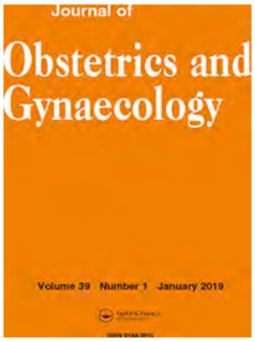

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ORIGINAL ARTICLE

A novel preoperative scoring system based on 18-FDG PET-CT for predicting lymph node metastases in patients with high-risk endometrial cancer

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ABSTRACT

The purpose of this study was to develop a model predicting the probability of pelvic-paraaortic node metastases in high-risk endometrial cancer patients. This trial included 41 high-risk endometrial cancer patients. All of the patients underwent an 18-FDG PET-CT followed by surgical staging, including a pelvic and paraaortic lymphadenectomy. We developed a useful scoring system combining weighted risk factors derived from a regression model: (3 × presence PET-CT involvement) + (3 × PET-CT maximum standardised uptake value $\geq$20) + (2 × diabetes comorbidity) + (1 × age $\geq$60 years) + (1 × body mass index $\geq$30). The area under the curve of the resulting score was 0.848. There was 75% sensitivity, 89% specificity and a 75% positive predictive value and 89% negative predictive value when a score of 6 was used as the cut-off. Our novel preoperative scoring system is an accurate method for the preoperative evaluation of lymph node metastases, and thus will aid gynaecological oncologists in selecting EC patients who may benefit from a lymphadenectomy.

KEYWORDS
PET-CT; endometrial cancer; lymphadenectomy

IMPACT STATEMENT

- **What is already known on this subject?** Endometrial cancer (EC) is a common gynaecological malignancy. Surgical staging is currently the standard treatment and the gold standard for evaluating lymph node metastases (LNm) is a surgical assessment (Chan et al. 2006). Three previous randomised clinical studies failed to find a clear therapeutic role for the lymphadenectomy; thus, the utility of this surgical procedure in high-risk early-stage EC remains under debate (Benedetti Panici et al. 2008; Kitchener et al. 2009; Signorelli et al. 2015). Non-invasive techniques that accurately identify lymph node metastases would reduce costs and complications.
- **What do the results of this study add?** Our developed novel scoring system that is based on positron emission tomography-computer tomography (PET-CT) with 2-deoxy-2-(18F) flouro-2-D-glucose (FDG) may facilitate the identification of patients at an increased risk of LNm.
- **What are the implications of these finding for clinical practice and/or further research?** This study shows that our novel preoperative scoring system provides an accurate method for the preoperative evaluation of LNm, and thus could guide gynaecologic oncologists in selecting the high-risk endometrial cancer patients who may benefit from a systematic lymphadenectomy. Further larger, prospective studies are needed to confirm the accuracy and the feasibility of our scoring system.

Introduction

Endometrial cancer (EC) is the most common gynaecological malignancy in high-income countries, and its incidence is increasing. EC is the eighth most common cause of cancer deaths in the US, with approximately 43,470 diagnosed cases and 7950 deaths occurring annually (Amant et al. 2005; Jemal et al. 2010). In Turkey, the incidence of adenocarcinoma of the endometrium is 5.0%, and the five-year overall survival rate is 90% (Solmaz et al. 2015).

Lymph node metastasis (LNm) is the most important prognostic factor in early-stage EC (Amant et al. 2005; Chan et al. 2006; Solmaz et al. 2015). Currently, the gold standard for evaluating LNm is a surgical assessment (Chan et al. 2006). While surgical staging is the accepted standard, a routine lymphadenectomy remains controversial. Three previous randomised clinical studies failed to find a clear therapeutic role for a lymphadenectomy; thus, the utility of this surgical procedure in high-risk early-stage EC remains under debate (Benedetti Panici et al. 2008; Kitchener et al. 2009; Signorelli et al. 2015). The proper detection of female patients who would benefit from a systematic lymphadenectomy is critical, because nearly 80% of high-risk early-stage

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EC patients who undergo a lymphadenectomy turn out to be negative for LNm (Mariani et al. 2008; Todo et al. 2010).

