PET/CT and MRI in Evaluating Cervical Cancer

Runjun Shi, Jie Chen, Jinchang Wu* and Jundong Zhou*

Department of Radiotherapy, Suzhou Affiliated Hospital of Nanjing Medical University, Suzhou, 215000, China

Abstract: Positron emission tomography (PET)/computed tomography (CT) and magnetic resonance (MR) imaging are two most important imaging tools for evaluating cervical cancer in clinic. They have improved the accuracy of tumor staging and prognosis predicting in a large part. PET/CT is superior for lymph node (LN) status and metastasis to other imaging modalities. And it could differ among tumor types and grades according to maximum standardized uptake value (SUVmax). MRI is not sensitive to LN metastasis, but it shares the advantage of therapeutic response and recurrence evaluation with PET/CT. Recently, emerging functional imaging modality Diffusion-weighted imaging (DWI) has been showing its superiority on evaluation of cervical carcinoma as well. This article describes both advantages and limitations of MR imaging and PET/CT in evaluating cervical cancer, and reviews the current role of imaging techniques mentioned above.

Keywords: Positron emission tomography, magnetic resonance, cervical cancer, staging, treatment response, recurrence.

INTRODUCTION

Cervical cancer is the most common gynecological oncology in the world. Every year, more than 500,000 cases are diagnosed cervical cancer worldwide and over one third of patients in advanced stage suffer recurrence [1, 2]. With the high rate of incidence and relapse, cervical carcinoma becomes the major threat to women's health.

Several prognostic factors for cervical cancer have been identified, including International Federation of Gynecology and Obstetrics (FIGO) staging, histological subtype, differentiated histology, pelvic and para-aortic lymph node metastasis [3]. However, these risk factors can be identified from surgical specimens only. A noninvasion method for assessing tumor staging and pathological features would be useful. PET/CT and MR imaging are advanced imaging techniques frequently used in clinic. Currently, they have achieved more favorable positions in evaluating cervical carcinoma and directing approach to therapy.

This article reviews comparative effectiveness of PET/CT and MRI to evaluate cervical cancer in terms of staging, treatment response and recurrence from up-to-date studies, aiming to establish a general diagnosis and treatment idea with imaging techniques for the improvement of survival rate of cervical cancer patients.

*Address correspondence to these authors at the Department of Radiotherapy, Suzhou Affiliated Hospital of Nanjing Medical University, Suzhou, 215000, China; E-mail: zhoujundong330@163.com, wjinchang@sina.com

STAGING OF CERVICAL CANCER

Primary Tumor

As is recommended by National Comprehensive Cancer Network (NCCN) Guidelines, treatment of cervical cancer is generally stratified by International Federation of Gynecology Obstetrics (FIGO) Staging, which is usually determined by clinical examination. In the guideline, radical hysterectomy with bilateral pelvic lymph node dissection is the preferred treatment for early-stage disease (Stage IIA or less); while for advanced-stage disease (Stage IIB or greater), hysterectomy is not suggested [4]. And at some oncology centers, chemo radiotherapy rather than surgery is used as the primary treatment modality for women with early stage disease when there is a large tumor (IB2 and IIA2) [2]. Obviously, information we get from the primary tumor seriously impacts the final decision of treatment plan.

In clinic, ^{18}F-fluorodeoxyglucose(FDG) PET/CT is commonly used to detect the occult primary tumor or metastases from some known tumor. Lee *et al*. reported a series of 56 patients with cervical cancer who were prospectively assessed with 18F-FDG-PET/CT and contrast-enhanced CT or contrast-enhanced CT/MR imaging [5]. Their conclusion was that sensitivity of PET/CT (69%) in detection of primary tumors was higher than that of contrast-enhanced CT (16%) ($P<0.001$) or contrast-enhanced CT/MR imaging (41%) ($P = 0.039$), while specificity of these methods did not differ (88%, 76%, and 59% for PET/CT, contrast-enhanced CT, and contrast-enhanced CT/MR imaging, respectively; $P >0.4$). Another review summarized that FDG-PET was able to detect 99% of

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primary cervical cancers with hydration, diuretics and bladder drainage for reducing urinary activity [6]. Maximum standardized uptake value (SUVmax), which classifies the ability of tumor glucose metabolism into different levels, performs the visual qualitative and quantitative analysis of PET/CT. Kidd *et al*. found the relationship between FDG uptake and histologic features and differentiation in 2009 [1]. It is reported that squamous cell tumors had a significantly higher SUVmax than non-squamous cell cancers, and a higher SUVmax was also demonstrated in poorly differentiated tumors [1].

