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Lymph node metastasis in early stage endometrial cancer

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Summary

Objective: The aim was to investigate which criteria were most important in predicting the risk of nodal metastasis if deep myometrial invasion occupying less than half of the myometrium in patients with endometrial cancer (EC). *Materials and Methods:* Among the patients with EC who were operated in the present clinic between 2002 and 2015, and those who had less than half-depth myometrial tumour invasion were included in the study. In these patients, the relationship of pelvic lymph node metastasis (PLNM) with the criteria of age, histologic subtype, grade, tumour size, abdominal fluid cytology, cervical involvement, and lymphovascular space invasion (LVSI) was analysed. *Results:* A total of 567 patients were examined and 329 of these were analysed. Lymphadenectomy was performed in 89% of the patients, pelvic lymphadenectomy in 53% (156/294) of the patients, and both pelvic and para-aortic lymphadenectomy in 47% (138/294). PLNM was found in 7.9% of the patients (26/329). The rates of non-endometrioid histologic subtypes, LVSI, and peritoneal malignant cytology were found to be significantly higher in the patients with PLNM compared to those without PLNM ($p = 0.040$, $p = 0.001$, and $p = 0.034$). When the effects of age, subtype, tumour size, abdominal fluid, grade, and LVSI were evaluated with logistic regression analysis, it was observed that the effects of subtype and LVSI were statistically significant (OR (95%CI): 4.616 (1.085, 19.636), $p = 0.038$ and OR (95%CI): 3.530 (1.446, 8.613), $p = 0.006$, respectively). TThe other variables included in the logistic regression analysis were not statistically significant ($p > 0.05$). The specificity was 99.6% in this statistical model. Conclusion: It is considerably safe to apply a treatment plan based on the criteria of histologic subtype and LVSI in patients with less than half depth myometrial invasion.

Key words: Endometrial cancer; Deep myometrial invasion; Lymph node metastasis.

Introduction

Worldwide, endometrial cancer (EC) is the seventh most common malignancy. In developed countries, it is the fourth most common malignancy after breast, lung, and colorectal cancer [1]. Among gynaecological cancers, it is the second most common cancer after cervical cancer in developing countries, whereas it is the most common gynaecological cancer in developed countries [2]. In Turkey, it is the fourth most common cancer after breast, thyroid, and colorectal cancer, and its annual incidence is increasing. The incidence was reported to be 4.3 in 2002 and 9.3 in 2013 [3].

Patients with EC present mostly in Stage 1. Although the survival is very favourable in this stage, according to cancer statistics, the annual incidence and mortality rates are increasing [4-7]. Unclear predisposing factors, the absence of an appropriate screening test, defects in treatment or the presence of different therapeutic options may be responsible for this increase. Different approaches, including fertility-sparing treatment and leaving the ovaries in eligible patients, are also used with success, but the standard treatment in patients with EC is surgical staging [8-15]. In 1988, the International Federation of Gynecology and Obstetrics (FIGO) introduced the concept of surgical staging of EC [11]. However, this approach, and especially the therapeutic role of lymphadenectomy in early-stage EC treatment, is controversial [16]. Lymph node metastasis (LNM) is a significant risk factor in terms of the recurrence of EC. According to a study by Lurain *et al.*, the risk of recurrence increases from 8% to 48% if LNM is present [17]. FIGO categorized pelvic and para-aortic LNM separately in patients with EC in an amendment in 2009 and indicated that we should know whether the pelvic and para-aortic lymph nodes were involved to identify the stage accurately. In fact, the presence of a patient group who does not require lymphadenectomy has currently been widely accepted, although a complete consensus has not been made. In the selection of these patients, the criteria, including age, histologic subtype, grade, lymphovascular space invasion (LVSI), depth of myometrial invasion (DMI), CA-125, and tumour size, have been evaluated. Among these, DMI is a criterion that changes the stage. The other criteria for poor prognosis are also more common in patients with more than half DMI [18]. At this point, it may be thought that these criteria are dependent on the criterion of DMI, and lymphadenectomy is generally recommended if the DMI is more than half. However, it is not very clear which criterion is most important when deciding whether to perform lymphadenectomy in cases where DMI is less than half. In

