Prognostic factors determining recurrence in early-stage endometrial cancer

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Summary

Objective: This study aimed to determine the clinically important prognostic factors for loco-regional or distant recurrence in early-stage endometrial cancer. *Materials and Methods:* This study complied with the Declaration of Helsinki, and the local ethics committee approved the study. Cases who underwent primary surgery of early-stage endometrial cancer at the Institution from 2000 to 2012 were reviewed retrospectively. Patients who did not detect recurrence were classified as group 1 (n = 200); those who detected recurrence were classified as group 2 (n = 23). Clinically prognostic factors were evaluated by univariate analyses. *Results:* The average age for group 2 (LUSI) was 63.8 years (p = 0.0001). Patients with grade 3 histology were all detected within group 2 (p = 0.0001). Endometrioid adenocarcinoma displaying squamous differentiation was found with a rate of 58.3% in group 2 (p = 0.0001). Lower uterine segment involvement (LUSI) and lymphovascular space invasion (LVSI) rates were 86.9% in group 2 (p = 0.0001). The rate of tumor size > 2 cm was 56.6% in group 2 (p = 0.0001). The median depth of myometrial invasion (DMI) was 5.1 mm (p = 0.034) and the average in myometrial thickness was 14.5 mm in group II (p = 0.0001). The percentage of myometrial invasion was 35.8% in Group II (p = 0.0001). Tumor free-distance was 9.4 mm in group II (p = 0.0001). *Conclusion:* Age and clinicopathological parameters of the tumours are significant predictors for recurrence in early-stage endometrial cancer.

Key words: Early-stage endometrial cancer; Prognostic factors; Recurrence.

Introduction

Endometrial cancer is the most common gynecologic malignancy accounting for approximately 43,470 new cancer diagnoses in the United States in 2010 and around the world there are over 198,000 new cases of endometrial cancer per year, and over 50,000 deaths [1, 2]. Although one in 40 women will be diagnosed with uterine cancer in their lifetime, endometrial cancer is one of the most treatable gynecologic malignancies as it often presents early in natural course [3]. Once a diagnosis is made, the cornerstone of management is surgery, consisting of total hysterectomy, bilateral salpingo-oophorectomy, with or without pelvic and para-aortic lymphadenectomy, to determine the Stage of the disease and guide adjuvant treatment [4]. An estimated 90% of patients with endometrial cancer will present symptoms of abnormal or post-menopausal bleeding that allows for early detection. Thus, over 75% of cases are confined to the uterus at the time of diagnosis, resulting in high rates of overall survival. As the majority of patients are diagnosed with Stage I disease, the risk of recurrence within this group is relatively low, ranging from 2-15% [5]. Furthermore, a subset of patients within this group, those with low-grade histology and disease confined to the endometrium, have an even lower rate of recurrence. However, recurrence develops in 40-60% of patients who had metastases to the adnexa or lymph nodes [6]. Therefore, after initial treatment, outpatient follow-up is necessary to detect subclinical recurrence, which may be curable by salvage therapy. For these reasons, endometrial cancer patients make up a large proportion of the patient population routinely followed by gynecologic oncologists.

There is a group of factors which are effective in the determination of the prognosis to consider during post-operative patients' evaluation. These prognostic factors can be summarized as age, histological grade, histopathological type, LUSI, LVSI, tumor size, tumor free-distance (TFD), depth of myometrial invasion (DMI), myometrial thickness (MT), and percentage of myometrial invasion (MIP) [4-7]. To further improve treatment and follow-up for uterine corpus cancers, a number of molecular markers have been extensively studied. DNA ploidy, hormone receptors, p53, bcl-2, and proliferation markers have already been shown with consistent results to be prognostic factors through retrospective studies [4]. Post-operative evaluation of early-stage endometrial cancers in terms of clinicopathological prognostic factors is to determine the patients who carry the risk of recurrent disease and likely to benefit from adjuvant treatment, consisting in modalities such as radiation, chemotherapy, and hormonal therapy.

The goal of this study was to evaluate clinicopathologic parameters associated with development of recurrence in early-stage endometrial carcinoma by drawing on 12 years of experience at a single institution.

