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The prognostic significance of serum CA125 levels with ER, PR, P53 and Ki-67 expression in endometrial carcinomas

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ABSTRACT

Objectives: The present study evaluates the relationship between the expression levels of hormone receptors (HRs), Ki-67, p53 and serum cancer antigen 125 (CA125) levels in endometrial cancer and clinicopathological risk factors, and determines their prognostic values.

Material and methods: This retrospective study included 49 patients with endometrial cancer whose estrogen receptor (ER) and progesterone receptor (PR) Ki-67 and p53 expression levels were determined through immunohistochemical methods, and whose preoperative serum CA125 levels were measured. These factors relationship with various clinicopathological factors, progression-free survival (PFS) and overall survival (OS) was investigated.

Results: The study included 49 patients with EC with a mean age of 61 ± 10 years. The rate of HR positivity was significantly higher in the endometrioid histology group than in the non-endometroid histology group ($p = 0.026$). A high level of Ki-67 expression was found to be associated with a non-endometroid histology ($p = 0.016$), and a high tumor grade ($p < 0.001$) and a high p53 expression were found to be associated with advanced disease stage ($p = 0.026$). A positive correlation was found between p53 and Ki-67, a negative correlation was found between p53 and Ki-67 and the presence of HR. Significant relationship was not found between HR status, p53, Ki-67, CA125 and either other clinicopathological risk factors or survival.

Conclusions: While HR positivity indicates favorable clinicopathological prognostic factors, high Ki-67 and high p53 expression indicate unfavorable ones. However, no direct effect of these factors on prognosis was found in this study.

Key words: endometrial cancer; prognosis; hormone receptor; ki67; p53; CA125

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INTRODUCTION

Endometrial cancer (EC) is the most common gynecological cancer in women in developed countries [1] and most cases are diagnosed in the early stage [2]. Despite high overall survival rate associated with EC, recurrences occur in more than 10% of patients with early stage disease if adjuvant therapy is not administered [3–5], and some do not survive 5 years. Various classification systems have been developed to determine the risk of recurrence, to predict prognosis and to guide therapy in EC. In the Bokhman classification, EC is divided into two groups based on histology, grade and hormone receptor status. In addition, risk stratification systems have been developed that involve the International Federation of Gynecology and Obstetrics (FIGO) stage, histology, grade and lymphovascular invasion (LVI) [2]. Currently, genetic factors are also being investigated as a prognostic factor, although they are relatively expensive and are not available at all centers. Imaging studies, including magnetic resonance imaging (MRI) and F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT), have been found to be useful in EC [6], although they do not always determine

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the final stage of the tumor, the histology, grade or risk class accurately. Surgical staging (total hysterectomy, bilateral salpingo-oophorectomy and lymph node dissection) is thus recommended as part of the initial treatment of EC [7] and risk stratification is carried out accordingly. That said, the currently used risk stratification systems do not always predict prognosis accurately, and so additional factors are sought to improve the current risk stratification systems. Various studies have reported a relationship between the clinicopathological characteristics of EC and immunohistochemical markers such as Ki-67, p53 and hormone receptors (HR) [8], and serum cancer antigen 125 (CA125) [9] levels. These inexpensive and easy-to-apply methods have yet to be systematically investigated and to be included in the current risk stratification systems.

Objectives

The present study investigates the relationship between immunohistochemically detected estrogen receptors (ER), progesterone receptors (PR), Ki-67, p53 expressions and serum CA125 levels and various clinicopathological risk factors and metabolic parameters in preoperative PET/CT scans, with a further investigation of the role of immunohistochemical factors and serum CA125 levels in predicting the prognosis of EC.

MATERIAL AND METHODS

Patients

For this retrospective study, patients diagnosed with EC in Tepecik Training and Research Hospital between March 2012 and January 2016 were reviewed. The following criteria were investigated for patients to be included in the study:

1. Undergoing surgical staging for EC (a total hysterectomy, bilateral salpingo-oophorectomy and lymphadenectomy);
2. Evaluating histopathologically tumor diameter, grade, histology, LVI, HR, p53 and Ki-67 expressions of EC;
3. Having preoperative CA125 levels and PET/CT scans.

Forty-nine patients who met all of these conditions were included in the study. Surgical stage, grade and histology were determined according to the 2009 FIGO classification. HR, p53 and Ki-67 expressions were evaluated using immunohistochemical methods. Patients with early stage disease and without negative prognostic factors (LVI, non-endometrioid histology, tumors other than stage 1A and grade 1–2 tumors) underwent no treatment other than surgery, whereas those with advanced-stage tumors and those at risk of recurrent disease received adjuvant therapy (chemotherapy and/or radiotherapy). The patients were placed on a postoperative follow-up program involving ultrasonographic assessment and monitorization of serum CA125 levels, along with medical history and physical examination findings. Pap smears, CT, MRI or PET/CT were performed as required.