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Table 1. — *Histologic subtypes in patients with a myometrial invasion depth of less than 50%.*

Histologic subtype	n	%
Endometrioid	305	93%
Serous	13	4%
Clear cell	6	1.5%
Carcinosarcoma and other	5	1.5%

Table 2. — *Demographic characteristics of patients with DMI ≤ 50% (n= 329).*

Characteristics	Min-max	Mean ± sd
Age	35-84	59.00 ± 10.10
Gravida	0-14	3.96 ± 2.54
Parity	0-14	3.10 ± 2.07
Abortus	0-8	0.86 ± 1.27
Nulliparity *n, %*	27	8.2
BMI	18.90-60.82	32.47 ± 5.98
Diabetes mellitus, *n, %*	76	23.1
Hypertension, *n, %*	143	43.5
DM + HT, *n, %*	60	18.2
Smoking, *n, %*	40	12.2
Menopause, *n, %*	192	58.4

BMI: body mass index, DM: diabetes mellitus, HT: hypertension

Stage 1, DMI is also less than half in most patients [19]. In this study, the authors investigated the criteria related with LNM in patients with EC. However, they excluded the EC patients who had more than half DMI from the study to eliminate the effect of DMI. They also investigated the relationship of histology, grade, tumour size, peritoneal cytology, LVSI, and age with LNM in patients with less than half DMI. The retrospective nature and the number of lymph nodes removed shows large variations are limitations in this trial.

Materials and Methods

The patients who were operated on in the present clinic between October 2002 and February 2015 and whose pathological result turned out to be EC were retrospectively screened from the data recorded by the present clinic. A total of 567 patients were examined. One hundred eighty-one patients with more than half DMI and 57 patients whose tumours were limited to the endometrium were excluded from the study. Three hundred twenty-nine patients who were observed to have tumour invasion in the myometrium but whose invasion depth did not exceed half of the myometrium

Table 3. — *Clinicopathological properties of the patients with less than half DMI.*

Characteristics (n=329)		n	%
Approach	Laparatomic	303	92.1
	Laparoscopic	26	7.9
Incision type	Phannenstiel	48	14.6
	Subumbilical median	127	38.6
	Sub and supraumbilical median	128	38.9
	Laparoscopic	26	7.9
Lymphadenectomy	No	35	10.6
	Yes	294	89.4
Only pelvic LND		156	47.4
Pelvic + para-aortic LND		138	41.9
Pelvic LNM		26	7.9
Pelvic and para-aortic LNM		4	1.2
Only para-aortic LNM		2	0.6
Number of pelvic nodes removed *(min-max), mean ± sd*		0-60	16.93 ± 8.65
(+) pelvic node number *(min-max), mean ± sd*		0-16	0.36 ± 1.70
Number of para-aortic nodes removed *(min-max), mean ± sd*		0-25	4.35 ± 4.75
Histologic subtype	Endometrioid	305	92.7
	Non-endometrioid	24	7.3
Grade	1	119	36.2
	2	168	51.1
	3	40	12.2
	missing	2	0.6
Tumour diameter	≤ 2 cm	150	45.6
	> 2 cm	176	53.5
	missing	3	0.9
Presence of LVSI		69	21.0
Omentectomy		160	48.6
Appendectomy		19	5.8
Omentum metastasis		6	1.8
Appendix metastasis		0	0
Positive peritoneal cytology		24	7.3

LND: lymph node dissection; LNM: lymph node metastases; LVSI: lymphovascular space invasion.

Table 4. — *Clinicopathologic characteristics of the patients with positive and negative pelvic lymph nodes.*

