The Role of 18F-Flourodeoxyglucose (18F-FDG) Positron Emission Tomography/Computed Tomography (PET/CT) in Pelvic and Para-aortic Lymph Node Staging of Uterine Cervical Cancer

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Abstract: *Aim:* We aimed to evaluate the sensitivity of 18F-Flourodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) in the detection of pelvic and paraaortic lymph node metastases of uterine cervical cancer.

Material and Method: 32 female patients (mean age: 56.1±12.6) who underwent 18F-FDG PET/CT for preoperative staging of uterine cervical cancer between April 2009 and October 2013 were included to the study. Ethical committee approval was taken from Ankara University Medical Faculty Ethics Committee. All the patients had been performed trans-vaginal examination and diagnosed as uterine cervical cancer before 18F-FDG PET/CT. 18F-FDG PET/CT findings were compared with histopathological examination results. Sensitivity, specificity and accuracy of pelvic MRI and 18F-FDG PET/CT were calculated in the detection of pelvic and paraaortic lymph node metastases.

Results: 18F-FDG uptake was seen in primary cervical lesions of all the patients. Mean SUV max of primary cervical lesions was calculated as 13.6±6.6 (range: 6.7-25). In 16 (50%) patients, 18F-FDG uptake was not seen in pelvic and paraaortic lymph nodes. In the remaining patients, 18F-FDG uptake was detected in pelvic nodes in all the patients (50%) and in paraaortic nodes in 6 (18%) patients. Mean SUV max of pelvic lymph nodes were calculated as 8.4±5.2 and of paraaortic lymph nodes 12.45±6.41. 18F-FDG uptake was detected in a total of 47 lymph node stations in 16 patients. Mean SUVmax of all lymph nodes were calculated as 8.9±5.83 (range: 2.6-21.9). According to 18F-FDG PET/CT findings, disease was upstaged from I to IV in 1 (3%) patient, II to III in 2 (6%) patients, III to IV in 1 (3%) patients and I to III in 2 (6%) patients, and down staged from III to I in 1 (3%) patient, respectively. In the patient-based analysis, 18F-FDG PET/CT was TP, TN, FP and FN in 14 (%44), 14 (44%), 2 (6%) and 2 (6%) patients, respectively. Patients based sensitivity; specificity and accuracy of 18F-FDG PET/CT were calculated as 87%, 87% and 87%, respectively. In the lesion-based analysis, 18F-FDG PET/CT was TP, FP, TN and FN in 30, 7, 37 and 5 lymph node stations, respectively. Lesion based sensitivity; specificity and accuracy of 18F-FDG PET/CT were calculated as 85%, 84% and 84%, respectively.

Conclusion: 18F-FDG PET/CT is a reliable imaging tool with its high sensitivity and specificity in the pelvic and paraaortic lymph node staging of uterine cervical cancer. When performed in the preoperative staging it changes disease stage about in ¼ of patients. In combination of pelvic MRI, primary staging of primary cervical lesions and also pelvic/paraaortic lymph nodes can be done successfully.

Keywords: Uterine cervical cancer, Preoperative staging, 18F-FDG PET/CT, Lymph node metastasis.

INTRODUCTION

Uterine cervical cancer is the second common reason for cancer related death in women [1]. Today, preoperative staging of disease is mostly done clinically. Physical examination, radiograms, colonoscopy, colposcopy and intravenous pyelogram are routinely utilized diagnostic procedures for preoperative evaluation. Although computed tomography (CT), magnetic resonance imaging (MRI) and 18F-Flourodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) have been performed for evaluation of local invasion, lymph node involvement and distant metastases, they have not been included staging protocols [2]. Clinical staging system is a weak parameter to prediction of disease prognosis. For this reason, some gynecological oncologists believe to importance of addition of surgical staging to routine staging protocols. In advanced stage cases, knowledge of pelvic and paraaortic lymph node involvement in preoperative period is very important to application of simultaneous and/or neoadjuvant chemo-radio therapy and discrimination of radiation therapy field [3-4].

Surgery is the gold standard for pelvic and paraaortic lymph node staging of uterine cervical cancer. Preoperative pelvic CT or MRI might be insufficient to evaluate of lymph node involvement, in especially normal sized lymph nodes. 18F-FDG PET/CT is a functional imaging tool that has been routinely utilized for preoperative evaluation of lymph nodes and distant metastases in several cancer types.