Immunohistochemical analysis

For immunohistochemistry (IHC), Hematoxylin and Eosin (HE) staining was used to select appropriate paraffin blocks and to identify the viable tumor areas. IHC was performed by the streptavidin biotin peroxidase method. Serial five-µm sections were obtained and these slides were baked overnight at 60°C, dewaxed in xylene, and hydrated with distilled water through decreasing concentrations of alcohol. All slides were treated with heat-induced epitope retrieval in the microwave (in 10 mM/L citrate buffer, pH 6.0, for 20 minutes, followed by cooling at room temperature for 20 minutes) and blocked for endogenous peroxidase and biotin. Sections were incubated with primary antibodies in an automated system (Autostainer Link 48; Dako) for 20–30 minutes (depending on the antibody) at the following dilutions: ER (FLEX Monoclonal Mo a Hu Estrogen Receptor, Clone 1D5, RTU; Dako) at 1:100; PR (FLEX Monoclonal Mouse, X-Hu Progest Recept, Clone PgR 636, RTU; Dako) at 1:200; Ki67 (polyclonal, Dako; 1/500 dilution, clone Ki67-MIB-1), and p53 (polyclonal, Dako; 1/500 dilution, clone P53-DO-7).

Immunohistochemically ER, PR,Ki67 and p53 stained sections were examined under light microscope. The percentage of ER, PR, Ki-67, and p53- positive cells was evaluated. Positive cells showed brown staining limited exclusively to the nuclei.

In the assessment of HR status, the patients were divided into two groups as those testing negative for both ER and PR (HR-) and those testing positive for either ER or PR (HR+). A tumor staining ≥ 1% was considered to be predictive of ER or PR positivity.

F-18 FDG PET/CT

The images of the patients from the vertex of the skull to the thigh were captured using a PHILIPS GEMINI TF 16 Slice PET/CT device. The patients received an intravenous injection of 0.15 mCi/kg F-18 FDG following 6 hours of fasting. CT images (140 kV, 100 mAs, 5 mm slice thickness) were captured first, followed by PET emission images (1.5 minutes per bed position). The maximum standardized uptake value (SUVmax) of the primary tumor was recorded and the SUVmean and metabolic tumor volume (MTV) were calculated considering 41% of SUVmax as the threshold value. The total lesion glycolysis (TLG) value was calculated by multiplying the MTV by the SUVmean.

Survival

The progression-free survival (the time from the date of diagnosis to the date of progression or death due to EC)

and overall survival (the time from the date of diagnosis to death due to EC or to the date of last follow-up visit) of all patients were calculated.

Statistical Analysis

In the statistical analysis, p53, Ki-67 and serum CA125 levels were considered as continuous variables and HR status was considered as a categorical variable. Patients with EC were grouped based on various clinicopathological factors [grade, histology, FIGO stage, myometrial invasion (MI), cervical invasion (CI), LVI, lymph node metastasis (LNM), distant metastasis (DM), and tumor size]. p53, Ki-67, CA125 and HR were compared between the groups with a Mann-Whitney U-test. The Spearman's correlation coefficient (Rho) was used to evaluate the correlation between the PET parameters and p53, Ki-67, CA125 and HR status. Kaplan Meier survival curves were drawn for all patients. The relationships between p53, Ki-67, CA125, age and PFS and OS were evaluated with a Cox regression analysis. The difference between the HR-negative and HR-positive groups in terms of PFS and OS was investigated with a Log Rank test. A Log Rank test was also used for survival analysis of patients grouped according to clinicopathological risk factors.

RESULTS

Patients

The study included 49 patients with EC with a mean age of 61±10 years (range 37–83) of which 30 had an endometrioid and 19 had a non-endometrioid **(mixed = 10, undifferentiated = 4, serous = 2, squamous = 1, clear cell = 1 and mucinous carcinoma = 1)** histology, **26** had grade 1–2 and **23** had grade 3 tumor, and 43 had FIGO stage 1–2 and 6 had FIGO stage 3-4 disease. Among all patients, MI was ≤ 50% in 29 patients, CI was negative in 40 patients, LVI was negative in 23 patients, LNM was negative in 46 patients, DM was negative in 46 patients and tumor diameter was ≤ 4 cm in 20 patients.

Comparison of hormone receptor status, p53, Ki-67 and CA125 among the clinicopathological groups

Of the total, three patients tested negative for both ER and PR; 43 tested positive for both ER and PR; and three tested positive for only PR. In an evaluation of all study patients, the mean values were 24.6 ± 0.01 (range 0–95) for p53, 34.6 ± 0.01 (range 5–80) for Ki-67, and 31.2 ± 0.007 (range 4.4–189.8) IU/mL for CA125.

