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Preoperative detection of lymph node metastasis in endometrial cancer: The role of 18-FDG PET/CT

Endometrial kanserde preoperatif lenf nodu metastazi tespiti: Endometrial kanserde 18-FDG PET/BT'nin rolü

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Abstract

Aim: Fluorine-18 2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)/CT imaging technique combines the advantages of localization and functional imaging, and thus has become a preferred method for detection of metastases to the lymph nodes (LN) of patients with endometrial cancer. The aim of this study was to evaluate the efficacy of 18F-FDG PET/CT imaging results in the detection of metastasis of endometrial cancer to lymph nodes.

Methods: This is a retrospective cohort study conducted between 2009 and 2015. The study group consisted of females who were admitted to our clinic and diagnosed with endometrial cancer (n=135). We included patients who underwent LN dissection with pre-operative 18F-FDG PET / CT imaging, and evaluated the capability of this method in terms of its effectiveness in determining metastases to the lymph nodes. Assessments and comparisons were performed with gold-standard pathological methods.

Results: The 18F-FDG PET/CT method for identification of lymph node metastases had a sensitivity of 76%, a specificity of 80%, a positive predictive value of 46.34% and a negative predictive value of 93.62%. The overall diagnostic accuracy was 79.26%.

Conclusion: Our analysis suggests that 18F-FDG PET/CT has a high negative predictive value with regards to lymph node metastasis in endometrial cancer and may be used effectively in evaluating lymph node metastasis in this cohort.

Keywords: Endometrial cancer, Lymph node metastasis, 18F-FDG PET/CT, Prognosis

Öz

Amaç: Fluorine-18 2-floro-2-deoksi-D-glukoz (FDG) pozitron emisyon tomografisi (PET)/ BT görüntüleme tekniği, lokalizasyonun ve fonksiyonel görüntülemenin avantajlarını birleştirdiğinden, endometrial kanserli hastalarda lenf nodu (LN) metastazlarının tespiti için tercih edilen bir yöntem haline gelmiştir. Bu çalışmada 18F-FDG PET/BT görüntüleme sonuçlarının, endometrial kanserin lenf nodu metastazının belirlenmesindeki etkinliğini araştırmayı amaçladık.

Yöntemler: Bu çalışma 2009-2015 yılları arasında yapılan retrospektif kohort bir çalışmadır. Çalışma grubu kliniğimize başvuran ve endometriyal kanser tanısı alan tüm kadınlardan (n=135) oluşmaktaydı. Çalışmaya, ameliyat öncesi 18F-FDG PET/BT çekilen ve LN diseksiyonu yapılan hastaları dahil edildi. Bu yöntemin lend nodu metastazını belirlemede etkinliği değerlendirildi. Değerlendirmeler ve karşılaştırmalar altın standard patolojik tanı yöntemleriyle yapıldı.

Bulgular: Lenf nodu metastazlarının tanımlanmasında 18F-FDG PET/BT yönteminin %76 duyarlılık, %80 özgüllük, %46.34 pozitif prediktif değeri ve %93.62 negatif prediktif değeri gösterdiği bulundu. Genel tanısal doğruluk ise %79,26 idi.

Sonuç: Analizlerimiz, 18F-FDG PET/BT'nin, endometriyal kanser hastalarında lenf nodu metastazı açısından yüksek negatif prediktif değere sahip olduğunu ve bu hastalarda lenf nodu metastazı araştırmada uygulanabilir bir görüntüleme yöntemi olduğunu göstermiştir.

Anahtar kelimeler: Endometrial kanser, Lenf nodu metastazı, 18F-FDG-PET/BT, Prognoz

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Introduction

Endometrial cancer (corpus uteri cancer) is a particularly important type of cancer in women, due to its high frequency [1]. Fortunately, it is easily diagnosed, and the progression is slow [2]. Therefore, many cases are at the early stage at time of diagnosis and have good prognoses. Most studies have shown that survival rates of up to 90% are achievable with the classical surgical methods of total hysterectomy and bilateral salpingo-oophorectomy [3]. Endometrial cancer is known to be associated with several factors that contribute to poor prognosis: advanced staging with FIGO criteria, non-endometrioid histological subtype, higher level grade, presence of >50% myometrial invasion, and lymph node metastasis (LNM) [4]. As such, it is crucial to accurately identify the extent of the disease diagnosis to implement appropriate treatment and management.

