RESEARCH ARTICLE

Is Surgical Staging Necessary for Patients with Low-risk Endometrial Cancer? A Retrospective Clinical Analysis

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Abstract

Purpose: The aim of this study was to compare the tumor-free and overall survival rates between patients with low-risk endometrial cancer who underwent surgical staging and those who did not undergo surgical staging. Materials and Methods: Data, including demographic characteristics, grade of the tumor, myometrial invasion, cervical involvement, peritoneal washing, lymph node involvement, lymphovascular space invasion, postoperative complication, adjuvant treatment, cancer recurrence, and tumor-free and overall survival rates, for patients with low-risk endometrioid endometrial cancer who were treated surgically with and without pelvic and paraaortic lymph node dissection (LND) were analyzed retrospectively. The patients diagnosed with endometrioid endometrial cancer including the following criteria were considered low-risk: 1) a grade 1 (G1) or grade 2 (G2) endometrioid histology; 2) myometrial invasion of <50% upon magnetic resonance imaging (MRI); 3) no stromal glandular or stromal invasion upon MRI; and 4) no evidence of intra-abdominal metastasis. Then the patients at low-risk were divided into two groups; group 1 (n=117): patients treated surgically with pelvic and paraaortic LND and group 2 (n=170): patients treated surgically without pelvic and paraaortic LND. Results: There was no statistical significance when the groups were compared in terms of lymphovascular space invasion, cervical involvement, positive cytology, and recurrence, whereas the administration of an adjuvant therapy was higher in group 2 (p<0.005). The number of patients with positive pelvic nodes and the number of metastatic pelvic nodes were significantly higher in the group with positive LVI than in the group without LVI (p<0.005). No statistically significant differences were detected between the groups in terms of tumor-free survival (p=0.981) and overall survival (p=0.166). Conclusions: Total hysterectomy with bilateral salpingo-oophorectomy and stage-adapted postoperative adjuvant therapy without pelvic and/or paraaortic lymphadenectomy may be safe and efficient treatments for low-risk endometrial cancer.

Keywords: Endometrial cancer - low-risk, lymphovascular space invasion - pelvic-paraaortic lymphadenectomy

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Introduction

Endometrial cancer is the fourth most common cancer in women after breast, colorectum, and lung cancers in developed countries (Ferlay et al., 2012). The International Federation of Gynecology and Obstetrics (FIGO) recommended a surgical procedure for staging the disease, which consists of peritoneal washing, total hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node (PLN) dissection with or without paraaortic lymph node (PALN) dissection (Pecorelli, 2009). As well, the National Comprehensive Cancer Network (NCCN) accepted PALN dissection as a routine operation in all patients with endometrial cancer (NCCN, 2009). However, the practice of lymphadenectomy (LND) in these patients has long been a topic of controversy. While some studies supported LND to assess the extent of the disease as far as possible and to identify the appropriate adjuvant therapy to improve the outcome (Goudge et al., 2004; Havrilesky et al., 2005; Chan et al., 2007; Singh et al., 2007), others were opposed to LND in patients with a low risk for nodal metastases due to complications, including increased blood loss and operation time, vascular injury, lymphocyst formation, and lymphedema (Homesley et al., 1992; Abu-Rustum et al., 2006), and two randomized trials showed that LND did not affect the progression-free or overall survivals (Benedetti et al., 2008; Kitchener et al., 2009). Nevertheless, the definition of low risk is not uniform, despite several studies having investigated the clinicopathological risk factors for lymph node involvement in endometrial cancer (Mariani et al., 2000; Akbayir et al., 2012; Zhang et al., 2012; Kumar et al., 2013; Vargas et al., 2014).

The aim of this study was to compare the outcomes of patients with a low risk for endometrial cancer who underwent LND to those of patients who did not undergo LND.

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Materials and Methods

This study was based on a retrospective review of all patients diagnosed with low-risk endometrioid endometrial cancer and treated surgically with and without pelvic and paraaortic LND at our institution between January 2005 and January 2014. The inclusion criteria for the subjects were: 1) a grade 1 (G1) or grade 2 (G2) endometrioid histology, 2) a myometrial invasion of <50% upon magnetic resonance imaging (MRI) or computed tomography if there was a contraindication to the MRI, 3) no stromal glandular or stromal invasion upon MRI, and 4) no evidence of intra-abdominal metastasis. The exclusion criteria were 1) a grade 3 or non-endometrioid tumor, 2) a previous or concurrent malignancy, 3) history of previous radiation therapy, 4) evidence of a myometrial invasion of more than 50%, and 5) cervical or intra-abdominal metastasis.