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In this study, we aimed to evaluate the sensitivity of 18F-FDG PET/CT in the detection of pelvic and paraaortic lymph node metastases of uterine cervical cancer in the comparison of surgical staging as gold standard.

MATERIAL AND METHODS

Patients

32 female patients (mean age: 56.1±12.6) who underwent 18F-FDG PET/CT for preoperative staging of uterine cervical cancer between April 2009 and October 2013 were included to the study. Ethical committee approval was taken from Ankara University Medical Faculty Ethics Committee. All the patients had been performed trans-vaginal examination and diagnosed as uterine cervical cancer before 18F-FDG PET/CT.

18F-FDG PET/CT

PET/CT images were acquired with GE Discovery ST PET/CT scanner (General Electric, Milwaukee, Wisconsin, USA). Patients were kept hungry at least 6 hours before scanning and blood glucose levels were checked before FDG injection. Intravenous contrast agents were not applied. Whole body 18F-FDG PET/CT imaging was performed approximately 1 hour after an intravenous injection of 296-370 MBq 18F-FDG. Patients were rested in a quiet room without administrating muscle relaxant during waiting period. Images were obtained while patients were in supine position, from skull base to mid thighs. CT image was obtained from the integrated PET/CT scanner with the use of a standardized protocol involving 140 kV, 70 mA, a tube rotation time of 0.5 s per rotation, a pitch of 6 and a section thickness of 5 mm. Immediately, after the CT part, PET images were acquired for 4 minutes per bed position. Emission PET images were reconstructed with non-contrast CT data for attenuation correction. Patients were allowed to breath normally during procedure.

Image Analysis

Whole body PET/CT images were interpreted by two experienced nuclear medicine physicians by visual inspection at least on three planes (transaxial, coronal, sagittal). Comparison was made between focus increasing uptake and background and blood pool activity. After then their anatomic confirmation was done with CT images. The criterion for malignancy was accepted FDG hypermetabolism at the site of pathological changes on CT or marked focal hypermetabolism at the physiological uptake sites. Maximum standardized uptake value (SUV_{max}) was calculated for all pathologic lesions.

Data Analysis

18F-FDG PET/CT findings were compared with histopathological examination results. When the detected metastatic lesions on 18F-FDG PET/CT were confirmed histologically, these lesions were accepted as true positive (TP). If recurrence was excluded by pathological examinations in patients with positive lesions on 18F-PET/CT, findings were classified as false positive (FP). Patients with negative scan but positive recurrence proved by histological examination were accepted as false negative (FN). Negative 18F-FDG PET/CT scans in patients with no detected recurrence in the follow-up period were accepted as true negative (TN).

Statistical Analysis

TP/FP and TN/FN results were described according to criterion mentioned above. Sensitivity and specificity were computed using these data. Statistical analyses were performed using the SPSS software, version 16 (SPSS Inc., Chicago, Illinois, USA). Student T test was used for comparison of mean values of different groups.

RESULTS

Patients

18F-FDG PET/CT was performed to 32 patients (mean age; 56.1±12.6; range; 28-77) during the study. Before PET/CT, according to cervical pap-smear examination, 28 (87%) patients had been diagnosed as squamous carcinoma and 4 (13%) patient adenocancer. Before PET/CT, clinically, 11 (34%), 7 (22%), 12 (37%) and 2 (7%) patients had been staged as stage I, II, III and IV, respectively (Table **1**).

Pelvic MRI

Pelvic MRI has been performed to all the patients for evaluation of local spread of disease. MRI could detect all primary cervical lesions. Additionally, local invasion to parametrium, vagina and rectum were seen in 5 (15%), 3 (9%) and 1 (3%) patient, respectively. MRI showed pelvic lymph node metastases in 15 (46%) and additionally paraaortic lymph node metastasis in 1 (3%) patient, while there was no detected lymph node in 17 (%53) patients.