In early cases of endometrial cancer, pelvic lymph node metastases are mostly present in extrauterine regions, but performing lymphadenectomy is greatly disputed [5,6]. Most of the trials have demonstrated better staging (surgical) and prognostic evaluation when lymphadenectomy is performed, with no positive effect on survival [7,8]. Current treatment recommendations do not include lymphadenectomy as a routine practice.

Generally, magnetic resonance imaging (MRI) is the imaging of choice in endometrial cancer [9,10]. However, MRI has some limitations, such as of low accuracy and reproducibility [11]. At this point, positron emission tomography (PET), which accrues data via glucose-metabolism levels, has emerged as an option to MRI as a modality that provides functional data [12], but this method is also hampered by sensitivity-related problems and cannot localize tumors. Fluorine-18 2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)/CT imaging technique combines the advantages of localization and functional imaging, and thus has become a preferred method for detection of metastases to the lymph nodes of patients with endometrial cancer [13-15]. Despite the advantages brought by 18F-FDG PET/CT [16], the studies in this field demonstrate contrasting results and many have concluded that further studies are necessary. The current aim of this study was to analyze the predictive capabilities of 18F-FDG PET/CT in detecting the absence or presence of metastasis in lymph nodes of women scheduled for surgery due to endometrial cancer.

Materials and methods

Patients

This is a retrospective study conducted between 2009 and 2015. The study group consisted of females who were admitted to our clinic and diagnosed with endometrial cancer (n=135). We included patients who underwent LN dissection with pre-operative 18F-FDG PET/CT imaging. Each of these patients had undergone lymph node dissection involving the paraaortic region of the pelvis (after imaging via 18F-FDG PET/CT was performed), and all procedures had been performed by an experienced gynecological oncologist at the Obstetrics and Gynecology Department of Acibadem Kayseri Hospital. Stage determination in the clinical aspect was made according to results and reports obtained from surgical specimens. Two independent experienced gynecological pathologists assessed the specimen in accordance with the "International Federation of Gynecology and Obstetrics" (FIGO) 2009 system. The study group included 86 patients with stage IA, 15 patients with stage IB, 4 patients with stage II, and 30 patients with III/IV cancer (Table 1). Histological grade was assessed per WHO classification (Table 1). The Ethical Committee of Acibadem Mehmet Ali Aydinlar University approved this study protocol (decision No. KB 7/14/2016). All participants provided written informed consent for the procedures and their inclusion in the study.

Imaging procedure

The imaging protocol used in our study was largely based on the study of Dolanbay et al. [17] Briefly put, 18F-FDG PET/CT investigations of patients were performed by the utilization of a high-resolution PET/CT scanner integrated with a computerized tomography device that was capable of 16-slice multidetector imaging CT (Philips Healthcare, The Netherlands). The hydration of all patients was achieved orally or through IV physiologic serum infusions before injection of fluorodeoxyglucose (FDG), and blood glucose levels were measured. Patients were administered intravenous 296-703 (MBq) FDG if their serum glucose levels were under 200 mg/dL. Following injection, patients lay or sit in a secluded room. After urination, they were directed with appropriate positioning to the CT scanner. All patients were positioned in the regular head-first supine position and moved to just above the first scanning position of the CT, after which imaging was performed. PET/CT images were analyzed in two separate sessions by one independent reader with 10 years of experience in the field of nuclear medicine and oncology who was blinded to patient history and pathological findings. The state of the 'sentinel' lymph nodes was defined as either metastatic or reactive.

Statistical analysis

Data was entered into the SPSS version 15.0 computer software for Windows operating system, in which all statistical analysis was performed (IBM, NY, USA). The mean and standard deviation results of continuous variables were determined. Categorical variables were presented as frequency (count) and percentage. ROC analyses were performed, and sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) were calculated.

Results

Patient characteristics

Mean (min-max) age of the study group was 60.59 (36-81) years. The stages of the patients according to surgical FIGO staging were as follows: Stage IA in 63.7% (86/135, <50% myometrial invasion), stage IB in 11.1% (15/135; >50% myometrial invasion), stage II in 2.96% (4/135; cervical stromal invasion), stage IIIA in 2.96% (4/135; local or regional spread), stage IVA in 1.48% (2/135) and stage IVB in 0.74% (1/135) of patients. Data for grade were available in 113 cases. Among these, 29.6% (40/113) were grade 1, 37% (50/113) were grade 2, and 17% (23/113) were grade 3. Histological evaluation revealed adenocarcinoma in 83.7% (113/135), serous histology in 9.62%

(13/135), mixed histology in 5.92% (8/135), small cell histology in 0.74% (1/135) (Table 1).