The data for the patients, including age, gravida and parity, preexisting medical hypertension and diabetes mellitus, preoperative grade of the tumor, final pathological evaluation of the grade, myometrial invasion, cervical involvement, peritoneal washing, lymph node involvement, lymphovascular space invasion, postoperative complication, adjuvant treatment, cancer recurrence, tumor-free survival, and overall survival, were analyzed retrospectively. Adjuvant radiation was offered to patients with a G1 or G2 histology with a myometrial invasion of more than 50% and cervical involvement, in addition patients ≥ 60 years and had tumor size ≥ 2 cm.

Statistical analyses were completed using the SPSS for Windows 11.5 program. The Kolmogorov-Smirnov test was used to determine whether the distribution of discrete numeric variables was close to a normal distribution. Definitive statistics were identified as discrete numeric variables, mean±standard deviation, or median (minimum-maximum); nominal and ordinal variables were identified as case number and percentage (%).

The statistical significance between the groups in terms of mean values was determined using the Student's t-test, and the statistical significance between the groups in terms of median values was determined by the Mann-Whitney U test. Nominal variables were evaluated by Pearson's chi-square or Fisher's exact test. The statistical significance between the groups in terms of overall survival was determined using the log-rank test and the Kaplan-Meier method.

Regarding overall 1-3-year and 5-year survivals, mean life expectancy and 95% confidence intervals were calculated. A P value of less than 0.05 was considered statistically significant.

Results

The study group included 287 patients diagnosed with endometrial cancer and was divided into two groups. Group 1 included patients who underwent total hysterectomy and bilateral salpingo-oophorectomy without pelvic and paraaortic lymph node dissection (n=117); group 2 included patients who underwent surgical staging, which consists of peritoneal washing, total hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissection with or without paraaortic lymph node dissection (n=170). The characteristics of the study group are shown in Table 1.

There was no statistical significance when the groups were compared in terms of lymphovascular space invasion, cervical involvement, positive cytology, and recurrence, whereas the administration of an adjuvant therapy was higher in Group 2 (p<0.005) (Table 1). We were not able

Table 1. Comparison of Demographic and Clinico-pathological Characteristics between Group 1 and Group 2

Features	Group 1 (n=117)	Group 2 (n=170)	p-value
Age at diagnosis (year)	59.6±11.2	55.4±10.3	<0.001†
Gravida	2 (0-13)	3 (0-9)	<0.001‡
Parity	1 (0-9)	2 (0-7)	<0.001‡
Hypertension	57 (48.7%)	85 (50.0%)	0.831¶
Diabetes mellitus	23 (19.7%)	40 (23.5%)	0.436¶
Tumor grade I/II	73 (62.4%) / 44 (37.6%)	92 (54.1%) / 78 (45.9%)	0.163¶
Lymphovascular space invasion	17 (14.5%)	22 (12.9%)	0.700¶
Cervical involvement	15 (12.8%)	21 (12.4%)	0.906¶
Positive cytology	3 (2.6%)	2 (1.2%)	0.401ϕ
Adjuvant therapy	36 (30.8%)	104 (61.2%)	<0.001¶
Recurrence	15 (12.8%)	20 (11.8%)	0.788¶
FIGO stage			
1A		72 (42.4%)	
1B		62 (36.5%)	
2		18 (10.6%)	
3A		3 (1.8%)	
3C1		11 (6.5%)	
3C2		4 (2.4%)	
Patients with positive pelvic lymph nodes		15 (8.8%)	
Positive pelvic lymph nodes number		0 (0-5)	
Patients with positive paraaortic lymph nodes		4 (2.4%)	
Positive paraaortic lymph nodes number		0 (0-1)	
Postoperative complication		3 (1.8%)	

†Student's t test; ‡Mann-Whitney U test; ¶Pearson's chi-square test. ϕFisher's exact test

to evaluate myometrial invasion in group 1 and compare the groups owing to the lack of pathological reporting.

When the surgically staged group was evaluated to determine the stage and pelvic-paraaortic lymph node involvement, stage 1 was the most common stage, with 134 (78.8%) patients. Fifteen patients had positive pelvic lymph nodes (8.8%), while only four patients had paraaortic lymph node metastasis (2.4%) (Table 1).