Magnetic resonance (MR) imaging is another practical tool for cervical cancer, especially when we need to assess its size, location, and extension into the surrounding tissues. It is found that the correlation coefficient of the three-dimensional (3D) tumor volume measurement using T2W imaging was 0.96 in the surgery group with and without neoadjuvant chemotherapy respectively [7]. In a single-centre experience, Rizzo *et al*. concluded that pre-surgical MR is accurate (80%) in evaluating the minimum thickness of uninvolved cervical stroma; and the maximum depth of stromal invasion measured by MR differed ±9 mm from the pathological results in 95% of cases [8]. The sensitivity of MR imaging in the evaluation of bladder and rectal invasion is 71–100%, with a specificity of 88–91%, and a negative predictive value of MR imaging approaching 100% [2]. And this remarkable result can help us avoid overestimating local invasion into the parametrium, bladder, and rectum. Moreover, Kusmirek *et al*. once compared clinical staging with MR imaging in the accuracy rates for cervical cancer patients staging IB or greater and concluded that MR imaging, of which accuracy rates approaching 95% for stage IB or greater, is more accurate for cervical cancer beyond early stages [2]. However, in early stage disease, clinical staging is still the most accurate.

In recent years, Diffusion-weighted imaging (DWI) has increasingly been regarded as the best method for detecting and diagnosing diseases originated from abdominal and pelvic tissues, especially for cervical cancer [9]. As the expression of diffusion coefficient of water in living tissue on MR examination, apparent diffusion coefficient (ADC) plays an important role in evaluating malignancy [10]. Chen *et al*. compared the ADC values of thirty-three patients with cervical carcinoma and twenty patients with other pelvic abnormalities. They discovered that the optimal ADC threshold values for distinguishing between normal cervical tissue and cervical carcinoma was 1.359 × 10^{-3} mm^2 /s, with the sensitivity of 100%, and specificity of 84.8%. For more credibility, Hou *et al*. selected thirteen relevant studies for statistical analysis and found that ADC value in cervical cancer tissues was significantly lower than that of normal tissue [9]. It is suggested that increased signal intensity on DWI and decreased signal on ADC might be useful in the diagnosis of cervical cancer. Besides, DWI has been proven to be a useful functional imaging tool to distinguish among tumor types and assess tumor grade. Downey *et al*. analyzed the ADC values of sixty patients with FIGO stage I cervical cancer from the aspects of tumor types and differentiation [11]. Their findings were that a statistically significant difference did not exist in ADC percentiles between squamous cell carcinoma and adenocarcinoma though; median ADC was significantly higher in well or moderately differentiated tumors compared with poorly differentiated tumors. But in another study, the ADCs between squamous cell carcinoma and adenocarcinoma were proved to be significantly different [12].

Nodal Staging

Though absent from FIGO staging, nodal status is one of the strongest prognostic factors for cervical cancer and many other malignancies, and plays an important role in determining the final therapy. For instance the status of para-aortic lymph nodes (PALN) can have a serious impact on overall and disease-free survival rates of patients with cervical cancer; and extending the radiation fields to this area can lead to an increased morbidity in patients with PALN spread highly suspected by imaging or proven by pathological examination [13]. Surgical staging has been used to assess the pelvic and para-aortic lymph node metastases in patients with cervical carcinoma for a long time, and is considered to be the gold standard. Nonetheless, the delay to starting regular treatment, attributable to either pre-operative preparation or post-operative morbidity, is inevitable.