Results of 18F-FDG PET/CT in preoperative staging

Diagnostic capability of the 18F-FDG PET/CT modality was evaluated with ROC analysis according to 'gold standard' pathological findings. Overall accuracy was determined as 79.26% and the AUC was found to be 0.780 (0.054) (Table 2).

Figure 1 depicts a sample case of a 72-year-old female patient for demonstrative purposes. Her complaint was severe vaginal bleeding. After endometrial sampling, the pathological finding was adenocarcinoma of endometrium. 18F-FDG PET CT whole body findings were as follows: Increased 18F-FDG uptake of a iso-hypodense-hypermetabolic lesion was detected on corpus uteri (SUVmax 17.0). There was intense 18F-FDG uptake in both parauterine and paracervical lymph nodes (SUVmax 8.9). Obturator lymph nodes, especially those on the left, and bilateral iliac lymph nodes (SUVmax 8.2) showed increased 18F-FDG.

Table 1: Baseline characteristics of study participants

Parameters	All patients		
Age	Mean: 60.58 years (min-max: 36-81 years)		
FIGO stage	IA	86	63.7%
	IB	15	11.1%
	II	4	2.96%
	IIIA	4	2.96%
	IIIB	0	0
	IIIC	23	17%
	IVA	3	1.5%
	IVB	1	0.74%
Grading	1	40	29.6%
	2	50	37%
	3	23	17%
Histological type n (%)	Adenocarcinoma	113	83.7%
	Serous	13	9.62%
	Mixed	8	5.92%
	Small cell	1	0.74%

Table 2: The diagnostic efficacy of 18F-FDG PET/CT for detecting lymph node metastasis

		Metastasis		
		Present	Absent	Total
PET	Positive	19	22	41
	Negative	6	88	94
	Total	25	110	135
Sensitivity	76.00%		PPV	46.34%
Specificity	80.00%		NPV	93.62%
FNR	24.00%		LR (+)	3.80
FPR	20.00%		LR (-)	0.30
Accuracy	79.26%		AUC	0.780 (0.054)
			P-value	<0.001

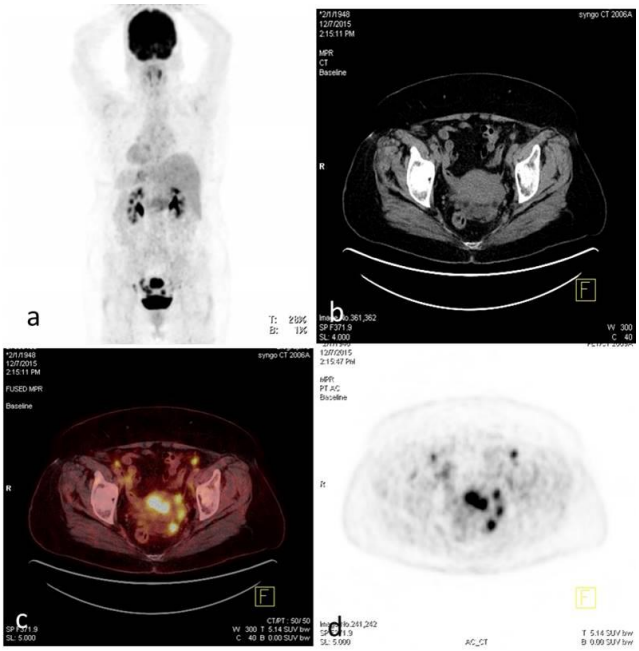

Figure 1: 18F-FGD PET/CT a) 18F-FDG MIP image, b) Axial images CT, c) 18F-FDG PET CT fusion d) 18F-FDG PET

Discussion

The current study aimed to determine the performance of 18F-FDG PET/CT in detecting metastases to the lymph nodes in endometrial cancer. Although we found a sensitivity value of 76%, a specificity percentage of 80% and a relatively low PPV of 46.34%, we believe the most important parameter was NPV which was found to be 93.62%. This result shows that this imaging method may have most practical use in determining patients without LNM (due to higher NPV and specificity) in endometrial cancer, which may prove critical in the management of endometrial cancer by restricting lymphadenectomies in low-risk patients.