The surgically staged group (group 2) was evaluated by being divided into two subgroups according to lymphovascular invasion. The median stage was 1B in the group with negative LVI, while it was 2 in the other group with positive LVI. The median stage of the group with positive LVI was significantly higher than of the other group (p<0.001) (Table 2).

The number of patients with positive pelvic nodes and the number of metastatic pelvic nodes was significantly higher in the group with positive LVI than in the group without LVI (p<0.005). However, there was no statistically significant difference between the subgroups in terms of paraaortic lymph node involvement and the number of metastatic lymph nodes (p=0.429 and p=0.468) (Table 2).

Table 2. Relationship between Lymphovascular Space Invasion (LVI) and Stage of the Disease and Pelvic-Paraaortic Lymph Node Metastases

Features	Positive	p-value
	LVI (n=22)	<0.001†
FIGO stage		
1A	2 (9.1%)	
1B	7 (31.8%)	
2	5 (22.7%)	
3A	1 (4.5%)	
3C1	6 (27.4%)	
3C2	1 (4.5%)	0.005‡
Pelvic lymph node involvement		
Negative	16 (72.7%)	
Positive	6 (27.3%)	<0.001†
Positive pelvic lymph node number	1 (0-5)	0.429‡
Paraaortic lymph node involvement		
Negative	21 (95.5%)	
Positive	1 (4.5%)	0.468†
Positive paraaortic lymph node number	0 (0-1)	

†Mann-Whitney U test; ‡Fisher's exact test

In total, 21 patients underwent surgical staging, and 34 patients who did not undergo staging were excluded from the study due to the lack of knowledge about tumor-free survival. Therefore, the statistical analysis of tumor-free survival was conducted using the remaining groups. There was no statistically significant difference between the groups in terms of tumor-free survival (p=0.981). One-year tumor-free survival was 93.2%, three-year tumor-free survival was 88.4%, and five-year tumor-free survival was 86.2%, with an average tumor-free life span of 7.16 years (95% Confidence Interval: 6.76-7.56) in the group with no staging. The tumor-free survivals for the group with staging were as follows: one-year tumor-free survival was 91.2%, three-year tumor-free survival was 88.8%, and five-year tumor-free survival was 85.0%, with an average tumor-free life span of 7.14 years (95% Confidence Interval: 6.78-7.50) (Figure 1).

When overall survivals were compared, no significant difference was detected between group 1 and group 2 (p=0.166). The overall survivals of group 1 were as follows: One-year overall survival was 94.9%, three-year overall survival was 87.3%, and five-year survival was 88.1%, with an average overall life span of 7.11 years (95% Confidence Interval: 6.70-7.51). Alternatively, one-year survival was 95.3%, three-year survival was 91.6%, and five-year survival was 90.4% in the surgically staged group, with an average overall life span of 7.42 year (95% confidence interval: 7.13-7.71). (Figure 2)

Discussion

Endometrial cancer is one of the most common malignant tumors of the female genital tract, and

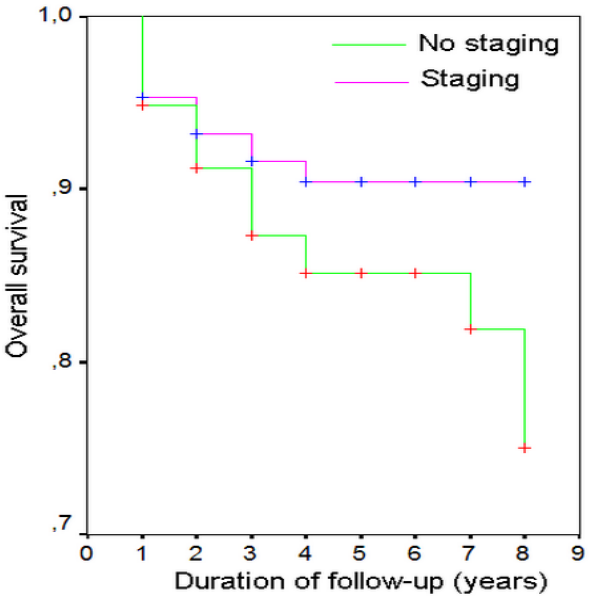

Figure 2. Overall Survival. The Kaplan-Meier curve of the clinical outcome for overall survival demonstrates no significant difference between the groups

