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^{18}F-FDG PET/CT can correct the clinical stages and predict pathological parameters before operation in cervical cancer

Zhuo Yang[a], WeiNa Xu[b], YaNan Ma[c], KuiRan Liu[a], Yan Li[a], DanBo Wang[a,*]

[a] Department of Obstetrics and Gynecology, Shengjing Hospital Affiliated to China Medical University, Sanhao Street No. 36, Heping District, Shenyang, Liaoning, People's Republic of China
[b] Department of Nuclear Medicine, Shengjing Hospital Affiliated to China Medical University, Sanhao Street No. 36, Heping District, Shenyang, Liaoning, People's Republic of China
[c] Department of Biostatistics and Epidemiology, China Medical University, Puhe Street No. 77, Shenbei New District, Shenyang, Liaoning, People's Republic of China

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ABSTRACT

Objectives: To evaluate the value of the positron emission tomography-computed tomography (PET/CT) imaging in correcting the clinical stages and predicting pathological parameters before operation in cervical cancer.
Methods: Medical records of preoperative PET/CT from 113 patients with cervical cancer were retrospectively reviewed and compared with clinical examination and pathological parameters.
Results: The accuracy of tumor staging by PET/CT was 94.7%. The sensitivity and specificity to diagnose lymph node (LN) metastasis were 53.8% and 95.0%, respectively, with 98.4% and 59.2% for deep cervical stromal invasion. The positive predictive value was 58.3% and 75.9%, and the negative predictive value was 94.1% and 96.7%. Using maximum standardized uptake value (SUV_{max}) = 1.05 and metabolic tumor volume (MTV) of LN = 0.50 or MTV of cervical lesions = 11.60 as cut-off value to diagnose LN metastasis individually, we have found that the sensitivity and specificity for SUV_{max}, MTV of LN and cervical lesions were 53.8% and 94.0%, 46.2% and 94.0%, 88.9% and 73.0%, respectively. For deep cervical stromal invasion, with cervical lesions SUV_{max} = 7.83 or MTV = 8.76 as cut-off value, the sensitivity and specificity were 92.2% and 57.1%, 75.0% and 76.2%, respectively.
Conclusion: PET/CT stage preoperative cervical cancer more objectively and accurately compared to traditional staging system. The LN metastasis and deep cervical stromal invasion of cervical cancer could be well predicted before operation by PET/CT so that the doctors can choose individualized treatment options.

1. Introduction

Cervical cancer is the second most common cancer after breast cancer, accounting for 12% of all tumors diagnosed in women worldwide [1]. There are nearly 530,000 new cases diagnosed every year, about 85% of which occur in developing countries. In China, about 131500 of new cases is diagnosed, which takes nearly 1/3 of the global number. Cervical cancer has become the leading genital cancer of women in China [2].

Different from that the majority of malignant tumor in which surgery is the main choice of therapy, cervical cancer is sensitive to radiation therapy. The five-year survival rate of advanced cervical cancer can reach above 50% with the comprehensive therapy based on radiation therapy. But if the patients mistake the operation therapy, they would lose the opportunity of obtaining satisfactory treatment, which directly lead to the poor prognosis. However, if indications are appropriate, surgery is still considered the preferred treatment for cervical cancer. Both the operation therapy and radiation therapy have important value, and they do not substitute but complement each other. The choice of treatment plans for cervical cancer mainly depends on the strict and accurate preoperative clinical staging, which are pivotal for the clinical outcome of cervical cancer therapy. The international standard of clinical staging in cervical cancer has been following the International Federation of Gynecology and Obstetrics (FIGO) staging system [3].

Localized at the unique anatomy position, the cervix can be checked with naked eyes, which makes the preoperative diagnosis of cervical cancer feasible. Pathological diagnosis-clinical

* Corresponding author.
E-mail address: wangdb@sj-hospital.org (D. Wang).

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stage-treatment plan has become the standard therapy model in cervical cancer. The clinical stage is the key of the optimum therapy. However, there still exist some most confused limitations to this FIGO physique examination staging system: (1) the parametrial and pelvic side wall invasion may be mistaken or disturbed by inflammation or endometriosis or obesity or imparity of the patients. (2) The tumor size, especially in the endogenous type, may be measured inaccurately by doctor's visual inspection. (3) The lymph node (LN) and distant metastasis could not be assessed before operation correctly. Compared to pathological staging, clinical examination staging results in 20–40% patients under or over staged [4]. For patients with the neoadjuvant chemotherapy, the postoperative pathological parameters might be under graded or false negative, and lead to delay or disturb the postoperative adjuvant therapy, if there is no accurate assessment provided before treatment.

Integration of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography with computed tomography (PET/CT) has unique advantages when used for tumor evaluation as this technique can assess not only tumor morphology but also the malignancy with the use of ^{18}F FDG. It could create the outline of the tumor via the volume of interest (VOI), and measure the maximum standardized uptake value (SUV_{max}) and the metabolic tumor volume (MTV) objectively. Such quantitative information produced by PET/CT not only makes it possible for accurate diagnosis of the primary local lesion, but also for a more comprehensive assessment of the whole body status. Therefore PET/CT has been widely used in the diagnosis of primary tumors, tumor staging, assessment of tumor metastasis and tumor recurrence monitoring in cervical cancer [5–7] and others malignant tumor [8–11]. A detailed evaluation of tumor by PET/CT could correct the mistake of traditional tumor classification and provide the evidence for individualized treatment plan [5].