Table 1: Descriptive Data of Whole Patient Group

Patient no	Age	Preoperative Diagnosis	Pathological Subtype	Clinical Stage	Lymph Nodes According to MRI	Lymph Nodes According to 18F-FDG PET/CT (SUVmax)
1	28	Squamous cell carcinoma	Large Cell Nonkeratinized Type	IVB	Bilaterally parailiac	Left retrocrural (6.5), paraaortic (18.1) ,paravertebral (21.2), bilaterally parailiac (10.9) and presacral (2.9)
2	77	Squamous cell carcinoma	Large Cell Nonkeratinized Type	IIB	Negative	Negative
3	77	Squamous cell carcinoma	Large Cell Nonkeratinized Type	IA	Left inguinal and left obturatory	Bilaterally inguinal (3.4), parailiac (7.0)
4	67	Squamous cell carcinoma	Large Cell Keratinized Type	IIIB	Negative	Negative
5	52	Squamous cell carcinoma	Small Cell Type	IIB	Negative	Right parailiac (4.0)
6	57	Squamous cell carcinoma	Large Cell Nonkeratinized Type	IIB	Left parailiac and obturatory	Negative
7	69	Squamous cell carcinoma	Large Cell Nonkeratinized Type	IIIB	Bilaterally parailiac	Aortocaval (16.9), bilaterally parailiac (17.9)
8	42	Squamous cell carcinoma	Small Cell Type	IIIB	Paraaortic, paracaval, aortocaval and bilaterally parailiac	Bilaterally lumbal (4.0), aortocaval (4.0), parailiac (15.0) and pararectal (2.1)
9	65	Squamous cell carcinoma	Large Cell Keratinized Type	IVA	Pararectal and bilaterally parailiac	Common iliak ve bilateral internal iliak (5.5) lenf nodları.
10	43	Squamous cell carcinoma	Small Cell Type	IIB	Negative	Negative
11	57	Squamous cell carcinoma	Large Cell Nonkeratinized Type	IIB	Right parailiac	Negative
12	62	Squamous cell carcinoma	Small Cell Type	IIIB	Negative	Negative
13	56	Squamous cell carcinoma	Large Cell Nonkeratinized Type	IIB	Negative	Bilaterally parailiac (5.5)
14	45	Squamous cell carcinoma	Small Cell Type	IIIB	Right parailiac	Bilaterally parailiac (15.7), pararectal (10.2)
15	55	Squamous cell carcinoma	Large Cell Nonkeratinized Type	IB	Negative	Negative
16	38	Squamous cell carcinoma	Large Cell Nonkeratinized Type	IB	Negative	Negative
17	67	Squamous cell carcinoma	Large Cell Nonkeratinized Type	IA	Negative	Negative
18	53	Squamous cell carcinoma	Large Cell Nonkeratinized Type	IIIB	Bilaterally parailiac	Paraaortik (11.0), bilaterally parailiac (10.0)
19	56	Squamous cell carcinoma	Large Cell Nonkeratinized Type	IB	Negative	Bilaterally parailiac (4.1)
20	57	Adeno carcinoma	Villoglandular Type	IB	Negative	Bilaterally parailiac (13.5)
21	72	Squamous cell carcinoma	Large Cell Keratinized Type	IIIB	Left parailiac	Left parailiac (5.6)
22	56	Squamous cell carcinoma	Large Cell Keratinized Type	IIB	Negative	Negative
23	28	Adeno carcinoma	Clear Cell Type	IB	Negative	Negative
24	52	Squamous cell carcinoma	Large Cell Nonkeratinized Type	IA	Negative	Negative

(Table 1) Contd….

Patient no	Age	Preoperative Diagnosis	Pathological Subtype	Clinical Stage	Lymph Nodes According to MRI	Lymph Nodes According to 18F-FDG PET/CT (SUVmax)
25	42	Adeno carcinoma	Well-differantiated Type	IIIB	Left parailiac	Bilaterally parailiac (2.9)
26	43	Squamous cell carcinoma	Large Cell Keratinized Type	IB	Negative	Negative
27	57	Squamous cell carcinoma	Large Cell Nonkeratinized Type	IB	Negative	Negative
28	43	Squamous cell carcinoma	Large Cell Nonkeratinized Type	IIIB	Bilaterally parailiac	Negative
29	39	Squamous cell carcinoma	Large Cell Keratinized Type	IIIB	Bilaterally parailiac	Right parailiac (7.5), paraortic (11.5)
30	39	Squamous cell carcinoma	Large Cell Nonkeratinized Type	IIIB	Bilaterally parailiac	Bilaterally parailiac (4,1), paraaortic (4,7), sacral (2,6)
31	39	Squamous cell carcinoma	Large Cell Keratinized Type	IB	Negative	Negative
32	42	Adeno carcinoma	Clear Cell Type	IIIB	Right parailiac	Left parailiac (8.5)

18F-FDG PET/CT

18F-FDG uptake was seen in primary cervical lesions of all the patients. Mean SUVmax of primary cervical lesions was calculated as 13.6±6.6 (range: 6.7-25). According to histopathological subtypes; SUVmax was calculated as 14.38±7.3, 15.2±1.2, 15.36±6,6 and 6.5±2.8 in large cell keratinized, large cell, small cell and adeno carcinoma subtypes, respectively. In the analysis according to clinical disease stage, SUVmax of primary lesions of patients with stage I, II, III and IV disease were found as 18.1±7.2, 10.9±6.5, 12.8±6.7 and 15.9±1.5, respectively. Difference between SUVmax of groups according to either histopathological subtype and clinical stage was not statistically significance.