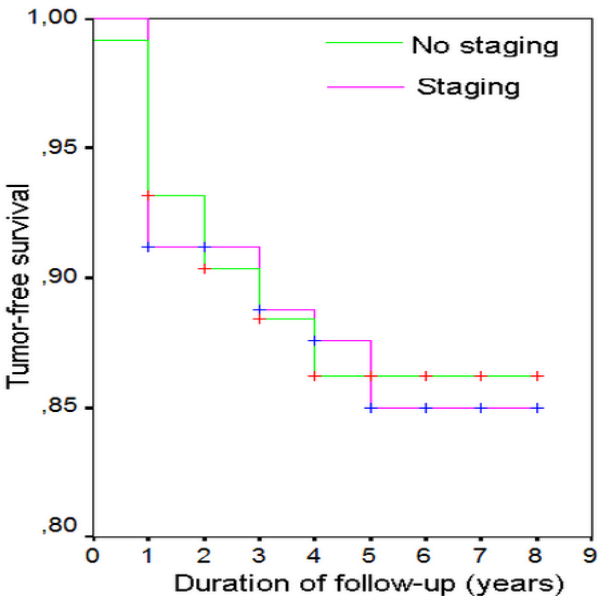

Figure 1. Tumor-free Survival. The Kaplan-Meier curve of the clinical outcome for tumor-free survival demonstrates no significant difference between the groups

lymphatic metastasis is the principal spread route (Ayhan et al., 1989). Therefore, systemic LND has been included in the complete surgical staging of the disease (Pecorelli 2009; NCCN, 2011). However, the definition of "low risk" for endometrial cancer, which includes endometrioid type, G1 or G2, myometrial invasion ≤50%, tumor size <2 cm, no cervical or adnexal involvement, and no operative evidence of macroscopic extrauterine spread, has led to a debate regarding the optimal surgical management of patients with low-risk endometrial cancer, particularly with regard to the role of LND (Mariani et al., 2000; Hidaka et al., 2010).

As it is questionable whether patients with a low-risk disease unjustifiably undertake risks for potentially serious complications due to lymph node dissection, this topic has been the focus of several investigations (De Wilde et al., 2014). Studies that evaluated omitting lymph node dissection in patients with a low-risk disease have reported favorable outcomes in terms of recurrence and tumor-free and overall survivals. One of these studies is a recent Cochrane review that consisted of two randomized controlled trials, one of which is the A Study in the Treatment of Endometrial Cancer (ASTEC) trial including 1,408 patients who were randomized either in the group that underwent surgical staging with LND or in the group without LND (Kitchener et al., 2009). The other controlled trail of the review included 250 patients with omitted lymph node dissection and 264 with pelvic LND (Benedetti et al., 2008). The two controlled trials reported there was no significant difference in recurrence and overall survival between the groups (May et al., 2010).

Other researchers also demonstrated that LND did not improve disease-free or overall survivals in preoperative stage I patients, despite it potentially improving surgical staging, as well as concluded that systemic LND could be omitted in patients with low-risk endometrial cancer (Benedetti et al., 2008; Hidaka et al., 2010). Moreover, excellent disease-free or overall survivals, all of which were ≥ 96%, were reported from different institutions that evaluated omitting lymph node dissection in low-risk endometrial cancers, one of which evaluated patient outcomes after omitting LND based on an intraoperative assessment of the uterine specimen. This indicated that the reliability of an intraoperative evaluation for low-risk cancer was sufficient to omit systemic LND (Eltabbakh et al., 1997; Mariani et al., 2000; Hidaka et al., 2007; Kang et al., 2009; Hidaka et al, 2010; Dowdy et al., 2012; Bell et al., 2014). On the other hand, intraoperative gross examination was reported to be less sensitive when used alone and alternative methods were suggested to determine early-stage endometrial cancer (Sethasathien et al., 2014).

In line with the mentioned studies, we included patients with low-risk endometrial cancer and did not find a significant difference in tumor-free and overall survivals between the group that underwent surgical staging including pelvic-paraaortic LND and the group that did not undergo systemic LND in the present study (p=0.981, p=0.166). In addition, there was no statistical significance regarding recurrence between the groups (p=0.788).