Positron emission tomography-computer tomography (PET-CT) with 2-deoxy-2-(18F) flouro-2-D-glucose (FDG) is a combined functional and morphological imaging technique. PET is a functional method based on the increased glucose metabolism of malignant tumours. Cancer cells actively take up and accumulate FDG; thus, this imaging method reveals tumour distribution and metabolism in various malignancies, including gynaecological cancers (Gambhir 2002; Amit et al. 2011). PET-CT is often used in the postsurgical assessment of endometrial cancer, but few studies have addressed the clinical utility of this imaging modality in the pre-treatment stage (Westerterp et al. 2007). A non-invasive technique that accurately identifies LN metastases would have the additional benefit of reducing costs and complications.

The purpose of this study is to estimate the accuracy of FDG PET-CT in preoperatively diagnosing the metastases of the pelvic-paraaortic lymph nodes, and to develop a model predicting the probability of pelvic-paraaortic node metastases in high-risk endometrial cancer.

Materials and methods

This multicentre, retrospective study was conducted at the Tepecik Education and Research Hospital, the Mugla Sıtkı Kocman University Education and Research Hospital, and the İstanbul Dr Sadi Konuk Education and Research Hospital. The study was approved by our institutional review board. Patients with pathologically proven grade 3 endometrioid carcinoma, serous carcinoma or clear cell carcinoma were considered for this study. A preoperative PET-CT was performed on all of the patients for the abdominal and pelvic staging of endometrial cancer at our institution between 1 January 2014 and 1 October 2016. Patients were excluded from the analysis if they had a previous diagnosis of another malignant disease, if the time interval between PET-CT and primary surgery was longer than 8 weeks, or if surgery was not their primary treatment. After surgery, all the patients were clinically and radiologically followed up according to the institution's protocol. An adjuvant therapy was applied if necessary according to the final FIGO stage.

Demographic, clinical and pathological characteristics, as well as survival data, were obtained from the patients' medical records and institutional tumour records. All the medical records and operative reports were reviewed. We gathered information on the patient age, body mass index (BMI), parity, past history of hypertension, diabetes status, preoperative Ca 125 level and histological type and grade of EC.

All the studies were performed with the same PET-CT scanner (Discovery ST or Discovery 600; GE Healthcare, Milwaukee, WI) in two radiology centres. Patients fasted for at least 6 hours before an IV administration of 3.7 MBq/kg 18-FDG, and subjects with a blood glucose level greater than 150 mg/dL, or 200 mg/dL in diabetic patients, were excluded. The examination started 60–80 minutes after the uptake period. A single experienced nuclear medicine physician assessed the images. The diagnosis of pathological LN on PET-CT images was based on the presence of the focal increased tracer uptake on PET imaging.

The surgical standard treatments for all the patients included a peritoneal cytology, total extrafascial hysterectomy, bilateral salpingo-oophorectomy and systematic pelvic (including the superficial and deep obturator, external and superficial LNs and deep common iliac LNs) and aortic (precaval and paracaval, superficial and deep intercavoaortic, and a paraaortic up to the left renal vessel) lymphadenectomy. Laparotomy was done for all of the surgical operations. The histopathological findings were analysed by two highly experienced pathologists (who were blinded to the imaging results), and served as the standard of reference. The uterus, pelvic and aortic LNm lesions were sliced and stained with haematoxylin and eosin before the microscopic examination. The patients' tumours were staged according to the FIGO 2009 staging criteria (Creasman 2009).

All the statistical analyses were performed using MedCalc software (MedCalc, Mariakerke, Belgium). A p value $<.05$ was considered as statistically significant. The data are presented as means ± SD. The Chi-square test and Student's t test were used for comparative analysis of unpaired data. The sensitivity, specificity, positive predictive values (PPVs) and negative predictive values (NPVs) were calculated with their associated 95% confidence intervals (CIs). The potential risk factors identified in the unadjusted analyses ($p<.05$) were used to create a logistic regression model, in which the LN metastasis was the dependent variable. Continuous variables were transformed into categorical variables using approximate optimal cut-off points identified by receiver operating characteristic (ROC) curve analysis. The mean values of age (<60 vs. ≥60 years) and BMI (<30 vs. ≥30 kg/m^2) were used in the analysis. The statistically significant odds ratios identified using the multivariable models were rounded to the nearest whole number. Such rounded values served to weight each factor, and the weighted values were summed to generate an overall score to predict the probability of an LNm presence. An ROC curve was used to evaluate the cut-off, the sensitivity and the specificity values.

