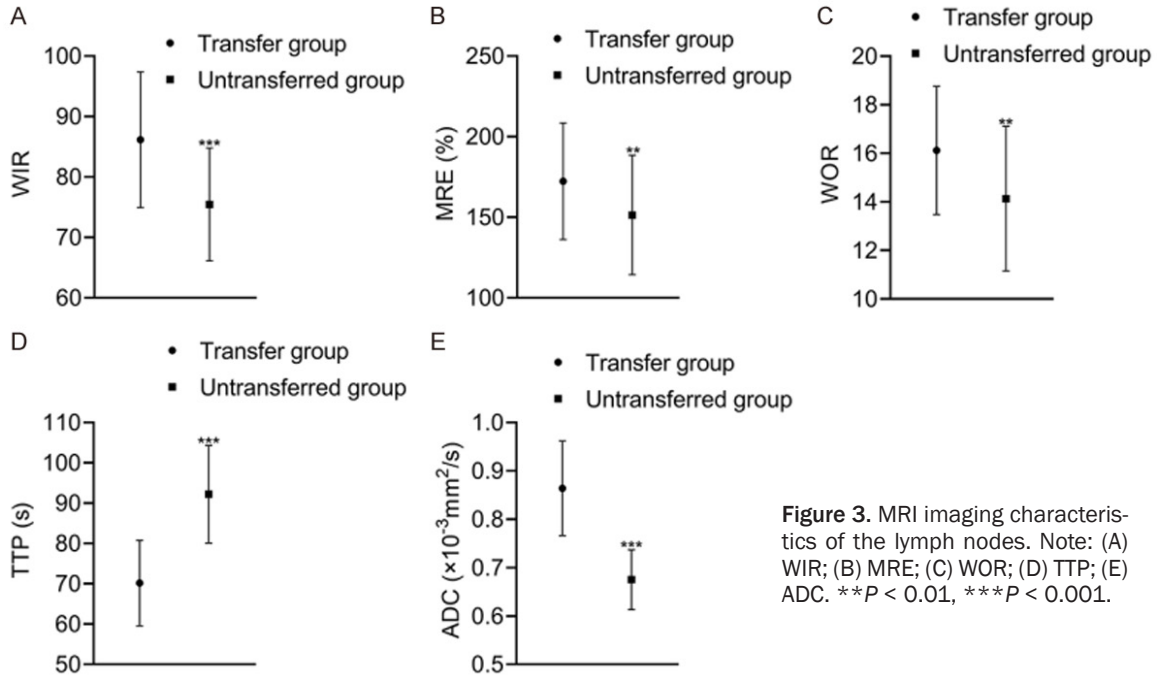

Figure 3. MRI imaging characteristics of the lymph nodes. Note: (A) WIR; (B) MRE; (C) WOR; (D) TTP; (E) ADC. $^{**}P < 0.01$, $^{***}P < 0.001$.

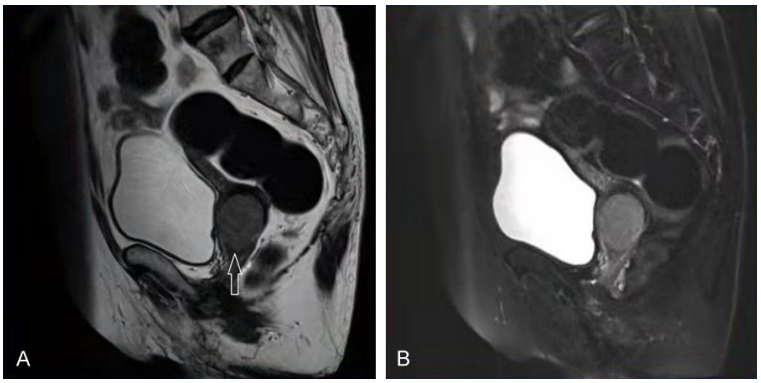

Figure 4. Typical MRI images from a cervical cancer patient. Note: (A) A sagittal SET1 weighted image in which a massive and long T1 signal occupying lesion can be seen in the uterine neck; (B) A sagittal SET2 weighted image, and a massive long T2 signal occupying lesion can be seen in the uterine neck.

shaped enhancement and the uniform enhancement of the lymph nodes, so its application is limited [15]. MRI can visually display tumors, easily identify lymph nodes and blood vessels, and accurately determine tumor size, the depth of the tumor infiltration, and the lymph node metastasis. Cervical cancer cells are composed of smooth muscle fibers with low water content, which limit the free movement of water molecules. Therefore, a low signal is shown on the junctional zone of the ADC image, and a high signal is shown in the endometrium on the DWI image, and a low signal is shown in the muscle layer and the junctional zone. Conventional MRI can clearly distinguish the junction zone, the endometrium, and the muscle layer [16]. In cervical cancer, increased tissue density, changes in the intracellular structure, and small extracellular spaces may lead to the limited diffusion of water molecules, so DWI shows a high signal and a low ADC. On T2WI, the imaging of cervical cancer is dominated by a high quasi-circular and irregularly shaped signal, with a clear contrast from the cervical stroma, endometrium, and parametrial fat [17]. Torabi et al. [18] determined the lymph node metastasis based on the performance of MRI dynamic enhancement and found that the peak amplitude of metastatic lymph nodes after dynamic enhancement was lower and the time to peak was longer. In this study, the metastatic group exhibited higher WIR, MRE, WOR and ADC, and lower TTP than the non-metastatic group, and the sensitivity, specificity, and accuracy of the MRI were 76.32%, 80.00% and 78.57% respectively, for the diagnosis of lymph node metastasis of cervical cancer, indicating that the MRI parame-