On the other hand, there have been studies supporting systemic lymph node dissection due to the risk of node metastasis, even in early-stage endometrial cancer. It has been previously reported that all patients with paraaortic lymph node metastasis exhibit pelvic lymph node metastasis (Larson and Johnson, 1993). Pelvic lymph node metastasis and paraaortic lymph node metastasis were present in ranges of 8.2-15.1% and 8-8.5%, respectively, of patients with stage 1 endometrial cancer in two studies, whereas another reported percentages of 20 and 16, respectively (Ayhan et al., 1989; Larson and Johnson, 1993; Wang et al., 2013). Although systemic LND was found to have benefits and therapeutic effects in intermediate and high-risk patients (from stage IB to IV), there was no significant improvement in the survival rates of patients with a low-risk disease. It has been suggested the reasons for which include inaccuracies in preoperative biopsies, the risk of metastasis, and the impact of the procedure on the postoperative adjuvant treatment decision (Ben-Shackar et al., 2005; Chan et al., 2006; Chan et al., 2007; Singh et al., 2007; Todo et al., 2010). Moreover, studies indicated that complete pelvic LND could be performed to detect metastatic disease in the lymph nodes and to avoid understaging the disease (Benedetti et al, 2008; Fatiou et al., 2009). It was also demonstrated that LND significantly improved cause-specific and overall survivals, but not the progression-free survival, and systemic lymph node dissection was proposed (Bassarak et al., 2010).

In the present study, 42.4% (n=71) of patients who underwent surgical staging had stage IA low-risk endometrial cancer, and the remaining were of the intermediate-high risk group. The percentage of patients who underwent adjuvant therapy was higher in the group with LND than in the group without LND (p<0.001). The percentage of metastatic pelvic lymph nodes was 8.8%, whereas it was 2.4% for paraaortic lymph nodes. We also evaluated the impact of LVI on the stage and lymph node involvement. Positive LVI was significantly associated with an advanced stage and pelvic node metastasis, but not paraaortic node metastasis. In line with this study, LVI, deep myometrial invasion, and cervical glandular and stromal involvement were reported to be superior predictive criteria for pelvic lymph node metastasis (Akbayir et al., 2012; Zhang et al., 2012).

The major limitation of this study is its retrospective nature and the small number of cases.

In conclusion, the results of the current study indicate that total hysterectomy with bilateral salpingo-oophorectomy and stage-adapted postoperative adjuvant therapy without pelvic and/or paraaortic LND may be a safe and efficient treatment for low-risk endometrial cancer. We think that such an approach is important in terms of prevention the surgical over-treatment.

References

Abu-Rustum NR, Alektiar K, Iasonos A, et al (2006). The incidence of symptomatic lower-extremity lymphedema following treatment of uterine corpus malignancies: a 12-year experience at memorial sloan-kettering cancer center. *Gynecol Oncol*, **103**, 714-8.

Akbayir O, Corbacioglu A, Goksedef BP, et al (2012). The

novel criteria for predicting pelvic lymph node metastasis in endometrioid adenocarcinoma of endometrium. *Gynecol Oncol*, **125**, 400-3.

ASTEC study group, Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK (2009). Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet*, **373**, 125-36.

Ayhan A, Yarali H, Urman B, et al (1989) Lymph node metastasis in early endometrium cancer. *Aust N Z J Obstet Gynaecol*, **29**, 332-5.

Bassarak N, Blankenstein T, Bruning A, et al (2010). Is lymphadenectomy a prognostic marker in endometrioid adenocarcinoma of the human endometrium? *BMC Cancer*, **10**, 224.

Bell JG, Patterson DM, Klima J, et al (2014). Outcomes of patients with low-risk endometrial cancer surgically staged without lymphadenectomy based on intra-operative evaluation. *Gynecol Oncol*, **134**, 505-9.

Ben-Shachar I, Pavelka J, Cohn DE, et al (2005). Surgical staging for patients presenting with grade 1 endometrial carcinoma. *Obstet Gynecol*, **105**, 487-93.

Benedetti Panici P, Basile S, Maneschi F, et al (2008). Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. *J Natl Cancer Inst*, **100**, 1707-16.

Chan JK, Cheung MK, Huh WK, et al (2006). Therapeutic role of lymph node resection in endometrioid corpus cancer: a study of 12,333 patients. *Cancer*, **107**, 1823-30.

Chan JK, Wu H, Cheung MK, et al (2007). The outcomes of 27,063 women with unstaged endometrioid uterine cancer. *Gynecol Oncol*, **106**, 282-8.

De Wilde RL, Rafei A, Herrmann A (2014). Can a lymphadenectomy be avoided in early-stage endometrial adenocarcinoma? *Arch Gynecol Obstet*, **290**, 973-8.

Dowdy SC, Borah BJ, Bakkum-Gamez JN, et al (2012). Prospective assessment of survival, morbidity, and cost associated with lymphadenectomy in low-risk endometrial cancer. *Gynecol Oncol*, **127**, 5-10.