Results

This trial included 15 patients with a serous carcinoma, 7 patients with clear cell adenocarcinoma grades 1–2, and 19 patients with endometrioid-type grade 3 endometrial cancer. All of the patients underwent an 18-FDG PET-CT followed by surgical staging, including a pelvic and a paraaortic lymphadenectomy. The demographic and surgical data are shown in Table 1. The median age was 61.4 years (range: 44 − 79 years). The median PET-CT tumour diameter was 3.95 cm (range: 12 − 80 mm) and the rate of lymph node involvement was 29.3%. The histopathological characteristics of the patients are presented in Table 2. Of the patients, 70.8% ($n=29$) had FIGO stage I disease. The rate of lymphovascular space invasion was 39% (Table 2).

We evaluated the maximum standardised uptake value (SUV_{max}) at different levels to determine the optimal cut-off point for predicting LNm. The ROC curve indicated that an $SUV_{max} \geq 20$ was optimal for predicting LNm. Additionally, we

Table 1. Clinical and surgical characteristics of the study population.

Characteristic	$N = 41$
Age (years)	61.4 (44–79)
Parity	2.8 ± 1.6 (0–11)
BMI	32.2 ± 3.7 (27–42)
Hypertension	15 (36.6)
Diabetes mellitus	15 (36.6)
Hypertension and diabetes mellitus	8 (19.5)
Preoperative CA 125 (U/mL)	40.9 ± 30.8 (4–185)
PET-CT Tm diameter (mm)	39.6 ± 16.4 (12–80)
SUV_{max}	15.7 ± 5.2 (4–28)
Number of lymph nodes removed	
Pelvic	18 (10–25)
Paraaortic	13 (10–19)
Lymph node involvement	12 (29.3)

Values are expressed as means (range) or numbers (percentage); number of the lymph nodes removed is expressed as a median (range).
BMI: body mass index; SUV_{max}: maximum standardised uptake value.

Table 2. Histopathological characteristics of the study population.

Cancer type	
Endometrioid	19 (46.3)
Serous papillary	15 (36.6)
Clear cell	7 (17.1)
Grade	
I	18 (43.9)
II	4 (9.7)
III	19 (46.3)
Stage	
IA	20 (48.8)
IB	9 (22)
IIIC1	9 (22)
IIIC2	3 (7.3)
LVSI(+)	16 (39)

Values are expressed as numbers (percentage).
LVSI: lymphovascular space invasion.

Table 3. Predictive values of SUV_{max} and PET-CT Tm diameter in determining lymph node metastasis.

Lymph node metastasis	$SUV_{max} \geq 20$	PET-CT Tm ≥4 cm diameter
Area under the curve	0.817	0.66
Sensitivity	0.83	0.66
Specificity	0.90	0.65
Negative predictive value	92.9	81.8
Positive predictive value	76.9	42.1

SUV_{max}: maximum standardised uptake value.

found that the PET-CT tumour diameter was a poor predictor of LNm (area under the curve [AUC] = 0.664) (Table 3). Upon an unadjusted analysis, the age ≥60 years, BMI ≥30, comorbid diabetes, $SUV_{max} \geq 20$ and the presence of involvement at PET-CT were all associated with an increased risk of LNm in females (Table 4). Variables showing significant associations with LNm (as the dependent variable) upon the unadjusted analysis were included in a logistic regression model. All risk factors (age ≥60 years, BMI ≥30, comorbid diabetes, $SUV_{max} \geq 20$ and the presence of involvement at PET-CT) showed significant associations with LNm (Table 5).

A useful scoring system combining weighted risk factors derived from the regression model was devised, as follows: (1 × age ≥60 years) + (1 × BMI ≥30) + (3 × PET-CT involvement) + (2 × comorbid diabetes) + (3 × SUV_{max} >20). The AUC of the resulting score was 0.848. There was 75% sensitivity,

Table 4. Unadjusted odds ratios, using demographic factors and preoperative characteristics as risk factors, for the presence of LN metastases in the study population.