Materials and Methods

All patients who underwent primary surgical staging for endometrial cancer at the Gynecologic Oncology Unit at the Çukurova University Medical Faculty from January 2000 to December 2011 were identified retrospectively. Inclusion criteria were then based on surgical pathological staging system

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which had been accepted by International Federation of Gynecology and Obstetric (FIGO) for endometrial cancer in 1988 and revised in 2009. Patients categorized in the former classification as Stage IA, IB, and IA in the current classification were included to this study. Of those patients, 223 underwent a primary surgery with a total hysterectomy and bilateral salpingo-ophorectomy and peritoneal cytology with or without pelvic and/or para-aortic lymphadenectomy at the Institution. Patients previously provided curative treatment through surgery was not given adjuvant treatment. With reference to the complaints of the patients developing recurrence, they were mainly vaginal bleeding, abdominal pain, and difficulty in breathing. Disease-relapse was diagnosed when physical examination with cytological or pathological examination, and systemic enhanced computed tomography (CT) indicated recurrent or metastatic tumors during the follow-up period. In 2005, positron emission tomography (PET), with or without CT scan, was performed instead of a routine CT scan in some patients. The histopathologic types of lesions were defined through the tissue biopsies obtained in accordance to the location of the re-laparotomy and lesion under office conditions. These recurrences were classified as isolated vaginal, pelvic, and extra-pelvic. Pelvic relapse was assumed as all of the tumors throughout the actual pelvis not isolated to vagina and pelvic node involvement. Extra-pelvic involvement, on the contrary, was defined as positive para-aortic nodes, abdominal masses, and distant metastasis. Distant recurrence was defined as any metastasis outside the abdominal or pelvic compartment. None of the patients developing recurrence received adjuvant treatment after primary surgery. Seventy-nine percent (n = 176) of these patients were subject to total abdominal hysterectomy and bilateral salpingo-oophorectomy, and 21% (n = 47) were subject to laparoscopic procedure. Pelvic and para-aortic lymphadenectomy was applied in cases in which endometrial sampling and preoperative frozen inspection was high-grade and there was non-endometrioid histology. Similar to ovarian cancers, omentectomy was performed in cases with clear cell and serous papillary differentiation within the tumor. Among these, those whose lymph node was negative and tumors limited to the uterus were included to this study. Microscopic histopathologic characteristics of surgical specimens were evaluated by an experienced gynecopathologists at our medical faculty. Patients with clear cell and serous papillary within the tumor were all considered to have grade 3 tumors. DMI was measured between the endomyometrial junction and the maximal MI. TFD was calculated by subtracting the DMI from MT. MI was derived by dividing DMI by MT and expressed as a percentage of MT. LUSI was defined as the transition area between corpus and cervix. The size of the tumor was defined as < 2 cm and > 2 cm to be measured on the vertical axes.

The clinico-pathological factors analyzed include the age at diagnosis, DMI, MT, MIP, TFD, histological grade and type, lymphovascular space invasion, LUSI and tumor size.

The study was carried out in accordance with the Helsinki Declaration, and the Ethical Committee of the Çukurova University Faculty of Medicine. Informed consent was obtained from all of the participants.

Statistical methodology included analysis of data SPSS 15.0 Evaluation Version (Statistical Package for Social Sciences Chicago, IL, USA) software was used. Categorical measurement was summarized as numbers and percentages; permanent measurement was summarized as mean and standard deviation (where necessary median and minimum-maximum). Chi-square test statistics method was used for the comparison of categorical variables. Mann Whitney U test statistics was used for the comparison of continious measurement between groups. Odds ratio was calculated for risk measurement. A p value of < 0.05 was considered statistically significance among the results.

Table 1. — *Histopathological subtypes distribution of 223 early-stage endometrial carcinomas at initial diagnosis*.