Table 6. CT, MRI, PET/CT, and PET/MRI for the diagnosis of lymph node metastasis versus the pathological findings (n)

Pathology results	Number of cases	CT		MRI		PET/CT		PET/MRI	
		Metastasis	Non-metastasis	Metastasis	Non-metastasis	Metastasis	Non-metastasis	Metastasis	Non-metastasis
Metastasis	76	52	24	58	18	64	12	72	4
Non-metastasis	120	30	90	26	96	12	108	8	112
Total	196	82	114	84	114	76	120	80	116

Table 7. The efficacy of CT, MRI, PET/CT, and PET/MRI for diagnosing lymphatic metastases (%)

Index	Sensitivity	Specificity	Accuracy
CT	68.42 (52/76)	75.00 (90/120)	72.45 (142/196)
MRI	76.32 (58/76)	80.00 (96/120)	78.57 (154/196)
PET/CT	84.21 (64/76)	90.00 (108/120)	87.76 (172/196)
PET/MRI	94.74 (72/76)	93.33 (108/120)	93.88 (184/196)
χ^2	16.653	18.581	33.734
P	0.001	< 0.001	< 0.001

ters between the patients with and without lymph node metastasis were significantly different, and that MRI can be used to diagnose metastasis in the lymph nodes. However, MRI could not provide detailed data about the structural changes within the lymph nodes, and it had a low diagnostic rate for tumors with early metastases and small lymph nodes.

The principle of PET/CT is different from that of CT, MRI, *etc*. It uses 18F-FDG as a visualizing agent to enhance the contours of the tumor lesions, to reflect the distribution of phosphorylation and the cellular uptake of glucose, so as to show the metabolism of the whole body tumor [19, 20]. PET/CT can not only accurately display the size and location of the lesion in relation to adjacent tissues and organs, but it can also effectively identify the nature of the tumor and provide information on the biological activity of the tumor during clinical treatment. PET/CT is more helpful for determining the tumor staging and progression than PET or CT alone [21]. In this study, the sensitivity, specificity, and accuracy of PET/CT for diagnosing lymph node metastasis were 84.21%, 90.00%, and 87.76%, respectively, which is similar to the results of Fu et al. [22]. However, PET-CT still has some false negatives and false positives in determining whether the lymph nodes are metastatic, because not only is the glucose metabolism increased in the malignant lymph nodes, but the benign lesions such as hyperplasia and inflammation are related to increased glucose metabolism, so false positives may occur. Meanwhile, the spatial resolution of PET-CT is not high, and the image quality is not as good as that of simple CT, with poor anatomical structure display and artifacts. Besides, a small increase in glucose metabolism also leads to false negatives. In addition, if the location of the primary lesion is hidden, the volume is too small or it is affected by the physiological uptake of the nucleus, there may be a missed diagnosis [23]. In the present study, the sensitivity, specificity, and accuracy of PET/MRI in the diagnosis of lymph node metastasis were 94.74%, 93.33% and 93.88%, respectively, higher than the PET/CT, MRI and CT, showing that PET/MRI is more accurate.

A retrospective study reported that the accuracy, sensitivity, and specificity of PET/MRI in diagnosing the paracervical invasion of cervical cancer were 78.5%, 64.9%, and 74.5% respectively, which were all higher than the MRI diagnostic results, indicating that PET/MRI can improve the accuracy and sensitivity of the diagnosis of the bladder invasion of cervical cancer [24]. The present study found that the accuracy of PET/MRI for diagnosing cervical cancer and the detection rate of vaginal invasion, uterine invasion, bladder invasion, and cervical invasion were all higher than accuracy of PET/CT, MRI and CT, indicating that PET/MRI can effectively detect the paracervical invasion of cervical cancer and guide clinical staging, which is consistent with the conclusions of the study mentioned above. However, this study still has some shortcomings, such as its small cohort and the uneven number of cases in the various stages of cervical cancer. The effects of the combined diagnoses of PET/MRI, PET/CT, MRI, and CT were not explored, so a larger cohort, a multicenter study, and further prospective studies are still needed to provide

imaging evidence for the formulation of treatment options for cervical cancer patients.

In summary, CT, MRI, PET/CT and PET/MRI can be used effectively to diagnose cervical cancer stages and lymph node metastases, and PET/MRI has higher sensitivity, specificity and accuracy, so it is helpful in guiding clinical diagnosis and treatment.

Disclosure of conflict of interest

None.

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