Among the patients grouped according to clinicopathological characteristics, the rate of HR positivity was significantly higher in the endometrioid histology than in the non-endometrioid histology group ($p = 0.026$). The mean Ki-67 level was lower in the endometrioid histology than in the non-endometrioid histology group ($p = 0.016$) and in grade 1–2 tumors than in grade 3 tumors ($p < 0.001$). The mean p53 level was higher in patients with advanced stage EC than in patients with early stage disease ($p = 0.026$). HR status, p53, Ki-67 and CA125 did not differ significantly when the patients were grouped according to MI, CI, LVI, LNM, DM and tumor diameter ($p > 0.05$). Furthermore, the mean CA125 level did not differ significantly with histology, grade or FIGO stage ($p > 0.05$). The results are presented in Table 1. Figures 1 and 2 present two sample cases.

Correlation Analysis between the PET parameters and hormone receptor status, p53, Ki-67 and CA125

In an analysis of the relationship between HR status, p53, ki67 and CA125 levels, a significant moderately positive correlation was found between p53 and Ki-67 ($r = 0.493$, $p < 0.001$), while a weak negative correlation was identified between HR status and p53 ($r = –0.294$, $p = 0.040$) and Ki-67 ($r = –0.295$, $p = 0.039$). No significant correlation was found between CA125 and other parameters, nor between HR status, p53, Ki-67, CA125 and the PET parameters of the primary tumor (SUV_{max}, SUV_{mean}, MTV and TLG). The results of correlation analysis are presented in Table 2.

Survival Analysis

The mean follow-up time was 35.7 ± 1.5 months (3–47 months). Disease progression was observed in 12 patients, and eight patients died during the follow-up period. The mean PFS of the patients was 39.2 ± 2.08 months and the mean OS was 42.4 ± 1.6 months.

No significant difference was observed in PFS or OS between the HR-positive group and the HR-negative group (Tab. 3). No significant relationship was found between p53, Ki-67, CA125 levels and PFS and OS (Tab. 4).

There was a significant difference between OS and PFS of patients grouped according to histology, grade, stage, MI, CI, LVI, LNM and DM. However, no significant relation was found between tumor diameter and OS and PFS. The results are presented in Table 5. Furthermore, age was a prognostic factor for both OS (HR = 1.085, $p = 0.041$) and PFS (HR = 1.100, $p = 0.012$).

Incidental Findings

Preoperative PET/CT revealed hypermetabolic incidental lesions among our cases diagnosed with endometrial cancer. Histopathological diagnoses of those incidental lesions were made and presented as interesting cases in Figures 3, 4 and 5.

Table 1. Comparison of HR, p53, ki67 and CA125 values between clinicopathological groups

		HR			p53		ki67		CA125	
	n	– (n)	+ (n)	P	mean ± SE	P	mean ± SE	P	mean ± SE	p
Histology										
Endometroid	30	0	30	0.026*	19.6 ± 4.3	0.151	29.4 ± 4	0.016*	25.9 ± 5.6	0.268
Nonendometroid	19	3	16		32.6 ± 7.4		42.8 ± 4.9		39.6 ± 11.8	
Grade										
1–2	26	0	26	0.060	18.8 ± 4.9	0.110	24.1 ± 3.6	< 0.001*	27.8 ± 6.4	0.833
3	23	3	20		31.3 ± 6.3		46.5 ± 4.5		35 ± 9.9	
FIGO stage										
1–2	43	3	40	0.800	20.9 ± 3.8	0.026*	33.4 ± 3.4	0.287	25.6 ± 4.1	0.411
3–4	6	0	6		51.6 ± 4.2		43.3 ± 9.8		71.2 ± 34.2	
MI										
≤ 50%	29	1	28	0.352	19.8 ± 4.4	0.258	30.6 ± 3.9	0.125	19.7 ± 2.5	0.411
> 50%	20	2	18		31.7 ± 7.3		40.4 ± 5.3		47.8 ± 12.9	
CI										
No	40	3	37	0.732	24.2 ± 4.1	0.810	34.4 ± 3.8	0.657	26.6 ± 4.9	0.095
Yes	9	0	9		26.6 ± 12.2		35.5 ± 5.8		51.3 ± 22.2	
LVI										
No	23	1	22	0.630	19.1 ± 5.7	0.093	29.5 ± 4.5	0.114	18.7 ± 2.9	0.107
Yes	26	2	24		29.6 ± 5.5		39.1 ± 4.5		42.2 ± 10.1	
LNM										
No	46	3	43	0.860	23.9 ± 4	0.650	35 ± 3.4	0.679	29 ± 5.3	1.000
Yes	3	0	3		36.6 ± 23.3		28.3 ± 13		64.3 ± 51.8	
DM										
No	46	3	43	0.860	23.4 ± 3.9	0.323	34 ± 3.3	0.485	25.1 ± 3.9	0.172
Yes	3	0	3		43.3 ± 26.8		43.3 ± 18.5		123.5 ± 55.7	
Tumor diameter										
≤ 4 cm	20	1	19	0.788	21.2 ± 5.8	0.426	31.7 ± 4.7	0.578	20 ± 3.3	0.242
> 4 cm	29	2	27		27 ± 5.5		36.6 ± 4.4		38.9 ± 9.2	
Total	49	3	46		24.6 ± 0.01		34.6 ± 0.01		31.2 ± 0.007	