	Group 1 n (%)	Group 2 n (%)	OR (95% CI)	p value
Endometrioid adenocarcinoma, with squamous differentiation	26 (13.0)	14 (58.3)	9.3 (3.77-23.28)	0.0001
Endometrioid adenocarcinoma	196 (98.0)	23 (100)	0.4 (0.05-4.38)	0.436
Mucinous adenocarcinoma	31 (15.5)	0 (0.0)	0.8 (0.83-0.92)	0.023
Uterine serous papillary carcinoma	0 (0.0)	2 (8.3)	0.1 (0.06-0.14)	0.011
Clear cell adenocarcinoma	0 (0.0)	4 (16.7)	0.1 (0.06-0.14)	0.0001

OR: odds ratio, CI: confidence interval, Group 1: non-recurrent, Group 2: recurrent. A p value < 0.05 was considered statistically significant.

Results

The clinicopathological variables of 223 women with early-stage endometrial cancer (FIGO 1988: Stage 1A and 1B; FIGO 2009: Stage 1A) were analyzed. Histopathological subtypes of the studied cases are shown the Table 1. Patients who did not detect recurrence were classified as group 1 (n = 200); those who detected recurrence were classified as group 2 (n = 23). The median age at initial treatment and recurrence was 56.0 years (range, 32-79 years) and 63.8 years (range 55-80 years), respectively. Women aged over 60 years were considered an unfavourable factor for the development of recurrence (p = 0.0001) (Table 2).

The mean follow-up time determined was 44.6 months (range 24-60 months). Eighteen (78.2%) recurrences were symptomatic: the most frequent symptom was vaginal bleeding, which was noted in fifteen patients, followed by abdominal pain in two and cough in one. Five (21.8%) recurrences were asymptomatic within this period. In fifteen (65.3%) women recurrence was vagnally-isolated, in seven (30.4%) women it was pelvic relapse, and one woman (4.3%) developed extrapelvic metastasis (lung). Isolated vaginal recurrence was the most commonly detected in group II (p = 0.0001). Table 2 shows the number of women by site of recurrence (Table 2).

Endometrioid adenocarcinoma with squamous differentiation was found in 14 cases (58.3%) within the recurrence group. In endometrioid adencarcinomas, it was found that the existence of squamous differentiation increased the risk of recurrence development by 9.3 times in univariate analysis (OR = 9.3, 95% CI 3.77, 23.28; p = 0.0001). In this study, mucinous adenocarcinomas within the group displaying recurrence were not found. Although the p value = 0.023, it was not significantly important because there were only four cases within the group not displaying recurrence. Within the group not displaying recurrence, it was found that four cases consisted in clear cell component (16.7%) and two cases consisted in uterine papillary serous component (8.3%).

Table 2. — *Clinicopathological and demographic characteristics of endometrial carcinomas*.

	Group 1 n (%)	Group 2 n (%)	*p* value
Grade			
1	127 (63.5)	0 (0.0)	
2	73 (36.5)	18 (78.2)	
3	0 (0.0)	5 (21.8)	0.0001
Site of recurrence			
Non-recurrence	200 (100.0)	0 (0.0)	
Isolated vaginal	0 (0.0)	15 (65.4)	
Pelvic	0 (0.0)	7 (30.4)	
Extra pelvic	0 (0.0)	1 (4.3)	0.0001
Age			
< 50	36 (18.0)	0 (0.0)	
50-60	117 (58.5)	6 (26.0)	
> 60	47 (23.5)	17 (74.0)	0.0001

Group 1: non-recurrent, Group 2: recurrent. A p value < 0.05 was considered statistically significant.

Table 3. — *Odds ratios for LUSI, LVSI, and tumor size in predicting the risks for recurrent endometrial carcinoma*.

	Group 1 n (%)	Group 2 n (%)	OR (95% CI) *p* value
LUSI			
–	180 (90.0)	3 (13.04)	45.0 (13.9-144.8)
+	20 (10.0)	20 (86.96)	0.0001
LVSI			
–	167 (83.5)	3 (13.04)	25.3 (8.1-78.8)
+	33 (16.5)	20 (86.96)	0.0001
Tumor size			
≤ 2 cm	173 (86.5)	10 (43.4)	6,4 (2.6-15.7)
> 2 cm	27 (13.5)	13 (56.6)	0.0001

OR: odds ratio, CI: confidence interval, LVSI: lympho-vascular space invasion, LUSI: lower uterine segment involvement. A p value < 0.05 was considered statistically significant.

Although the p value was < 0.05, the inadequacy of cases prevented a statistically significant evaluation (Table 1).