^{18}FDG-PET/CT is considered to be the most accurate imaging method of detection of node or distant metastases. Lv *et al*. analyzed the ^{18}F-FDG PET/CT and MRI images of 87 early-staged cervical cancer patients before surgery and correlated with histopathological findings. They proved that PET/CT has higher sensitivity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for detecting lymphatic metastases compared with MRI [14]. A meta-analysis of 41 studies came to the similar

conclusion. It summarized that the sensitivity and specificity of PET/CT in detecting metastatic lymph nodes were 82% and 95%, respectively (vs. 50 and 92% for CT, and 56 and 91% for MRI) [15]. Moreover, a study performed by Monteil *et al*. revealed that FDG-PET is less accurate than MRI for pelvic lymph node (PLN), but more accurate for PALN [16]. In addition, to investigate the associations of metabolic tumor volume (MTV) and SUVmax with the presence of PET- positive lymph nodes, Vural *et al*. reported a study of seventy-four patients with stage IB-IVB cervical cancer, in which they found SUVmax and MTV were significantly higher in patients with PET-positive LN compared to others (18.4 and 88.8 cm3 vs. 13.9 and 39.9 cm3 respectively, p = 0.007 for SUVmax, p = 0.0001 for MTV), and the cut-off values were 15.2 for SUVmax and 35 cm3 for MTV on ROC curve analysis [17]. However, PET/CT has limitations detecting microscopic tumor volumes [18]. So it is recommended that patients with positive pelvic nodes on PET take para-aortic lymphadene-ctomy for better overall and disease-free survival [1].

MR imaging is another approach to the noninvasive detection of nodal disease. Unlike PET/CT, MRI relies on the size of LN to determine involved disease, and nodes greater than 1 cm in size are thought to be positive [19]. With this standard size criterion, Akkas *et al*. found that the sensitivity of nodal metastases ranges from 29 to 86%, for it was inability to detect micro metastases in normal-sized lymph nodes [19]. What's worse, the utility of this imaging modality for differentiation of metastatic lymph nodes from hyperplasia is limited [20]. Thus, it is almost impossible to evaluate metastatic nodal accurately based on size criteria alone.

DWI is particularly sensitive to the microscopic motion of water molecules, and allows noninvasive characterization of biological tissues [21]. Liu *et al*. proved that DW imaging is feasible for differentiating metastatic from non-metastatic pelvic lymph nodes in patients with uterine cervical cancer with this special capacity [22]. Using the minimum ADC criteria ($\leq 0.881\times10^{-3}mm^2/s$), the sensitivity and specificity for differentiating metastatic from non-metastatic lymph nodes were 95.7% and 96.5%, respectively [22].

TREATMENT RESPONSE AND RECURRENCE

Among cervical cancer patients particularly in locally advanced stage, recurrence is a common problem. It is reported that one third of these patients will have disease recurrence within 2 years after treatment [1]. Clinically, tumor size, histological subtype, histological grade, FIGO stage, LN status and roughly characterized treatment response are most utilized as prognostic factors. However, information provided from these parameters is limited. More detailed tumor characterization pre, during and early post therapy is needed.

PET/CT is largely supported by sufficient evidence as an accurate tool to assess treatment response and recurrence. In many studies, metabolic response on the post-therapy FDG- PET was divided into three groups: complete metabolic response (CMR), partial metabolic response (PMR) and progressive disease (PD). And CMR is always associated with better outcomes. Schwarz *et al*. reviewed the records of 238 patients with cervical cancer and reported that the treatment failure of patients with CMR, PMR and PD was 23%, 65% and 96%, respectively [23]. Onal *et al*. also found that four-year overall survival (OS) rate was significantly better in patients with CMR compared to patients with PR/PD [24]. As the quantified expression of PET/CT, SUVmax appears to be greatly correlated with treatment outcomes. Chung *et al*. divided 276 uterine cervical cancer patients into two groups with the cut-off SUVmax of 5.25 and found a significant difference in OS between groups [25]. Kidd *et al*. even concluded that SUVmax was the second most important factor for recurrence-free survival (RFS), disease-specific survival (DSS), and overall survival (OS), following PET LN status [26]. In addition, MTV is also associated with post- treatment PET response and was considered as an independent prognostic factor for disease-free survival (DFS), but a study showed that MTV regressed at a slower rate than SUVmax declined [27, 28].