Clinicopathologic characteristics		Pelvic node (+) (n=26)	Pelvic node (-) (n=268)	*p* value
Histologic subtypes, *n (%)*	Endometrioid	21 (80.8)	250 (93.3)	[c]**0.040***
	Non-endometrioid	5 (19.2)	18 (6.7)	
LVSI, *n (%)*	Negative	13 (50.0)	56 (80.6)	[b]**0.001****
	Positive	13 (50.0)	212 (19.4)	
Tumour size, *n (%)*	≤2 cm	10 (38.5)	122 (45.6)	[b]0.605
	>2 cm	16 (61.5)	144 (53.7)	
	Missing	0	2 (0.7)	
Grade	1 & 2	22 (84.6)	231 (86.2)	[b]0.766
	3	4 (15.4)	36 (13.4)	
	Unknown	0	1 (0.4)	
PALND, *n (%)*		15 (57.7)	123 (45.9)	[b]0.345
PALNM, *n (%)*	Present	4 (15.4)	2 (0.7)	[b]**0.002****
	Absent	11 (42.3)	122 (45.5)	
	[†]Unknown	11 (42.3)	144 (53.7)	
No. of pelvic nodes removed, *median (Q_1-Q_3)*		14 (12.7-23.2)	16 (12-21)	[d]0.823
No. of aortic nodes removed, *median (Q_1-Q_3)*		5 (3-10)	3 (1-5)	[d]**0.021***
No. of (+) pelvic nodes, *median (Q_1-Q_3)*		2 (1-5.75)	0 (0-0)	[d]**<0.001****
Omentectomy, *n (%)*		14 (53.8)	145 (54.1)	[b]0.999
Appendectomy, *n (%)*		5 (19.2)	14 (5.2)	[c]0.018*
Omentum metastasis, *n (%)*		1 (3.8)	5 (1.9)	[c]0.429
Appendix metastasis, *n (%)*		0	0	-
Malign cells in abdominal fluid, *n (%)*		5 (19.2)	17 (6.3)	[c]**0.034***
Cervical involvement (stroma/mucosa), *n (%)*		3 (11.5)	16 (6.0)	[c]0.230

[†]Unknown cases (patients in whom PALND was not performed) are excluded from the respective analysis.
[b]Yates' continuity correction, [c]Student's t-test, [d]Mann-Whitney U-test.

Table 5. — *Classification table.*

			Estimated		
			Pelvic node		Percentage of accuracy
			-	+	
Observed	Pelvic node	-	264	1	99.6
		+	21	5	19.2
	General percentage				92.4

The cut-off value was accepted to be 0.350.

were accepted as the study group. The demographic and clinical-pathological properties of these patients were examined. The patients with pelvic lymph node metastasis (PLNM) were compared with the patients without PLNM. The criteria of histologic type, tumour size, age, tumour grade, and LVSI were subjected to multivariate analysis, and it was determined whether these criteria predicted lymph node involvement.

Results

There were 329 patients whose DMI was less than half. Endometrioid adenocarcinoma was found in 305 (93%) of the 329 patients, and non-endometrioid adenocarcinoma was found in 24 (7%) (Table 1). The demographic and clinical-pathological properties of these patients are summarized in Tables 2 and 3.

Lymphadenectomy (LND) was performed in 89.4% of the patients (n=294). While only pelvic LND was performed in 47.4% of the patients (n=156), pelvic plus para-aortic LND was performed in 41.9% (n=138). Pelvic node positivity was observed in 7.9% of the patients (n=26), whereas pelvic plus para-aortic node positivity was observed in 1.2% (n=4, four of 26 patients) and para-aortic node positivity only was observed in 0.6% (n=2).

As summarized in Table 4, there was also no statistically significant difference in terms of tumour diameter, tumour grade, para-aortic LND, the number of pelvic nodes removed, omentectomy, omentum metastasis, and cervical involvement ($p > 0.05$). In the group with PLNM, the rates of non-endometrioid subtypes and the presence of LVSI were found to be significantly higher than those in the group without PLNM ($p = 0.040$ and $p = 0.001$, respectively).

In the patients with PLNM, the rate of appendectomy and the rate of the presence of malignant cells in peritoneal cytology were found to be significantly higher ($p = 0.018$ and $p = 0.034$, respectively). The effects of age, subtype, tumour size, abdominal fluid, grade, and LVSI on pelvic node positivity were evaluated with logistic regression analysis. The model had an accuracy rate of 92.4%, a sensitivity of 19.2%, and a specificity of 99.6% (Table 5).