While there were no cases displaying grade 1 histology within the group with recurrence in this study, all of the cases with grade 3 histology were found in the developing recurrence group. Grade 2 histology was most commonly detected in the recurrence group (n = 18, 78.2%, p = 0.0001) (Table 2).

Considering this data, while LUSI was found in 86.9% of the group with recurrence, it was indicated by the univariate analysis that the presence of LUSI increased the risk of recurrence by 45 times (OR = 45.0, 95% CI 13.9, 23.28; p = 0.0001). In this study, LVSI was not classified as strong and mid-level. LUSI was observed as accompanying every recurrent case with LVSI in the univariate analysis of this study, and it was indicated that the risk for recurrence development was multiplied 25 times in the presence of LVSI (OR 25.3, 95% CI 8.1, 78.8; p = 0.0001). Tumor sizes were examined under two groups which were ≤ 2 cm and > 2 cm. Considering cases with recurrence, 43.4% were found with a tumor size ≤ 2 cm; 56.6% was found with a tumor size > 2 cm. In the univariate analysis conducted, it indicated that tumor sizes over 2 cm increased the risk for recurrence development 6.4 times (OR 6.4, 95% CI 2.6, 15.7; p = 0.0001) (LVSI, LUSI and tumor size values are shown in Table 3). TFD, DMI and MIP definitions in this study are similar to the above-mentioned publications. Examining the data in this study, while DMI was 4.2 mm, TFD was 15.0 mm, MT was 20.3 mm, and MIP was 20.9 in the group without recurrence, the numeric values found for the group with recurrence were as follows; DMI 5.1 mm (p = 0.034), TFD 9.4 mm, MT 14.5 mm, and MIP 35.8 (p = 0.0001) (Table 4).

Table 4. — *Correlation of clinicopathological variables and disease recurrence in early-stage endometrial adenocarcinomas*.

	Group 1		Group 2		*p*
	Mean (± SD)	Med (Min-Max)	Mean (± SD)	Med (Min-Max)	
Age	56.4 ± 8.5	56.0 (32.0-79.0)	63.8 ± 5.5	63.8 (55.0-80.0)	0.0001
DMI	4.2 ± 3.2	4.0 (0.0-15.0)	5.1 ± 2.0	5.0 (0.0-9.0)	0.034
MT	20.3 ± 4.8	20.0 (8.0-38.0)	14.5 ± 3.3	15.0 (9.0-20.0)	0.0001
MIP	20.9 ± 14.8	21.3 (0.0-49.0)	35.8 ± 11.2	40.0 (0.0-47.0)	0.0001
TFD	16.1 ± 5.4	15.0 (5.0-36.0)	9.4 ± 3.3	9 (5.0-36.0)	0.0001

Values are presented as number (%) or median (range). A p value < 0.05 was considered statistically significant. DMI: depth of myometrial invasion. MT: myometrial thickness. MIP: myometrial invasion percentage. TFD: tumor-free distance. Min: minimum. Max: maximum.

Discussion

Most uterine corpus cancers are diagnosed at an early stage and have a favorable prognosis. However, a substantial number of patients undergo disease recurrence after primary treatment [4]. As endometrial cancer is the most common gynecologic malignancy and boasts high survival rates due to early detection, it is not surprising that over ten percent of all female cancer survivors are from this condition alone [5]. In a meta-analysis by Fung-Kee-Fung *et al*. recurrence rates for patients with early-stage, low-risk endometrial cancer have been detected in less than 5% [8]. This investigation found a recurrence rate of approximately 10.31%, which is consistent with that found in the literature for all endometrial cancers [range, 6%-25%] [9-11].

In the present study, the authors analysed factors predictive of pelvic or distant recurrence in a set of 223 patients with FIGO-1988 Stage 1A and 1B, FIGO-2009 Stage 1A, early-stage endometrial carcinoma. The strengths of this study are the sample size and the fact that all patients were staged by histopathology. More than 80% of the recurrences in this study appeared within two years of diagnosis, which concurs with other studies that report a 70%-80% rate within three years [12-14]. Although these values show similarities with the literature, cases in this study were not subjected to risk grouping (low-, middle-, and high-risk). Therefore, it is not possible to integrate the available data according to a certain risk group.