Factor	Without LNm ($n = 29$)	With LNm ($n = 12$)	p value	OR (95%CI)
Age (≥60 years)	11 (37.9)	9 (75)	.031	0.5 (0.2–0.8)
Parity	2.7 ± 1.9	3.0 ± 1.0	.682	
BMI (≥30 kg/m^2)	15 (51.7)	12 (100)	.03	
Hypertension	11 (37.9)	4 (33.3)	.781	1.1 (0.4–2.8)
Diabetes mellitus	7 (24.1)	8 (66.7)	.01	0.3 (0.1–0.7)
Preop CA 125 (U/mL)	34.8 ± 34.9	55.4 ± 45.5	.126	
Preop CA125 (≥20 U/mL)	15 (51.7)	7 (58.3)	.699	
SUV_{max} (≥20)	3 (10.3)	10 (83.3)	≤.001	0.1 (0.04–0.3)
PET-CT involvement	5 (17.2)	9 (75)	≤.001	0.2 (0.01–0.5)
PET-CT Tm diameter (mm)	36.3 ± 13.8	47.5 ± 21.9	.056	

Values are expressed as numbers (percentage).
BMI: body mass index; PET-CT: positron emission tomography-computer tomography; LNm: lymph node metastasis; OR: odds ratio; CI: confidence interval.

Table 5. Odds ratios derived using the logistic regression model with LNm as the dependent variable.

Factor	OR (95%CI)	p value
Age (≥60 years)	2.2 (0.1–38.1)	.04
BMI (≥30 kg/m^2)	2.3 (1.0–5.2)	.038
Diabetes mellitus	4.0 (1.3–10.9)	.02
SUV_{max} (≥20)	6.2 (2.4–15.6)	.01
PET-CT involvement	5.1 (3.5–8.0)	.01

Values in parentheses are 95%CI.
BMI: body mass index; SUV_{max}: maximum standardised uptake value; PET-CT: positron emission tomography-computer tomography; OR: odds ratio; CI: confidence interval.

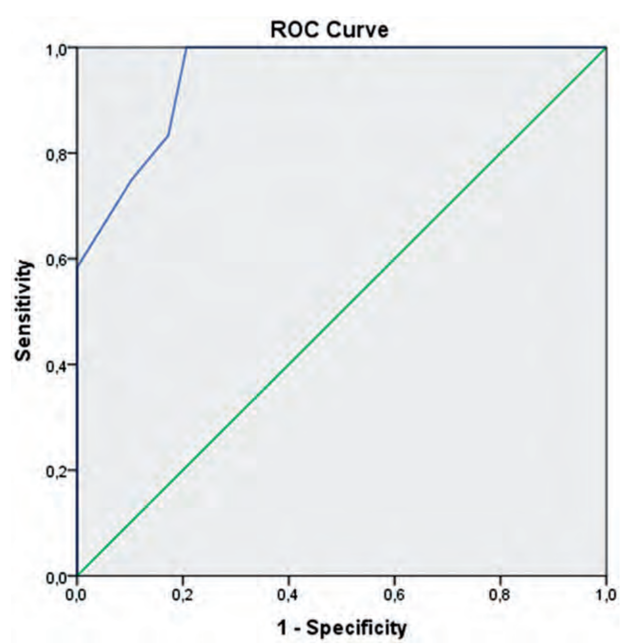

Figure 1. Receiver operating characteristic (ROC) analysis for the scoring system and lymph node metastasis.

89% specificity and a 75% positive predictive value and 89% negative predictive value when a score of 6 was used as the cut-off (Figure 1). The mean total score of all the study patients was 3.9 ± 3.3 (range: 0–10).

Discussion

This study shows that our novel preoperative scoring system provides an accurate method for the preoperative evaluation of LNm, and thus could guide gynaecologic oncologists in selecting the high-risk endometrial cancer patients who may benefit from a systematic lymphadenectomy.