HR — hormone receptor; CA 125 — cancer antigen 125; MI — myometrial invasion; CI — cervical invasion; LVI — lymphovascular invasion; LNM — lymph node metastasis; DM — distant metastasis; significant values ($p < 0.05$) are indicated with*

DISCUSSION

EC is divided into two groups, type 1 and type 2, based on the classification system proposed by Bokhman in 1983. Type 1 EC refers to a low-grade, HR-positive tumor with an endometrioid histology that is often associated with good prognosis [10], while type 2 EC refers to a high-grade, HR-negative tumor with a non-endometrioid histology that is associated with poorer prognosis than type 1 tumors [10]. This classification system has been considered insufficient, despite its benefits in determining prognosis and guiding therapy, leading to the development of risk stratification systems that take into account such factors as FIGO stage, grade, histology and LVI. In our study, a significant relation was found between patient age, tumor histology, grade, stage, MI, CI, LVI, LNM and DM and OS and PFS in accordance with the literature. However, tumor diameter was not a prognostic factor in our study. Although some studies have reported that tumor diameter has a prognostic value, it has not been included in the risk classification system yet [2]. Also we accepted the 4 cm tumor diameter for the threshold value that may have led to different results from the literature.

The present study evaluated the effects of widely available immunohistochemical analysis of HR status, Ki-67 and p53 expression and serum CA125 levels on prognosis, and examined whether or not they contribute to the risk classification system.

Various studies have evaluated the relationship between immunohistochemical parameters and clinicopathological factors and survival. In a study involving 164 patients with EC, Sivridis et al. [11] reported that the loss or ER or PR is

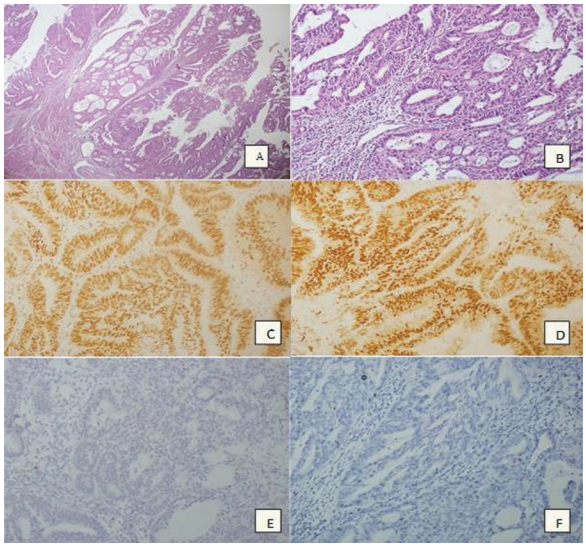

Figure 1. Endometrioid endometrial carcinoma, Figo grade 2; **A–B.** H & E, ×40, ×100; **C–D.** estrogen receptor (ER) and progesterone receptor (PR), strong positivite by immunohistochemistry (DAB, ×200), **E.** P53 negative (DAB, ×200), **F.** Ki67 10% positive (DAB, ×200)

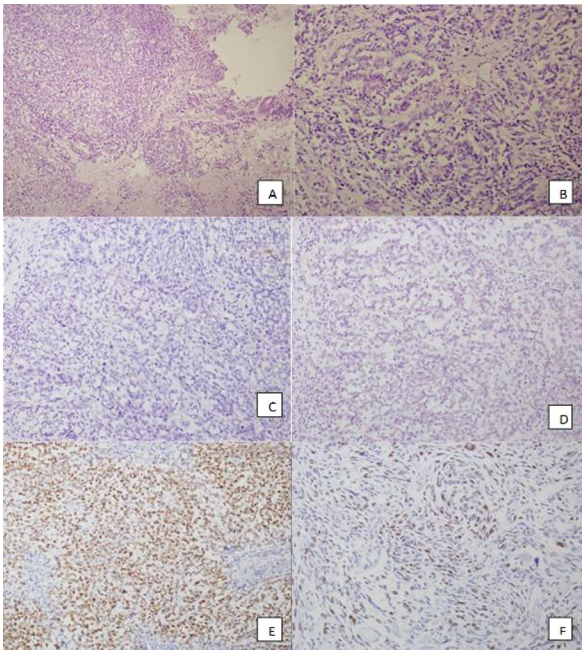

Figure 2. Undifferentiated endometrial carcinoma; **A.** Partly solid and partly gland forming tumor masses infiltrating the myometrium (H & E, ×100); **B.** A few glands were found in this tumor, which was predominantly undifferentiated (H & E, ×200); **C–D.** Expression of estrogen receptor (ER) and progesterone receptor (PR) were negative (DAB, ×200); **E–F.** Strong expression of P53 and Ki67 (DAB, ×200)