Many studies have described the factors that influence

recurrence risk and prognosis in uterine carcinoma. These studies have identified prognostic variables such as age, stage at initial diagnosis, histologic grade, DMI, and lymph node status as being associated with recurrence risk [10, 11, 15-18]. Numerous studies have highlighted grade according to this setting. Morrow *et al*. demonstrated that in patients with Stage I or II endometrial carcinoma, the greatest determinant of recurrence was grade 3 histology with a relative risk of 15 [18]. Creutzberg *et al*. also described high-risk patients in early-stage endometrial cancer as those with two out of the three following risk factors: older than 60 years, greater than 50% MI, and grade 3 histology [16]. Mariani *et al*. showed that MI greater than 66% was a significant predictor of distant failure and death in Stage I endometrial cancer patients [11]. Mundt *et al*. performed a large study including 455 patients with endometrial cancer. They showed that age was significant in a univariate analysis, but was not proven a significant prognostic factor in a multivariate analysis. They suggested that higher rates of recurrence and poorer survival rates reported in the elderly are more likely the result of imbalances in pathological factors and less aggressive therapy [19]. Several studies have also found age to be an independent prognostic factor [14, 20, 21]. Although in this present study cases were not evaluated in terms of prognosis and survival, a significantly important relationship was found between high-grades and recurrences. Furthermore, the average age for recurrent group found was 63.8; this value is statistically significant and compatible to the literature. The very often observation of LUSI and the differences in the definition of histology prevents to come up with a definite conclusion. Lavie *et al*. have reported that LUSI was significantly associated with grade 3 tumor, deep MI, and the presence of capillary space-like involvement [22]. Gemer *et al*. showed in patients with apparent Stage I endometroid endometrial cancer, the presence of LUSI was a poor prognostic factor, associated with a significantly higher risk of distal recurrence and death [23]. It is not possible to comment exactly on whether LUSI is an independent prognostic factors or not. However, data on hand shows that there is a significantly important correlation between this parameter and recurrence. LVSI was a predictor of nodal disease and an independent prognostic factor for relapse of disease in all stages of endometrial cancer [24]. In this study, however, the grading of LVSI was not classified as severe or mild. The presence of LVSI was significantly related to poor histological grade and deep MI. The data in the present study demonstrated a strong recurrent rate in patients with LVSI-positive tumors. These results are similar to the previous studies of Briët *et al*. and Cheewakriangkrai *et al*. in a general population of women with endometrial cancer [25, 26]. In the present study, it is not possible to state that tumor size was an independent factor; but when the tumor size was > 2 cm, a significant correlation appeared between the disease and recurrence. Shah *et al*. have reported tumor size correlates with extrauterine disease, but it was not an independent prognostic variable [27]. In a multivariate model, TFD was shown to correlate with surgicopathologic variables, recurrence risk, and survival by Lindauer *et al*. [28]. TFD, like DMI, is predictive of many surgicopathological variables and patient outcome in surgically-staged endometrial cancer. Although the performance characteristics may not be as powerful as DMI, the ease and reproducibility of this measurement may justify its inclusion in synoptic reporting of endometrial cancer. As is mentioned in the literature [28-30]. TFD in the recurrence developing cases an almost one cm increased depth of MI. A TFD of one cm maximized the balance of sensitivity and specificity in predicting recurrence. In the present study, there was a statistically significant correlation between the development of recurrence and following clinicopathologic prognostic factors: age, parity, histological grade, histopathological type, LUSI, lymphovascular space invasion, tumor size, tumor free-distance, DMI, MT, and MIP which were in the early-stage endometrial cancer. The data on hand is univariate analysis and as is emphasized in the literature, these variables are effective prognostic factors for predicting recurrence development. Most of the data are characterized by retrospective design, large sample size, multiprognostic variables, single institute experience, and sufficient follow-up. These data suggest that, in those patients who do recur, it is the intrinsic biology of the tumor that has the greatest prognostic importance.