When the variables that were thought to affect pelvic node positivity were evaluated with logistic regression analysis, the model was found to be significant (χ^2: 17.783, $p = 0.007$). The effect of the variable of subtype on pelvic

Table 6. — *Logistic regression analysis results of factors related to pelvic node positivity.*

	β	*p*	OR	95% CI	
				Lower	Upper
Age (≥ 65)	-0.640	0.244	0.527	0.180	1.548
Subtype (non-endometrioid)	1.529	0.038*	4.616	1.085	19.636
Tumour diameter (>2 cm)	0.277	0.531	1.319	0.555	3.133
Grade (3)	-0.835	0.233	0.434	0.110	1.713
LVSI (positive)	1.261	0.006**	3.530	1.446	8.613
Positive peritoneal cytology	1.018	0.102	2.767	0.818	9.367
Constant	-1.622	0.001**	0.198		

***p < 0.01.*

Being below the age of 65 years, having an endometrioid subtype, having a tumour diameter of 2 cm or smaller, having a grade of 1 or 2, being negative for the variable of LVSI, and being negative for the variable of abdominal fluid were considered reference categories, and analyses were performed accordingly.

node positivity was statistically significant, and the rate of pelvic node positivity was 4.616-fold higher in patients with a non-endometrioid subtype compared to patients with an endometrioid subtype (OR (95%CI): 4.616 (1.085, 19.636), $p = 0.038$). It was found that the effect of LVSI positivity on pelvic node positivity was statistically significant, and the rate of pelvic node positivity was 3.530-fold higher in patients with positive LVSI compared to patients with negative LVSI [OR (95%CI): 3.530 (1.446, 8.613), $p = 0.006$). The other variables analysed were not statistically significant ($p > 0.05$) (Table 6).

Discussion

In EC, disease limited to the uterus is considered Stage 3 if LNM is present and Stage 1 if LNM is absent. The most accurate method of identifying LNM is to remove lymph nodes surgically and to examine them. Therefore, systematic lymphadenectomy is often part of the surgical staging of endometrial carcinoma. However, this procedure is not performed universally. For example, only 8.6 % of the clinicians participating in a questionnaire study stated that they performed routine para-aortic lymphadenectomy in patients with EC [20]. The decision to perform lymphadenectomy is generally made depending on the properties of the tumour.

In this study, in which the authors investigated the criteria related with LNM, they examined patients with EC with less than 50% tumour invasion in the myometrium. In this patient group, the authors found the rate of the non-endometrioid subtype to be 7.3%. This rate is lower than the rate of the non-endometrioid subtype in all endometrial cancer patients. In previous studies that included both patients with less than half DMI and more than half DMI, higher non-endometrioid histology rates were reported [21]. Non-endometrioid subtypes are observed more frequently in patient groups with more advanced myometrial invasion. In fact, the rate of lymph node metastasis is substantially elevated even if myometrial invasion is absent when non-endometrioid histology is found [22]. Non-endometrioid histology is considered to be a strong lymph node predictor, and PLND and PALND are recommended including omentectomy [23, 24]. However, some studies have not found non-endometrioid histology to be associated with lymph node involvement. In a Brazilian study, lymph node positivity was found to be related with DMI, tumour size, and grade but not with histology [21]. In the present study, the authors found the LNM rate to be 6.9 % in the endometrioid subtype (21/305) and 20.8% in the non-endometrioid subtype (5/24). The relationship between non-endometrioid histology and lymph node involvement was statistically significant ($p = 0.04$).

Another criterion for which a relationship with lymph node involvement was investigated was peritoneal cytology. FIGO excluded peritoneal cytology as a criterion for changing the grade in 2009 but recommends that the evaluation of peritoneal cytology should be continued. In fact, there is no consensus on this subject. In a large study conducted by Garg *et al.* in 2013 with 14,704 patients obtained from the SEER database, peritoneal cytology was indicated to be an independent prognostic criterion, especially in Stage 1 and 2 patients [25]. The rate of peritoneal malignant cytology was found to be 7.3% in the present patient group. In univariate analysis, the rate of peritoneal malignant cytology was found to be significantly higher in patients with PLNM compared to patients without PLNM (19.2% versus 6.3%, $p = 0.034$).