associated with a non-endometrioid histology, while the loss of ER alone is associated with deep MI. The present study, however, could identify no significant relationship between hormone receptor status and survival. In another study involving 86 patients with EC [12], ER status was considered to be positive if the cytoplasmic estrogen-binding protein was ≥ 5 fmol/mg, and PR status was considered to be positive if the cytoplasmic progesterone-binding protein was ≥ 10 fmol/mg. When the patients in their study were grouped according to histology, grade and stage, no

Table 2. Correlation analysis of HR, p53, ki67, CA125 and PET parameters

	HR		P53		Ki67		CA125	
	r	p	r	p	r	p	r	p
SUVmax	–0.181	0.214	0.031	0.833	0.250	0.083	0.160	0.271
SUVmean	–0.181	0.214	0.009	0.949	0.247	0.087	0.169	0.245
MTV	–0.036	0.805	0.029	0.843	0.145	0.322	0.220	0.128
TLG	–0.114	0.434	0.047	0.746	0.185	0.203	0.227	0.117
HR	–		–0.294	0.040*	–0.295	0.039*	–0.030	0.837
P53	–0.294	0.040*	–		0.493	< 0.001*	0.109	0.454
Ki67	–0.295	0.039*	0.493	<0.001*	–		–0.018	0.903
CA125	–0.030	0.837	0.109	0.454	–0.018	0.903	–	

HR — hormone receptor; CA125 — cancer antigen 125; SUV_{max} — maximum standardized uptake value; MTV — metabolic tumor volume; TLG — total lesion glycolysis, significant values ($p < 0.05$) are indicated with*

Table 3. Survival analysis of patients grouped according to hormone receptors

	n	OS (months)	p	PFS (months)	p
HR negative	3	34 ± 3.5	0.483	34 ± 3.5	0.388
HR positive	46	35.8 ± 1.6		33.2 ± 1.9	

HR — hormone receptor; OS — overall survival; PFS — progression-free survival; survivals are shown as mean ± SE in the table

Table 4. Survival analysis results of p53, ki67 and CA125

	Overall survival		Progression free survival	
	p	HR	p	HR
P53	0.622	1.007	0.695	1.005
Ki67	0.685	1.007	0.888	1.002
CA125	0.512	1.005	0.059	1.010

HR — hazard ratio; CA125 — cancer antigen 125

Table 5. Survival analysis of patients grouped according to clinicopathological risk factors

	OS (months)		PFS (months)	
	mean ± SE	p	mean ± SE	p
Histology				
Endometroid	44.3 ± 1.3	0.019*	42.7 ± 1.6	0.015*
Nonendometroid	38.1 ± 3.2		32.4 ± 4.1	
Grade				
1–2	45.5 ± 0.3	0.011*	43.8 ± 1.2	0.018*
3	37.8 ± 3		33.2 ± 3.7	
FIGO stage				
1–2	44.1 ± 1.3	0.004*	42.6 ± 1.6	< 0.001*
3–4	28.5 ± 6.6		14.1 ± 5.7	
MI				
≤ 50%	44.1 ± 1.2	0.029*	42.6 ± 1.7	0.025*
> 50%	38.3 ± 3.2		33.1 ± 4	
CI				
No	43.7 ± 1.5	0.012*	42.4 ± 1.8	< 0.001*
Yes	34.7 ± 4.4		24.2 ± 5.5	
LVI				
No	45.9 ± 2.5	0.003*	45.3 ± 0.6	0.002*
Yes	33.2 ± 1.7		32.9 ± 3.4	
LNM				
No	43.5 ± 1.4	0.001*	41.4 ± 1.7	< 0.001*
Yes	20 ± 6.9		6 ± 2.5	
DM				
No	43.4 ± 1.5	0.002*	41.1 ± 1.8	< 0.001*
Yes	22 ± 3.5		10 ± 3.4	
Tumor diameter				
≤ 4 cm	43.2 ± 1.8	0.336	41.6 ± 2.4	0.204
> 4 cm	41.1 ± 2.3		36.9 ± 3	