Conclusion

Today, however, despite several studies that are being conducted in subjects of proto-oncogenes, proliferation markers, endometrial proteins, enzymes and angiogenesis, the clinical use of them is debatable. Although some of them are clinically significant, the additional knowledge they will contribute to the routine evaluation is uncertain. The increase in accumulated knowledge about the prognostic factors predicting recurrence in the early-stage endometrial cancer and an effective analysis of them will help the gynecologic oncologists in choosing an appropriate treatment modality for the prevention of recurrences. The determination of risk groups and avoidance from unnecessary adjuvant treatment will have a positive impact on both medication of the prognosis and cost analysis. Since this study was based on univariate analysis, it could not be concluded whether factors having predictive values for recurrences are independent variables or not. However, data on hand show that there is a strong correlation between clinically important prognostic factors and recurrence development. In order to develop a consensus on the prognostic factors determining recurrences in early-stage endometrial cancers, comprehensive, randomized, and prospective multivariate analyses which also cover molecular mechanisms are needed. Thus, prospective multi-center trials should be performed to make more progress in the treatment of gynecologic cancer patients, including uterine corpus cancer.

References

[1] Jemal A., Siegel R., Xu J., Ward E.: *CA Cancer J. Clin*., 2011, *61,* 133.

[2] American Cancer Society. Cancer facts and figures 2010 [Internet]. Atlanta, GA: American Cancer Society;©2011 [cited2011, Feb20]. Availablefrom:http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/ cancer-facts-and-figures-2010.

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

[4] Jeong N.H., Lee J.M., Lee S.K.: "Current status in the management of uterine corpus cancer in Korea". *J. Gynecol. Oncol.,* 2010, *21,* 151.

[5] Salani R., Nagel C.I., Drennen E., Bristow R.E.: "Recurrence patterns and surveillance for patients with early stage endometrial cancer". *Gynecol. Oncol*., 2011, *123*, 205.

[6] Otsuka I., Uno M., Wakabayashi A., Kameda S., Udagawa H., Kubota T.: "Predictive factors for prolonged survival in recurrent endometrial carcinoma: Implications for follow-up protocol". *Gynecol. Oncol*., 2010*, 119,* 506.

[7] Prat J.: "Prognostic parameters of endometrial carcinoma". *Hum. Pathol*., 2004, *35,* 649.

[8] Fung-Kee-Fung M., Dodge J., Elit L., Lukka H., Chambers A., Oliver T.: "Follow-up after primary therapy for endometrial cancer: a systematic review". *Gynecol. Oncol.,* 2006, *101*, 520.

[9] van Wijk F.H., van der Burg M.E., Burger C.W. *et al*.: "Management of recurrent endometrioid endometrial carcinoma: an overview". *Int. J. Gynecol. Cancer*, 2009, *19,* 314.

[10] Fujimoto T., Nanjyo H., Fukuda J. *et al*.. "Endometrioid uterine cancer: histopathological risk factors of local and distant recurrence". *Gynecol. Oncol*., 2009, *112*, 342.

[11] Mariani A., Webb M.J., Keeney G.L. *et al*.: "Surgical Stage I endometrial cancer: predictors of distant failure and death". *Gynecol. Oncol*., 2002, *87,* 274.

[12] Creutzberg C.L., van Putten W.L., Koper P.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.

[13] Creutzberg C.L., van Putten W.L., Koper P.C. *et al*.: "Survival after relapse in patients with endometrial cancer: results from a randomized trial". *Gynecol. Oncol*., 2003*, 89,* 201.

[14] Keys H.M., Roberts J.A., Brunetto V.L. *et al*.: "A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study". *Gynecol. Oncol.,* 2004, *92,* 744.

[15] Morrow C.P., Bundy B.N., Kurman R.J. *et al*.: "Relationship between surgical-pathological risk factors and outcome in clinical Stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study". *Gynecol. Oncol*., 1991, *40,* 55.

[16] Descamps P., Calais G., Moire C., Bertrand P., Castiel M., Le F.O. *et al*.: "Predictors of distant recurrence in clinical Stage I or II endometrial carcinoma treated by combination surgical and radiation therapy". *Gynecol. Oncol*., 1997, *64*, 548.