In 16 (50%) patients, 18F-FDG uptake was not seen in pelvic and paraaortic lymph nodes. In the remaining patients, 18F-FDG uptake was detected in pelvic nodes in all the patients (50%) and in paraaortic nodes in 6 (18%) patients (Table **2**). Mean SUVmax of pelvic lymph nodes were calculated as 8.4±5.2 and of paraaortic lymph nodes 12.45±6.41.

18F-FDG uptake was detected in a total of 47 lymph node stations in 16 patients. Mean SUVmax of all lymph nodes were calculated as 8.9±5.83 (range: 2.6-21.9). According to 18F-FDG PET/CT findings, disease was upstaged from I to IV in 1 (3%) patient, II to III in 2 (6%) patients, III to IV in 1 (3%) patients and I to III in 2 (6%) patients, and down staged from III to I in 1 (3%) patient, respectively.

Table 2: Lymph Node Status of Patients in Pelvic MRI, 18F-FDG PET/CT and Histopathology

Method	No of Patients with Positive Lymph Nodes	No of Patients without Positive Lymph Nodes
Pelvic MRI	15	17
18F-FDG PET/CT	16	16
Histopathology	14	18

While mean SUVmax of primary cervical lesions of patient with positive pelvic lymph nodes was calculated as 13.5±6.8, it was as 17.4±5.3 of patients with positive paraaortic lymph nodes (p=0.3).

Gold Standard

All the patients underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy and pelvic/paraaortic lymph node dissection. 18F-FDG PET/CT findings of these patients were compared with histopathological examination reports. In 32 patients, total 282 lymph nodes were dissected from 213 lymph node stations. 140 out of 213 lymph node stations were nonmetastatic histopathologically while 73 metastatic. According to gold standard, 10 (31%), 4 (13%), 15

(47%) and 3 (9%) patients were staged as stage I, II, III and IV.

In the patient-based analysis, 18F-FDG PET/CT was TP, TN, FP and FN in 14 (%44), 14 (44%), 2 (6%) and 2 (6%) patients, respectively. Patients based sensitivity, specificity and accuracy of 18F-FDG PET/CT were calculated as 87%, 87% and 87%, respectively (Table **3**).

Table 3: Sensitivity, Specificity and Accuracy of 18F-FDG PET/CT According to Patient and Lesion Based Analysis

	Sensitivity (%)	Specificity (%)	Accuracy (%)
Patient based	87	87	87
Lesion based	85	84	84

In the lesion-based analysis, 18F-FDG PET/CT was TP, FP, TN and FN in 30, 7, 37 and 5 lymph node stations, respectively. Lesion based sensitivity, specificity and accuracy of 18F-FDG PET/CT were calculated as 85%, 84% and 84%, respectively. While mean SUVmax of metastatic and FDG positive lymph nodes was computed as 8.96±3.3, it was 4.33±1.05 in nonmetastatic and FDG positive lymph nodes (p=0.04).

DISCUSSION

FIGO staging system is routinely used for staging of cervical cancer. This system based on clinical examination and conventional imaging methods [4]. While FIGO system is partially more successful in early stage of disease, its probability of error has been reported as 59%-67% in the advanced stages [4-6]. To support this insufficiency, disease was upstaged from I to IV in 1 (3%) patient, II to III in 2 (6%) patients, III to IV in 1 (3%) patients and I to III in 2 (6%) patients, and down staged from III to I in 1 (3%) patient.

Close relationship between progression free survival and age, performance status, tumor diameter and pelvic/paraaortic lymph node metastases has been reported [7]. Although cross-sectional imaging tools have not been included guidelines yet, CT and MRI widely have been performed to evaluate morphological risk factors such as tumor diameter, depth of stromal invasion and presence of lymph node metastasis. Although accuracy of CT in the staging of uterine cervical cancer has been reported between 58% and 88%, its sensitivity is low in the evaluation of tumor diameter, parametrial invasion and lymph node metastasis (44%) [5-6]. Despite the most successful method in the assessment of tumor dimension and parametrial invasion, sensitivity of MRI in the detection of lymph node metastasis is similar to CT [5].