OS — overall survival; PFS — progression-free survival; MI — myometrial invasion; CI — cervical invasion; LVI — lymphovascular invasion; LNM — lymph node metastasis; DM —distant metastasis; significant values ($p < 0.05$) are indicated with*

significant difference was observed in the mean ER and the mean PR among the different histological groups, whereas a low receptor level was found to be associated with high disease grade and advanced disease stage. Survival was found to be longer in ER-positive patients than in ER-negative patients, in PR-positive patients than in PR- patients, and in ER/PR double-positive patients than in ER/PR double-negative patients. In a study of 903 patients with grade 1–2 endometrioid EC [13], less than 1% staining in the tumor tissue was considered to be a negative reference point for ER and PR. A significant relationship has been identified between ER and PR negativity and deep MI, advanced disease stage and presence of LNM. The loss of ER and PR was found to be a negative prognostic factor for PFS and OS. In a study of 541 patients with EC involving grade 3 endometrioid carcinoma and serous carcinoma, Köbel et al. [14] considered more than 1% nuclear staining in tumor cells to be an indication of receptor positivity. When serous EC was evaluated separately, the rate of early-stage tumors was found to be significantly higher, and LVI positivity was found to be significantly lower in PR-positive patients than in PR-negative patients.

Ki-67 is an antibody indicating cellular proliferation that is believed to be related to the aggressiveness of a tumor [15]. Overexpressions of Ki-67 and p53 that were found to be associated with a poor differentiation in a study involving 144 patients with EC has been suggested to indicate tumor aggressiveness [16]. In a study by Canlorbe et al. evaluating 69 patients with EC [8], the positivity cut-offs for ER, PR, Ki-67 and p53 were reported to be 20%, 50%, 40% and 50%, respectively. In their study, ER and PR levels were significantly higher in grade 1–2 than in grade 3 EC, while Ki67 and p53 levels were significantly lower. In a study of 82 patients with EC [17], ≥ 10% receptor expression for ER and PR positivity was considered to be predictive and a 27% cut-off for Ki-67 was used for the grouping of patients. ER and PR negativity was found to be associated with high grade, advanced stage and deep MI, and high Ki-67 levels were found to be associated with deep MI. In their study, the rate of recurrence was found to be significantly higher among patients exhibiting all three of the ER negativity, PR negativity and high Ki-67 level characteristics.

In a study involving 73 patients with endometrioid carcinoma, Nielsen et al. [15] found a correlation between Ki-67 level and tumor grade, whereas no correlation was found between Ki-67 level and stage or progesterone receptor status. In another study, Ki-67 levels were found to be significantly higher in grade 3 than in grade 1–2 EC, and Ki-67 was further identified as an independent prognostic factor for survival [18]. Another study of 142 patients with EC also found Ki-67 and p53 expression to be independent prognostic factors [19]. In a study by Engelsen et al. [20] that involved preoperative curettage specimens of 236 patients with EC, pathological p53 expression (staining index > 4) was found to be associated with a high grade, advanced stage and non-endometrioid histology and high Ki-67 (> 35%) levels. In a study by Yamauchi et al. [21] involving 35 patients with EC, the presence of LNM was found to be significantly higher in p53-positive carcinomas than in negative carcinomas. Their study found a positive correlation between Ki-67 and p53 levels. Another study claimed that serum CA125 levels of < 30.0 IU/mL together with > 50% positive PR and/or < 40% Ki-67 indicate low risk for LNM [9].

In the present study, the rate of HR-positivity was higher in the endometrioid histology than in the non-endometrioid histology. Ki-67 levels were found to be higher in the