The other well-known prognostic factors include grade and DMI. The relationship of these criteria with survival was shown in a study conducted by Keller *et al.* 40 years ago [26]. In 1987, Gynaecologic Oncology Group (GOG) investigated the relationship between grade, DMI, and LNM in a multicentric prospective study including 621 patients. They found the risk of general pelvic node metastasis to be 9% in patients with Stage 1 EC and found no pelvic node metastasis in patients with grade 1 EC who had no myometrial invasion [19]. Actually, it is a disadvantage multicentric study on account of the number of lymph

nodes removed which shows large variations. In 2000, the issue was further clarified with a study conducted by the Mayo Clinic; the authors found no LNM in the patient group with EC when the tumour size was less than 2 cm, the grade was 1-2, and myometrial invasion was less than half. They proposed that only hysterectomy might be sufficient if no metastatic tumours were found intraoperatively [27]. However, lymphadenectomy was performed in 57 % of patients in their trial.

In the present study, the DMI was less than half in all of the patients. The proportion of grade 3 patients was 12.2% in this patient group. In this study, the authors observed that the criterion of grade was not significantly correlated with LNM. The proportion of the patients with a tumour size of 2 cm and above was higher in the group with LNM (54.1% *vs*. 61.5%), but the difference was not statistically significant. In the patient groups with more than half DMI, the proportions of the patients with high grade and a tumour size above 2 cm were higher. In the present study design, the authors excluded the patient group with a DMI of more than half. Thus, the criteria of grade and tumour size were not found to be significantly related with LNM in the group of patients with a DMI of less than half.

In the present study, the criteria of non-endometrioid histology, LVSI, and peritoneal malignant cytology were found to be correlated with LNM even if the DMI was less than 50%. The criteria of grade and tumour size were not found to be correlated with LNM. Among the variables the present authors included in multivariate analysis, including subtype, grade, size, peritoneal cytology and LVSI, histology, and LVSI were found to be significantly correlated with LNM. In this statistical model, the specificity was found to be very high (99.6%). In a similar study conducted with a patient group that was heterogeneous in terms of DMI, Bendifallah *et al.* examined the factors related to lymph node metastasis in patients with EC and found that only histology and LVSI were significant among the parameters, including age, histology, grade, tumour diameter, myometrial invasion, and LVSI, in multivariate analysis. However, all parameters were significant except for age in univariate analysis [28].

In different guidelines, risk categories based on DMI, grade, and histology have been established with the objective of convenience in therapeutic approach, and recommendations according to these categories have been made. As a result of these recommendations, therapeutic approaches in clinics have been changed, and lymphadenectomy has started to be abandoned in low- and intermediate-risk group patients. According to a study conducted by Arsene *et al.*, the rate of lymphadenectomy in this patient group was previously 88% but decreased to 19% after the 2010 recommendation of the European Society for Medical Oncology (ESMO). However, the requirement for a second operation increased significantly [19]. The ESMO defined the risk groups based on subtype, DMI and grade in their 2010 guidelines as follows: low risk: Stage IA (G1 and G2) with endometrioid type; intermediate risk: Stage IA (G3) with endometrioid type and Stage IB (G1 and G2) with endometrioid type; high risk: Stage IB (G3) with endometrioid type and all stages with non-endometrioid type. ESMO stated that systematic lymphadenectomy might not be performed in low- and intermediate-risk groups [23,2 4].

Two multi-centric, randomized-controlled studies conducted in 2009 paved the way for these amendments. In these studies, the investigators examined a total of 1,922 patients with Stage 1 EC in two groups, including those who underwent systematic pelvic lymphadenectomy and those who did not undergo the procedure, and showed that lymphadenectomy had no contribution to the overall and recurrence-free survival of the patients [29, 30].

There are numerous studies with different results related to the criteria that should be considered in the selection of patients who do not require lymphadenectomy. According to the present study, the most important criteria in the selection of patients who do not require lymphadenectomy when the DMI was < 50% included the histologic subtype, LVSI, and peritoneal cytology. These criteria can be used with high reliability in intraoperative assessment and in the decision to perform complementary surgery in patients who have undergone incomplete surgery.