[17] Kuten A., Grigsby P.W., Perez C.A., Fineberg B., Garcia D.M., Simpson J.R.: "Results of radiotherapy in recurrent endometrial carcinoma: a retrospective analysis of 51 patients". *Int. J. Radiat. Oncol. Biol. Phys*., 1989, *17,* 29.

[18] Zusterzeel P.L., Bekkers R.L., Hendriks J.C., Neesham D.N., Rome R.M., Quinn M.A.: "Prognostic factors for recurrence in patients with FIGO Stage I and Prognostic factors for recurrence in patients with FIGO Stage I and II, intermediate or high risk endometrial cancer". *Acta Obstet. Gynecol. Scand*., 2008, *87*, 240.

[19] Mundt A.J., Waggoner S., Yamada D., Rotmensch J., Connell P.P.: "Age as a prognostic factor for recurrence in patients with endometrial carcinoma". *Gynecol. Oncol.,* 2000, *79,* 79.

[20] Zaino R.J., Kurman R.J., Diana K.L., Morrow C.P.: "Pathologic models to predict outcome for women with endometrial adenocarcinoma: the importance of the distinction between surgical stage and clinical stage a Gynecologic Oncology Group study". *Cancer,* 1996, *77,* 1115.

[21] Kwon J.S., Carey M.S., Cook E.F., Qiu F., Paszat L.: "Patterns of practice and outcomes in intermediate- and high-risk Stage I and II endometrial cancer: a population-based study". *Int. J. Gynecol. Cancer,* 2007, *17,* 433.

[22] Lavie O., Uriev L., Gdalevich M., Barak F., Peer G., Auslender R., Anteby E., Gemer O.: "The outcome of patients with Stage I endometrial cancer involving the lower uterine segment". *Int. J. Gynecol. Cancer*, 2008, *18,* 1079.

[23] Gemer O., Gdalevich M., Voldarsky M., Barak F., Ben Arie A., Schneider D., Levy T., Anteby E.Y., Lavie O.: "Lower uterine segment involvement is associated with adverse outcome in patients with stage I endometroid endometrial cancer: results of a multicenter study". *Eur. J. Surg. Oncol*., 2009, 35, 865.

[24] Gemer O., Arie A.B., Levy T., Gdalevich M., Lorian M., Barak F., Anteby E., Lavie O.: "Lymphvascular space involvement compromises the survival of patients with Stage I endometrial cancer: Results of a multicenter study". *Eur. J. Surg. Oncol.,* 2007, *33,* 644.

[25] Briët J.M., Hollema H., Reesink N., Aalders J.G., Mourits M.J., ten Hoor K.A. *et al*.: "Lymphovascular space involvement: An independent prognostic factor in endometrial cancer". *Gynecol. Oncol.,* 2005, *96,* 799.

[26] Cheewakriangkrai C., Panggid K., Siriaungkul S., Khunamornpong S., Suprasert P., Srisomboon J.: "Lymphovascular space invasion as a prognostic determinant in uterine cancer". *Asian Pac. J. Cancer Prev.,* 2007, *8,* 363.

[27] Shah C., Johnson E.B., Everett E., Tamimi H., Greer B., Swisher E. *et al*.: "Does size matter? Tumor size and morphology as predictors of nodal status and recurrence in endometrial cancer". *Gynecol. Oncol*., 2005, *99*, 564.

[28] Lindauer J., Fowler J.M., Manolitsas T.P., Copeland L.J., Eaton L.A., Ramirez N.C. *et al.:* "Is there a prognostic difference between depth of myometrial invasion and the tumor-free distance from the uterine serosa in endometrial cancer". *Gynecol. Oncol.,* 2003, *91*, 547.

[29] Schwab K.V., O'Malley D.M., Fowler J.M., Copeland L.J., Cohn D.E.: "Prospective evaluation of prognostic significance of the tumor-free distance from uterine serosa in surgically staged endometrial adenocarcinoma". *Gynecol. Oncol.,* 2009, *112,* 146.

[30] Kondalsamy-Chennakesavan S., van Vugt S., Sanday K., Nicklin J., Land R., Perrin L. *et al*.: "Evaluation of tumor-free distance and depth of myometrial invasion as prognostic factors for lymph node metastases in endometrial cancer". *Int. J. Gynecol. Cancer,* 2010, *20,* 1217.

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