It is generally known that LN status is an important predictor of malignant tumor, and the wide use of FDG-PET improves its accuracy and availability in a large part. Besides, recent research found that PET LN status had the greatest influence on outcome of cervical cancer patients [26]. In this study, 234 cervical cancer patients treated with definitive radiation or chemo radiation therapy were included and their cervical tumor volume, SUVmax and LN status on PET were recorded. After measuring their prediction accuracies with the concordance index (c-statistic), the authors concluded that pretreatment FDG-PET LN status, cervical tumor SUVmax and tumor volume create good models for predicting cervical cancer RFS, DSS, and OS. Additionally, positive pelvic node on PET has been proved to be a useful marker in prediction of

distant recurrence in patients with locally advanced cervical cancer [29]. Onal *et al*. found that patients with PLN SUVmax≥7.5 had significantly higher rates of PALN metastasis and lower post-therapy CMR [30]. Moreover, OS and DFS rates were significantly higher in patients with SUVmax≤7.5 compared to patients with SUVmax ≥ 7.5 in their research. The presence of PALN metastases in locally advanced cervical cancer (LACC) is an important prognosis factor and influences the decision to choose the most appropriate therapy [31, 32]. Meanwhile, Gouy *et al*. found that the strategy of chemo radiotherapy is highly efficient in patients with PALN metastasis ≤ 5mm and without PALN involvement [31].

The influence of tumor volume has also been established as a prognostic factor in cervical cancer [1]. Several groups found that poor regression of initial tumor volume conferred a poor OS. MR imaging, another frequently used imaging method, is commonly considered as the first choice of evaluating tumor volume and its regression during therapy. To evaluate the utility of MR for predicting the local control rate of uterine cervical cancer, Saida *et al*. identified 109 patients with cervical cancer and analyzed the volumes of high signal intensity involving the uterine cervix on T2-weighted MR imaging measured before and just after therapy [33]. They concluded that in patients with local recurrence, mean volume measured just after treatment was significantly larger than those without recurrence, and thought it to be a useful clue in predicting the local control rate of cervical cancer. Lee *et al*. found that the percent volume reduction on PET/CT during CCRT was significantly greater than it calculated from MRI, though significant differences were not found after treatment [34]. So it appears that both PET/CT and MRI should be taken during CCRT to evaluate tumor response.

DWI plays a role in monitoring therapeutic response as well. Fu *et al* selected thirty-three patients with LACC and analyzed the ADC value of the effective group before, during and after neoadjuvant chemotherapy [35]. They discovered that the ADC change after successful chemotherapy is closely related with cellular characteristics preceding size reduction. Kim *et al*. also considered that DWI might have potentials in evaluating the therapeutic response to CCRT in patients with cervical cancer [36]. Moreover, ADC change between before and during chemo radiotherapy (CRT) [ΔADC] may be a useful predictor of pathological response to CRT for uterine cervical cancer as it is reported that ΔADC showed a moderate positive correlation with the tumor regression rates [37]. Kuang *et al*. classified seventy-five cervical cancer patients as CR, PR and SD according to final tumor size after 6 months of therapy completion, and compared the dynamic changes and tumor size in the three tumor groups [38]. Their final results were that the ADC increased percentage was higher in CR group than those in PR and SD groups after two weeks and four weeks of therapy; absolute ADCs after therapy completion were significantly different between CR, PR and SD groups.

CONCLUSION

PET/CT and MRI are essential imaging methods to assess tumor staging, therapeutic response and recurrence of cervical cancer. From this article, we found that PET/CT and MRI have their own characteristics in practical application. PET/CT is sensitive to primary tumors and metastases while MRI helps to bring about a more accurate tumor staging. And both of these techniques have their merits in respect of evaluating outcomes of treatment. Given this, combination of PET and MR may lead to an ideal model of assessing cervical cancer and other malignancies. Besides, DWI has shown its potential value in diagnosis and treatment of cervical carcinoma as well. Further comprehensive studies about the imaging techniques mentioned above are needed for perfect treatment and better therapeutic outcome.

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