In this study, we recruited 113 patients with cervical cancer and performed PET/CT to answer the following questions: (1) How the accuracy of the preoperative staging by PET/CT can be? (2) How PET/CT parameters correlate with pathological parameters and whether PET/CT can assess them before operation so that we can make individual treatment for patients? (3) Whether PET/CT could assess the pathological parameters accurately before operation for patients with neoadjuvant chemotherapy to correct the postoperative pathological parameters which might be under graded or false negative. We found that PET/CT imaging not only could be used for preoperative clinical staging but also evaluate LN metastasis and deep cervical stromal invasion, thus it provides a strict and accurate preoperative clinical staging and a good predication of pathological parameters before operation and guides individualized treatment options chosen.

2. Materials and methods

2.1. Patients and reference standards

113 Patients with newly diagnosed cervical cancer referred to the Department of Obstetrics and Gynecology in Shengjing Hospital Affiliated to China Medical University from January 2006 to June 2013 were recruited into this study. The patients for this study have to meet the following: (1) pathologically diagnosed to be cervical cancer; (2) FIGO clinical staging was between IB1 and IIA2 stage; (3) agreed to the therapy of radical hysterectomy plus systematic bilateral pelvic lymphadenectomy or/and aortic lymphadenectomy; (4) PET/CT recommended to be performed within 10 days before operation. Patients undergone neoadjuvant chemotherapy or radiation or non-operative therapy and patients with surgery contraindications were all excluded. This study was approved by the China Medical University Research Ethics Committee in accord with the Helsinki Declaration. The registration number was 2015PS121K.

The median age of recruited patients was 48 years (range: 26–70 years). According to FIGO staging guideline (2009) and clinical physical examination to determine the growth type of cervical lesions (the endogenous type/the exogenous type), all cases were staged between IB1 and IIA2, which were composed of fifty-six IB1 (30/26), seventeen IB2 (9/8), thirty-five IIA1 (6/29), and five IIA2 (0/5).

2.2. PET/CT scanning and image acquisition

The PET/CT scanning was performed on a GE PET/CT scanner (Model Discovery Elite, GE Medical Systems, WI, and USA). No sedative drugs administered, patients fasted for at least 6 h prior to undergoing PET/CT, with the plasma glucose concentration less than 7 mmol/L. Patients were injected intravenous injection with 3.7 MBq/kg of ^{18}F FDG (produced by GE Medical Systems, Mini Trace II and Trace Lab FXFDG, purity >99%) and 60 min later, the images were captured from the parietal to the middle thigh of the patients who were supine with their arms raised above the head. Patients were required to rest after ^{18}F FDG uptake and during scanning.

Spiral CT was performed first on patients under automatic-controlled exposure at 120 kV, 30–210 mA, during shallow breathing, and then PET was acquired in 3D mode, with the 3.25 mm of slice thickness. PET images were corrected for random, scatter and reconstructed using iterative algorithms.

2.3. PET/CT diagnosis and image analysis

Image readout was performed on an AW4.5 WorkStation (GE Healthcare), which allowed visualization of PET, CT and fused sections in transverse, coronal and sagittal planes. Two experienced specialists in nuclear medicine evaluated the images qualitatively for regions of focally increased glucose metabolism and quantitatively by determining the standard uptake values (SUVs) and informed us the clinical data of the patient at the moment of PET/CT scanning. We characterized malignancy as an increase in glucose uptake relative to the surrounding tissue with the SUV more than 2.5 which is clinical accepted worldwide. Using the Volume Viewer software (GE Healthcare), we acquired VOI and SUV_{max}. MTV was calculated using the 42% threshold method, as initially described by Miller and Grigsby [12]. Based on the depth of the cervical stromal invasion in the images, we estimated it whether >1/2 of the cervical stromal layer, and if it was, we made the diagnosis as deep cervical stromal invasion.

At last, two experienced clinicians determined PET/CT staging with reference to FIGO staging criteria (2009). In brief, first, they made sure the I or II stage and the A or B stage by the physical examination and PET/CT imaging, if there was the visible lesion limited in the cervix, it belonged to IB stage and if only the vaginal fornix was involved outside the cervix, it belonged to IIA stage; then they made sure the 1 and 2 stage according to PET/CT lesion diameter, if the lesion diameter $\leq$4 cm, it belongs to 1 stage while if >4 cm belongs to 2 stage.

2.4. Pathological diagnosis

Postoperative pathologic tissue was processed routinely and embedded in paraffin. 4–6 μm serial sections were cut and stained with haematoxylin-eosin (HE), and then examined and diagnosed by two pathologists who were blind to the patient's clinical stage. The diagnosis includes: pathological histology, pathological differentiation degree, cervical stromal invasion depth, LN metastasis and lymphatic vascular space invasion, vagina metastasis and parametrium metastasis. Then, two experienced clinicians deter-