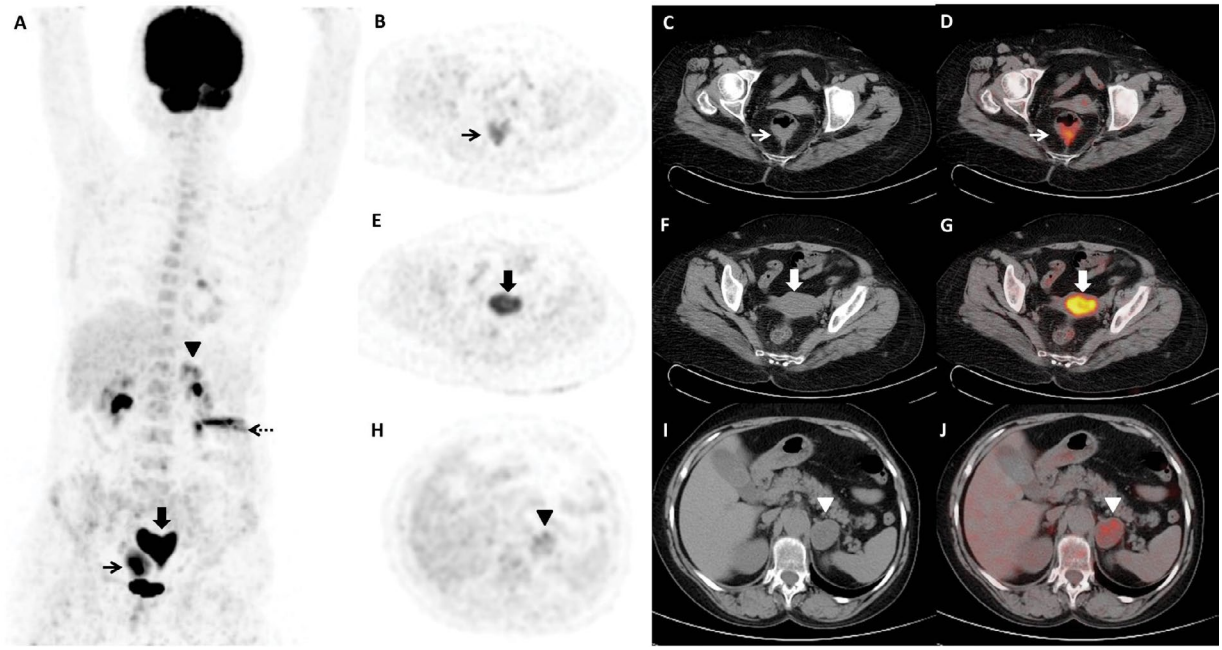

Figure 3. A preoperative PET/CT was performed on a 54-year-old case that was diagnosed with endometrioid carcinoma following an endometrial biopsy. Rectal wall thickening with increased FDG uptake (SUV_{max}: 9.8) (A–D; thin arrow) in addition to a hypermetabolic endometrial lesion (SUV_{max}: 19.6) (A, E–G; thick arrow), and a left adrenal lesion (SUV_{max}: 6.1) (A, H–J; arrow head) were noted upon PET/CT. The case was operated on, and the rectal lesion and the left adrenal lesion were diagnosed to be a primary colon adenocarcinoma and a pheochromocytoma, respectively, and the presence of three synchronous tumors in one case was noted. The increased FDG uptake, indicated by the dotted arrow (A), was caused by radiopharmaceutical contamination

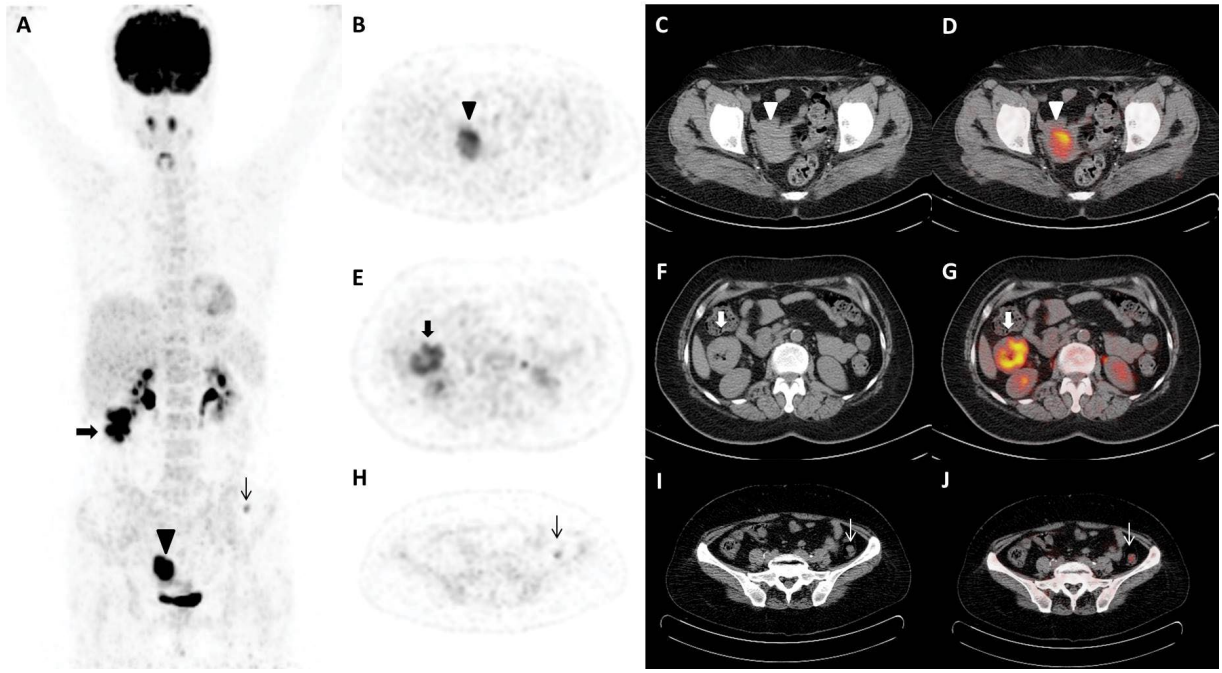

Figure 4. The preoperative PET/CT of a 62-year-old case diagnosed with a mixed endometrial carcinoma revealed an endometrial lesion with increased FDG uptake (SUV_{max}: 20.9) (A–D; arrow head), in addition to an hypermetabolic concentric wall thickness (SUV_{max}: 20.2) (A, E–G; thick arrow) in a segment of the ascending colon measuring approximately 5 cm, and a hypermetabolic polypoid lesion (SUV_{max}: 6.5) (A, H–J; thin arrow) measuring approximately 1 cm in the descending colon. A histopathological evaluation of the case that was operated on revealed a primary colonic adenocarcinoma in the ascending colonic lesion and an adenoma with low-grade dysplasia in the polypoid lesion in the descending colon