If staging surgery is not considered, reliable preoperative assessment and frozen section examination is critical in order to identify the risk groups clearly and to not miss patients with extrauterine invasion. In the literature, the rates of extrauterine metastasis have been reported to range between 3% and 46% in patients who are clinically thought to be Stage 1 [18, 31]. In addition, different rates have been reported in relation to the compatibility of frozen section examination with final pathology reports [32-38]. At this point, some study authors recommend comprehensive surgical staging to all patients with EC because of the presence of a certain error rate [38].

In the SEPAL study published in 2010, the survival rate was found to be more favourable in patients with intermediate- and high-risk EC who underwent pelvic and para-aortic lymphadenectomy. Here, isolated para-aortic lymph node involvement may be considered. In this study, aggressive surgery is recommended, especially in the high-risk group [39]. Isolated para-aortic lymph node involvement has been mentioned frequently in recent studies. The rate has been reported to be approximately 1% in low-risk patients and 16% in intermediate- and high-risk patients [40-43]. In the present study, isolated para-aortic lymph node involvement was found in two (1.4%) of 138 patients who had a DMI of less than 50% and underwent pelvic and para-aortic lymphadenectomy. However, all limitations of retrospective studies are present in these trials and in this trial. For example, which criteria were used to indicate additional para-aortic lymphadenectomy? Another

point, the number of lymph nodes removed shows large variations. In light of the literature, the present authors believe that both arguments are applicable with valid justifications. If the risk groups have been identified clearly and it is thought that staging surgery, which should be performed by a more experienced team, is not required, the patients can be treated without delay in general hospitals without referral to gynaecologic oncology centres. This approach may prevent the negative effect of a delay. On the other hand, staging surgery may be considered in all patients with EC because of the margin of error of preoperative assessments and frozen section examination and because of the potential therapeutic effect of lymphadenectomy. The option of not performing lymphadenectomy in low- and intermediate-risk patients may be limited by technical defects, comorbidities, and the surgeon's subjective opinion. Otherwise, lymphadenectomy may be considered as an option in all patients except for those for whom lymphadenectomy is not possible.

References

[1] Amant F., Moerman P., Neven P., Timmerman D., Van Limbergen E., Vergote I.: "Endometrial cancer". *Lancet*, 2005, *366*, 491.

[2] Siegel R., Naishadham D., Jemal A.: "Cancer statistics, 2013". *CA Cancer J. Clin.*, 2013, *63*, 11.

[3] "The Ministry of Health of Turkey Health Statistics Yearbook 2013". Mehmet Rifat Köse, Berrak Bora Başara, Cemil Güler, Gökalp Kadri Yentür: General Directorate of Health Research, Ministry of Health. Ankara, 2014. Available at: http://www.sagem.gov.tr

[4] Creutzberg C.L., van Putten W.L., Koper P.C., Lybeert M.L., Jobsen J.J., Wárlám-Rodenhuis C.C., et al.: "Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma". *Lancet*, 2000, *355*, 1404.

[5] Papanikolaou A., Kalogiannidis I., Goutzioulis M., Misailidou D., Makedos A., Vergote I., Makedos G.: "Pelvic lymphadenectomy as alternative to postoperative radiotherapy in high risk early stage endometrial cancer". *Arch. Gynecol. Obstet.*, 2006, *274*, 91.

[6] American Cancer Society. Available at: www.cancer.org/docroot/home/index.asp.

[7] Jemal A., Siegel R., Ward E., Hao Y., Xu J., Murray T., Thun M.J." Cancer statistics, 2008". *CA Cancer J. Clin.*, 2008, *58*, 71.

[8] Erkanli S., Ayhan A.: "Fertility-sparing therapy in young women with endometrial cancer: 2010 update". *Int. J. Gynecol. Cancer*, 2010, *20*, 1170.

[9] Tangjitgamol S., Manusirivithaya S., Hanprasertpong J.: "Fertility-sparing in endometrial cancer". *Gynecol. Obstet. Invest.*, 2009, *67*, 250.

[10] Chiva L., Lapuente F., González-Cortijo L., Carballo N., García J.F., Rojo A., Gonzalez-Martín A.: "Sparing fertility in young patients with endometrial cancer". *Gynecol. Oncol.*, 2008, *111*, 101.