As in most solid tumors, 18F-FDG PET/CT has been widely utilized to staging, restaging and evaluation of treatment response in gynecological tumors. Role of 18F-FDG PET/CT is limited in the diagnosis of ovarian cancer due to physiological ovarian activity. However it may have an additional value in the combination of CT or MRI to detect lymph node or distant metastases [8].

18F-FDG PET/CT has a limited sensitivity in the detection of stromal and parametrial invasion of uterine and cervical cancer due to its low spatial resolution. However, it is very successful in the assessment of pelvic and paraaortic lymph node metastases. Grigsby *et al*. showed that 18F-FDG PET/CT is more successful than CT in the detection of lymph node metastases and presence of FDG uptake in the paraaortic lymph nodes is closely related to disease free survival [9]. Yen *et al*. has found that of 18F-FDG PET/CT is more sensitive and specific than CT and MRI in their 135 cervical cancer patient series [10]. After studies, which show high sensitivity and specificity of 18F-FDG PET/CT, Centers for Medicare Services has approved its routine usage in preoperative staging of cervical cancer patients who have negative conventional imaging results for extrapelvic metastases [11]. Yıldırım *et al*. have reported sensitivity; specificity and accuracy of 18F-FDG PET/CT in the detection of paraaortic lymph node metastasis are 50%, 83% and 75%, respectively, in their 16 patient series who have negative conventional CT [12]. We have calculated these parameters as 87%, 87% and 87%, respectively. However pelvic MRI results of all the patients in our study were not negative. For this reason sensitivity of our study might have been found higher. In our study, FDG uptake has seen in pelvic/paraaortic lymph nodes in 3 out of 11 patients who have negative pelvic MRI. In 2 out of these 3 patients, lymph node metastases have confirmed by histopathologically. In our study, while mean SUVmax of FDG avid and metastatic lymph nodes was calculated as 8.96±3.3, it was 4.33±1.05 in nonmetastatic ones. Although some of FDG positive lymph nodes have been found nonmetastatic histopathologycally, probability of metastasis is especially higher in lymph nodes with intense FDG uptake. For this reason, probability of metastasis should be kept in mind in lymph nodes with intense FDG uptake even their dimensions are not pathological in MRI.

Similarly to most solid tumors, differentiation degree of primary tumor focus is an important indicator for disease free survival in uterine cervical cancer. FDG uptake degree is directly related with tumor differentiation. In our study, SUVmax of primary cervical lesions of clinical stage I, II, II and IV patients were calculated as 18.1±7.2, 10.9±6.5, 12.8±6.7 and 15.9±1.5, respectively. The absence of significant difference between stages may be an indicator of prognostic insufficiency of FIGO staging system. In this patient group, 18F-FDG PET/CT can be a prognostic predictor. In support of this hypothesis, mean SUVmax of primary cervical lesions of patients who have paraaortic lymph node metastases, as an advanced disease indicator has been found higher than those have not.

In this study, we could not evaluate the sensitivity of 18F-FDG PET/CT to reveal stromal or parametrial/ vaginal invasions due to limited spatial resolution of PET. MRI seems to be the most successful method it these purposes. However, addition of 18F-FDG PET/CT to pelvic MRI may contribute to more correct preoperative staging of cervical cancer by increasing accuracy of pelvic/paraaortic lymph node staging. Although the disease classically has been staged and treated clinically, according to modern approach, preoperative staging by pelvic MRI and 18F-FDG PET/CT may decrease unnecessary operation rates by changing disease stage. In the future possible use of 18F-FDG PET/MRI may give a chance to get together both modalities and make more successful staging in same course [13-14]. Generally, although treatment choice is radical hysterectomy and pelvic/paraaortic lymph node dissection in stage IA-IIA disease, it is intracavitary/external radiation therapy in stage IIB-IVA. In our series, disease stage of 7 (21%) patients has changed by 18F-FDG PET/CT and treatment plan has changed in 5 out of them. Similar to our results, Yıldırım *et al*. have reported 25% change in stage in their patients [12].

CONCLUSION

18F-FDG PET/CT is a reliable imaging tool with its high sensitivity and specificity in the pelvic and paraaortic lymph node staging of uterine cervical cancer. When performed in the preoperative staging it changes disease stage about in ¼ of patients. In combination of pelvic MRI, primary staging of primary cervical lesions and also pelvic/paraaortic lymph nodes can be done successfully.

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