Eltabbakh GH, Piver MS, Hempling RE, Shin KH (1997). Excellent long-term survival and absence of vaginal recurrences in 332 patients with low-risk stage I endometrial adenocarcinoma treated with hysterectomy and vaginal brachytherapy without formal staging lymph node sampling: report of a prospective trial. *Int J Radiat Oncol Biol Phys*, **38**, 373-80.

Ferlay J, Soerjomataram I, Ervik M, et al GLOBOCAN (2012) v1.0 databases Cancer Incidence and Mortality Worldwide (http://globocan.iarc.fr).

Fotiou S, Trimble EL, Papakonstantinou K, et al (2009). Complete pelvic lymphadenectomy in patients with clinical early, grade I and II endometrioid corpus cancer. *Anticancer Res*, **29**, 2781-5.

Goudge C, Bernhard S, Cloven NG, Morris P (2004). The impact of complete surgical staging on adjuvant treatment decisions in endometrial cancer. *Gynecol Oncol*, **93**, 536-9.

Havrilesky LJ, Cragun JM, Calingaert B, et al (2005). Resection of lymph node metastases influences survival in stage IIIC endometrial cancer. *Gynecol Oncol*, **99**, 689-95.

Hidaka T, Kato K, Yonezawa R, et al (2007). Omission of lymphadenectomy is possible for low-risk corpus cancer. *Eur J Surg Oncol*, **33**, 86-90.

Hidaka T, Nakashima A, Shima T, Hasegawa T, Saito S (2010). Systemic lymphadenectomy cannot be recommended for low-risk corpus cancer. *Obstet Gynecol Int*, **2010**, 490219.

Homesley HD, Kadar N, Barrett RJ, Lentz SS (1992). Selective pelvic and periaortic lymphadenectomy does not increase morbidity in surgical staging of endometrial carcinoma. *Am J Obstet Gynecol*, **167**, 1225-30.

Kang WD, Kim CH, Cho MK, et al (2009). Lymphadenectomy for low-risk endometrial cancer based on preoperative and intraoperative assessments. *Int J Gynecol Cancer*, **19**, 657-61.

Kumar S, Mariani A, Bakkum-Gamez JN, et al (2013). Risk factors that mitigate the role of paraaortic lymphadenectomy in uterine endometrioid cancer. *Gynecol Oncol*, **130**, 441-5.

Larson DM, Johnson KK (1993). Pelvic and para-aortic lymphadenectomy for surgical staging of high-risk endometrioid adenocarcinoma of the endometrium. *Gynecol Oncol*, **51**, 345-8.

Mariani A, Webb MJ, Keeney GL, et al (2000). Low-risk corpus cancer: is lymphadenectomy or radiotherapy necessary? *Am J Obstet Gynecol*, **182**, 1506-19.

May K, Bryant A, Dickinson HO, Kehoe S, Morrison J (2010). Lymphadenectomy for the management of endometrial cancer. *Cochrane Database Syst Rev,* **20**, CD007585.

NCCN clinical Practice Guidelines in Oncology databases. Uterine neoplasms V.1.2011 (http://www.nccn.org).

Pecorelli S (2009). Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet*, **105**, 103-4.

Sethasathien P, Charoenkwan K, Siriaunkgul S (2014). Accuracy of intraoperative gross examination of myometrial invasion in stage I-II endometrial cancer. *Asian Pac J Cancer Prev*, **15**, 7061-4.

Singh M, Zaino RJ, Filiaci VJ, Leslie KK (2007). Relationship of estrogen and progesterone receptors to clinical outcome in metastatic endometrial carcinoma: a gynecologic oncology group study. *Gynecol Oncol*, **106**, 325-33.

Todo Y, Kato H, Kaneuchi M, et al (2010). Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. *Lancet*, **375**, 1165-72.

Wang ZQ, Wang JL, Shen DH, Li XP, Wei LH (2013). Should all endometrioid uterine cancer patients undergo systemic lymphadenectomy? *Eur J Surg Oncol*, **39**, 344-9.

Vargas R, Rauh-Hain JA, Clemmer J, et al (2014). Tumor size, depth of invasion, and histologic grade as prognostic factors of lymph node involvement in endometrial cancer: a SEER analysis. *Gynecol Oncol*, **133**, 216-20.

Zhang C, Wang C, Feng W (2012). Clinicopathological risk factors for pelvic lymph node metastasis in clinical early-stage endometrioid endometrial adenocarcinoma. *Int J Gynecol Cancer*, **22**, 1373-7.