Precise preoperative identification of lymph node metastases in patients diagnosed with endometrial cancer is of utmost concern as surgical approach somewhat relies on this assessment. Various studies have shown that metastases in endometrial cancer are often present in various lymph nodes, i.e., the parametrial, interiliac and common iliac [16-18]. Therefore, the data that can be drawn from the imaging of these nodes (and others) could be extremely valuable for physicians. In 2012, Chang performed a systematic review of 7 studies (243 patients) utilizing the 18F-FDG PET or PET/CT methods for this purpose and reported high specificity of both modalities [19]. Even though they could not determine which of the methods was superior to the other, they concluded that both methods were unable to replace lymphadenectomy. Furthermore, they could not identify with the available data whether these two modalities had superiority to each other. However, they supported the use of hybrid methods in endometrial cancer. In a more recent systematic review which included 378 patients from 8 studies, the sensitivity and specificity of 18F-FDG PET/CT in the preoperative detection of LNM were 72% (95% CI: 63–80) and 94% (95% CI: 93–96), respectively. The authors also noted that this combined method may be particularly beneficial to investigate patients that were deemed at high risk in terms of disease spread, which is a common suggestion in various similar studies [12].

There are numerous studies in which the 18F-FDG PET/CT modality was evaluated for detection of nodal involvement in patients with endometrial cancer and various other cancers. A multicenter study by Atri et al. [20] gathered 215 patients from 22 institutions and after rigorous inclusion/exclusion criteria, analyzed 23 LNM-positive and 26 negative cases. They concluded that 18F-FDG PET/CT had significantly higher diagnostic capability compared with CT in the detection of pelvic lymph node metastasis (AUC: 0.82 vs. 0.75, *P*=0.02). Kitajima similarly suggested that 18F-FDG PET/CT was superior to other conventional methods of imaging in endometrial cancer; however, the identification of LNM was moderate [16]. A very similar study was then performed by Lee et al. [21] who determined a sensitivity of 53.3% and a specificity of 97.8% for LNM detection and suggested that future studies should focus on patients with higher grade tumors. In another study, Picchio et al. [18] investigated 18F-FDG PET/CT for staging high-risk endometrial cancer patients and found that it is helpful to determine lymph nodes in the abdomen and extra-abdominal regions. Furthermore, in a study which focused on

high-risk cases, the sensitivity, specificity, PPV, NPV and accuracy of 18F-FDG PET/CT in identifying lymph node metastases were reported as 78.6%, 98.4%, 91.7%, 95.3% and 94.7%, respectively. The authors also found that LNM was associated with SUVmax values [22]. Another study which also focused on patients with higher risk reported 77.8% sensitivity and a remarkable 100% specificity in pelvic LNM detection [23]. The higher specificity values obtained in such patients support the thesis that this imaging method is especially useful in high-risk patients. However, the current study reports that the 18F-FDG PET/CT imaging modality yielded a respectable level of accuracy (79.26%) in determining lymph node metastases among patients with various risk levels. Therefore, we believe our findings support (and add to) previous studies in showing that this method is highly accurate in determining patients without disease as demonstrated by relatively higher specificity and NPV values. Even though studies with extremely high sensitivity levels can be found in the literature [24,25], our results are supported by the majority of studies which have reported high specificity in the presence of varying lower levels of sensitivity for LNM identification [26-28]. Aside from endometrial cancer, this combined imaging method provides highly conclusive data for lymph nodes in vulvar [17], cervical [29,30] and ovarian cancer [31].

To summarize, PET-CT is used in various types of cancer for preoperative evaluation; however, the method is hampered by various limitations for LNM identification in many cancers. We designed this study to evaluate the LNM detection accuracy of 18F-FDG PET/CT in patients with endometrial cancer, therefore, we limited our study to these patients. The low number of cases in several FIGO stages and histological types could limit the generalization of our findings to these respective groups, which is a limitation of the study. Furthermore, we only assessed prediction of LNM; accuracy for other tumor characteristics, such as the malignancy of the primary tumor or distant metastases, require novel studies.

Conclusion

Our analysis demonstrates that 18F-FDG PET/CT is an effective method for the determination of the absence of lymph node metastases. Our results contribute to current data and provide further evidence that this combined imaging modality can enable the restriction of lymphadenectomy procedures in endometrial cancer.

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