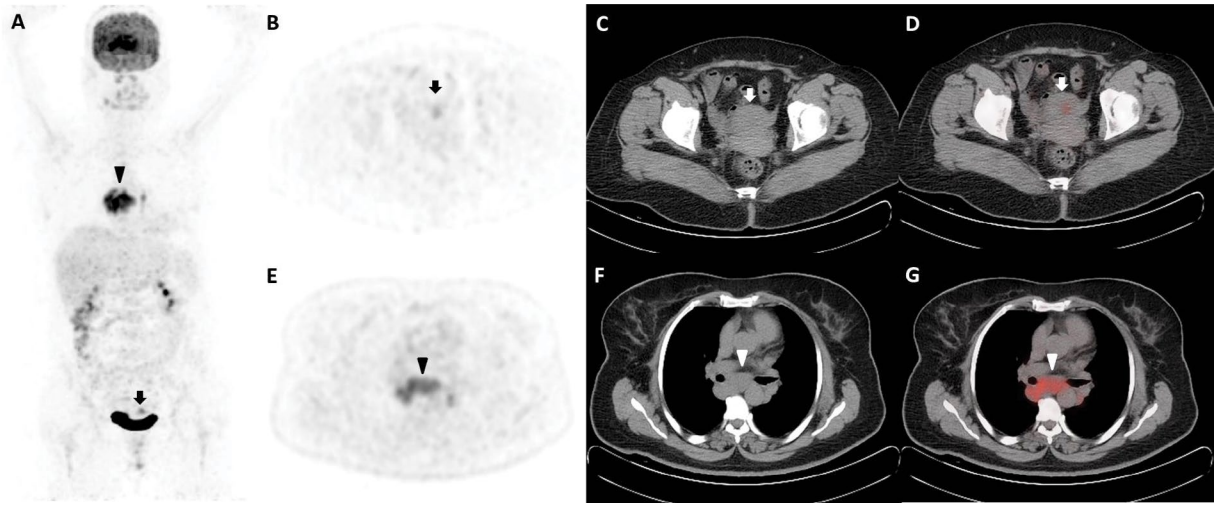

Figure 5. A preoperative PET/CT of a 48-year-old case diagnosed with endometrioid endometrial cancer revealed a slightly increased FDG uptake in the endometrium (SUV_{max}: 2.9) (A–D; arrow) and hypermetabolic multiple lymph nodes (SUV_{max}: 9.9) (A, E–G; arrow head) with no additional hypermetabolic lesion. The possibility of metastasis in the mediastinal lymph nodes was considered to be low, since the focus of the endometrial tumor seemed to be limited and there were no pathological lymph nodes in the pelvic or paraaortic regions, which are on the primary route of lymphatic dissemination of endometrial cancer. Consequently, a diagnostic biopsy of the subcarinal lymph nodes was performed. A positive mycobacterium tuberculosis growth was revealed in the culture of the biopsy material, in which a granuloma with caseification necrosis was found

non-endometrioid histology group, and grade 3 EC and p53 levels were higher in advanced stage disease. A negative correlation was found between the presence of HR and p53 and Ki-67 expression, and a positive correlation was found between p53 and Ki-67 expression. No significant relationship was found between HR, p53, ki67, CA125 levels and OS and PFS. Previous studies in literature support the findings of the present study, although there are also studies suggesting otherwise. The heterogeneous patient populations in studies may contribute to different results, and the authors also consider that different approaches to the evaluation of the immunohistochemical methods used in the studies may have contributed to the variations in results. For example, some studies used a cut-off value of < 1% to evaluate the loss of receptor, as in our study, whereas others used a cut-value off of < 10%. Furthermore, some studies have evaluated ER and PR separately, whereas the present study evaluated them in tandem. In addition, no standardized cut-off points have been described for the evaluation of pathological Ki-67 and p53 expressions, and studies have used variable cut-off points.

CONCLUSIONS

Despite the small number of patients in the present study, the findings suggest that HR positivity indicates favorable clinicopathological prognostic factors, while high Ki-67 and high p53 levels indicate unfavorable ones. **However, no direct effect of these factors on prognosis was found in this study,** and so further prospective studies involving a larger number of patients are needed to incorporate HR status, p53, Ki-67 and CA125 levels into the risk classification system.

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