[11] Creasman W.T., Odicino F., Maisonneuve P., Quinn M.A., Beller U., Benedet J.L., et al.: "Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer". *Int. J. Gynaecol. Obstet.*, 2006, *95*, 105.

[12] American College of Obstetricians and Gynecologists: "ACOG practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, 2005: Management of endometrial cancer". *Obstet. Gynecol.*, 2005, *106*, 413.

[13] Lee T.S., Jung J.Y., Kim J.W., Park N.H., Song Y.S., Kang S.B., Lee H.P.: "Feasibility of ovarian preservation in patients with early stage endometrial carcinoma". *Gynecol. Oncol.*, 2007, *104*, 52.

[14] Lee T.S., Kim J.W., Kim T.J., Cho C.H., Ryu S.Y., Ryu H.S., *et al.*: Korean Gynecologic Oncology Group. Ovarian preservation during the surgical treatment of early stage endometrial cancer: a nationwide study conducted by the Korean Gynecologic Oncology Group". *Gynecol. Oncol.*, 2009, *115*, 26.

[15] Wright J.D., Buck A.M., Shah M., Burke W.M., Schiff P.B., Herzog T.J.: "Safety of ovarian preservation in premenopausal women with endometrial cancer". *J. Clin. Oncol.*, 2009, *27*, 1214.

[16] Todo Y., Sakuragi N.: "Systematic lymphadenectomy in endometrial cancer". *J. Obstet. Gynaecol. Res.*, 2013, *39*, 471.

[17] Lurain J.R., Rice B.L., Rademaker A.W., Poggensee L.E., Schink J.C., Miller D.S.: "Prognostic factors associated with recurrence in clinical stage I adenocarcinoma of the endometrium". *Obstet. Gynecol.*, 1991, *78*, 63.

[18] Arsène E., Bleu G., Merlot B., Boulanger L., Vinatier D., Kerdraon O., *et al.*: "Implications of a two-step procedure in surgical management of patients with early-stage endometrioid endometrial cancer". *J. Gynecol. Oncol.*, 2015, *26*, 125.

[19] Creasman W.T., Morrow C.P., Bundy B.N., Homesley H.D., Graham J.E., Heller P.B.: "Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study". *Cancer*, 1987, *60*, 2035.

[20] Watanabe Y., Aoki D., Kitagawa R., Takeuchi S., Sagae S., Sakuragi N., *et al.*: "Disease Committee of Uterine Endometrial Cancer, Japanese Gynecologic Oncology Group. Status of surgical treatment procedures for endometrial cancer in Japan: results of a Japanese Gynecologic Oncology Group survey". *Gynecol. Oncol.*, 2007, *105*, 325.

[21] Anton C., di Fávero G.M., Köhler C., Carvalho F.M., Baracat E.C., Carvalho J.P.: "Surgical treatment of endometrial cancer in developing countries: reasons to consider systematic two-step surgical treatment". *Clinics (Sao Paulo)*, 2015, *70*, 470.

[22] Goff B.A., Kato D., Schmidt R.A., Ek M., Ferry J.A., Muntz H.G., *et al.*: "Uterine papillary serous carcinoma: patterns of metastatic spread". *Gynecol. Oncol.*, 1994, *54*, 264.

[23] Colombo N., Preti E., Landoni F., Carinelli S., Colombo A., Marini C., Sessa C.: "ESMO Guidelines Working Group. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up". *Ann. Oncol.*, 2013, *24*, vi33.

[24] Pecorelli S.: "Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium". *Int. J. Gynaecol. Obstet.*, 2009, *105*, 103.

[25] Garg G., Gao F., Wright J.D., Hagemann A.R., Mutch D.G., Powell M.A.: "Positive peritoneal cytology is an independent risk-factor in early stage endometrial cancer". *Gynecol. Oncol.*, 2013, *128*, 77.

[26] Keller D., Kempson R.L., Levine G., McLennan C.: "Management of the patient with early endometrial carcinoma". *Cancer*, 1974, *33*, 1108.

[27] Mariani A., Webb M.J., Keeney G.L., Haddock M.G., Calori G., Podratz K.C.: "Low-risk corpus cancer: is lymphadenectomy or radiotherapy necessary?" *Am. J. Obstet. Gynecol.*, 2000, *182*, 1506.