Recently, many randomised trials showed that a routine systematic pelvic and paraaortic lymphadenectomy statistically improved the surgical staging and helped physicians define the patient's prognosis, but did not confer any survival benefits, especially in an early-stage endometrial carcinoma (Benedetti Panici et al. 2008; Kitchener et al. 2009). Furthermore, a systematic pelvic and paraaortic lymphadenectomy is generally viewed as an overtreatment in low-risk groups, but there is still controversy in the high-risk subgroup, where almost 15% to 25% of women have pelvic, and 5% to 15% have aortic LNm (Signorelli et al. 2015). Most women in the high-risk group have negative LNm, and systematic lymphadenectomy results in unnecessary morbidities and costs (Abu-Rustum et al. 2006; Konno et al. 2011; Dowdy et al. 2012). In the 2016 National Comprehensive Cancer Network Guidelines Version 2, magnetic resonance, CT and PET-CT are recommended as preoperative staging procedures in suspected EC, especially in the high-risk group. In addition, PET-CT is the best imaging method for assessing and detecting LNm in high-grade FDG-avid tumours during the preoperative period.

Many studies have investigated the use of PET-CT for preoperative staging in EC patients. However, the main limitation of these studies is the heterogeneity of the study populations, which included both low- and high-risk patients (Antonsen et al. 2013; Kakhki et al. 2013). In the present study, we aimed to investigate the accuracy of PET/CT findings, especially PET-CT involvement and $SUV_{max} \geq 20$, for determining LNm, and performed systematic lymphadenectomy. As our results show, there is a gradual increase in the SUV_{max} with LNm. This supports the idea of an increased metabolic activity with disease progression. The gradual increase in SUV_{max} and the presence of PET-CT involvement can form the basis of a preoperative scoring system for the stratification of different surgical protocols in high-risk early-stage patients. We believe that patients who need complete surgical staging can be accurately identified with this non-invasive, preoperative imaging method.

The association between obesity and EC, which is well recognised, is explained by an unregulated oestrogen expression (He et al. 2013). An elevated BMI was significantly related to the presence of LNm in EC patients. In the present study, high-risk EC patients with BMI values ≥ 30 were at a 2.3-fold greater risk of LNm compared with the less obese patients (Ye et al. 2016). Diabetes, often associated with obesity, is also a risk factor for LNm in high-risk EC patients (Steiner et al. 2006). We found that the LNm risk for diabetic patients was four-fold greater than that of the non-diabetic patients, similar to the results of Steiner et al. in 2006. In addition, we found that the risk of LNm was 2.2-fold greater in the females aged ≥ 60 years than in the younger patients.

In light of this information, we developed a scoring system with utility for identifying LNm patients at high EC risk who should receive a systematic lymphadenectomy. We used a logistic regression to model the relationships among the PET-CT findings, BMI, age and comorbid diabetes. Our scoring system affords a good discriminatory power ($AUC = 0.848$), moderate sensitivity and PPV, and a high specificity and NPV (75%, 75%, 89% and 89%, respectively), when used to detect LNm in patients with high-risk EC.

In the present study, we found no statistically significant differences with regard to hypertension, parity, preoperative CA125 level and PET-CT tumour diameter in high-risk patients both with and without LNm. Hypertension and nulliparity are the most well-known risk factors of EC, due to the increased exposure to the unopposed oestrogen (Hacker and Friedlander 2010). However, we found no significant effect of these conditions on LNm in the high-risk EC patients. Signorelli et al. suggested that a PET-CT tumour diameter of ≥ 4 cm was borderline significant for LNm, contrary to our findings (Mariani et al. 2008). Furthermore, Yang et al. (2016) found that preoperative CA 125 levels predicted LNm in high-risk EC patients.

Our study had some limitations, particularly the relatively small study group. The retrospective nature of our study may also constitute a limitation. However, our study had the advantage of including only high-risk patients. In addition, we carried out this research at three tertiary centres, and worked with highly experienced gynaecological pathologists throughout the entire study period.

In conclusion, we have developed a novel scoring system that may facilitate the identification of patients at the increased risk of LNm, and may guide gynaecological oncologists during the preoperative period for a systematic lymphadenectomy in high-risk EC. Further larger, prospective studies are needed to confirm the accuracy and feasibility of our scoring system.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Disclosure statement

No potential conflict of interest was reported by the authors.

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