[28] Bendifallah S., Canlorbe G., Arsène E., Collinet P., Huguet F., Coutant C., *et al.*: "French multicenter study evaluating the risk of lymph node metastases in early-stage endometrial cancer: contribution of a risk scoring system". *Ann. Surg. Oncol.*, 2015, *22*, 2722.

[29] Benedetti Panici P., Basile S., Maneschi F., Alberto Lissoni A., Signorelli M., Scambia G., *et al.*: "Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial". *J. Natl. Cancer Inst.*, 2008, *100*, 1707.

[30] ASTEC Study Group, Kitchener H., Swart A.M., Qian Q., Amos C., Parmar M.K.: "Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study". *Lancet*, 2009, *373*, 125.

[31] Fujiwara H., Saga Y., Takahashi K., Ohwada M., Enomoto A., Konno R., et al.: "Omental metastases in clinical stage I endometrioid adenocarcinoma". *Int. J. Gynecol. Cancer*, 2008, *18*, 165.

[32] Valsecchi L., Mangili G., Frigerio L., Spagnolo D.L., De Sanctis L., Ferrari A.: "Reliability of preoperative evaluation of prognostic factors

in endometrial carcinoma". *Int. J. Gynaecol. Obstet.*, 1997, *59*, 35.
[33] Kumar S., Bandyopadhyay S., Semaan A., Shah J.P., Mahdi H., Morris R., et al.: "The role of frozen section in surgical staging of low risk endometrial cancer". *PLoS One*, 2011, *6*, e21912.
[34] Kumar S., Medeiros F., Dowdy S.C., Keeney G.L., Bakkum-Gamez J.N., Podratz K.C., *et al.*: "A prospective assessment of the reliability of frozen section to direct intraoperative decision making in endometrial cancer". *Gynecol. Oncol.*, 2012, *127*, 525.
[35] Quinlivan J.A., Petersen R.W., Nicklin J.L.: "Accuracy of frozen section for the operative management of endometrial cancer". *BJOG*, *108*, 798.
[36] Kayikçioğlu F., Boran N., Meydanli M.M., Tulunay G., Köse F.M., Bülbül D.: "Is frozen-section diagnosis a reliable guide in surgical treatment of stage I endometrial carcinoma?" *Acta Oncol.*, 2002, *41*, 444.
[37] Turan T., Oguz E., Unlubilgin E., Tulunay G., Boran N., Demir O.F., et al.: "Accuracy of frozen-section examination for myometrial invasion and grade in endometrial cancer". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2013, *167*, 90.
[38] Case A.S., Rocconi R.P., Straughn J.M. Jr., Conner M., Novak L., Wang W., et al.: "A prospective blinded evaluation of the accuracy of frozen section for the surgical management of endometrial cancer". *Obstet. Gynecol.*, 2006, *108*, 1375.
[39] Todo Y., Kato H., Kaneuchi M., Watari H., Takeda M., Sakuragi N.: "Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis". *Lancet*, 2010, *375*, 1165.
[40] Abu-Rustum N.R., Gomez J.D., Alektiar K.M., Soslow R.A., Hensley M.L., Leitao M.M. Jr., *et al.*: "The incidence of isolated paraaortic nodal metastasis in surgically staged endometrial cancer patients with negative pelvic lymph nodes". *Gynecol. Oncol.*, 2009, *115*, 236.
[41] Kumar S., Podratz K.C., Bakkum-Gamez J.N., Dowdy S.C., Weaver A.L., McGree M.E., *et al.*: "Prospective assessment of the prevalence of pelvic, paraaortic and high paraaortic lymph node metastasis in endometrial cancer". *Gynecol. Oncol.*, 2014, *132*, 38.
[42] Chiang A.J., Yu K.J., Chao K.C., Teng N.N.: "The incidence of isolated para-aortic nodal metastasis in completely staged endometrial cancer patients". *Gynecol. Oncol.*, 2011, *121*, 122.
[43] Mariani A., Dowdy S.C., Cliby W.A., Gostout B.S., Jones M.B., Wilson T.O., *et al.*: "Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging". *Gynecol. Oncol.*, 2008, *109*, 11.

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