

# Isolated para-aortic lymph node metastasis in completely staged endometrioid type endometrial cancer

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## Summary

**Purpose:** Majority of gynecologic oncologists perform low para-aortic dissection, while only one in ten incorporated para-aortic dissection to the level of renal vessels. The aim of this study is to demonstrate the necessity of para-aortic lymph node dissection (LND) in the surgical management of the endometrioid type endometrial cancer (EC). **Materials and Methods:** Endometrioid type EC patients who were operated at the present institution were included in the study. The patients were stratified according to the modified Mayo Clinic risk criteria. According to these criteria, the authors identified each patient as low risk or high risk for extra-uterine disease spread on final pathology reports. Low risk criteria for nodal disease were identified as grade 1 or 2 endometrioid type disease, equal or less than 1/2 myometrial invasion (MI), and greatest tumor diameter equal or less than 2 cm. **Results:** Three hundred eighty-six patients were operated with the diagnosis of endometrioid type EC. Two hundred forty-seven patients had high risk factors for extra-uterine disease; thus, complete surgical staging was performed to this group. The remaining 139 patients had low risk criteria. The median follow-up time was 35 months (minimum two months, maximum 97 months). Twenty-six patients (10.5%) died of disease during the follow-up period. Two hundred fifteen patients (87%) had negative nodes, while remaining 32 (12.6%) patients had pelvic and/or para-aortic LN metastasis. Thirteen patients (40.6%) had only pelvic LN involvement (Stage 3C1), 19 patients (59.4%) had either pelvic and/or para-aortic LN involvement (Stage 3C2), and six patients (18.6%) had isolated para-aortic LN involvement. **Conclusion:** The present authors advocate the value of para-aortic LND in surgical management of EC, and retroperitoneal LND should not be limited to pelvic nodes, a systematic para-aortic dissection up to left renal vein should be performed for the patients with at least one risk factor for nodal disease.

**Key words:** Endometrial cancer; Nodal spread; Lymph node dissection; Endometrioid type.

## Introduction

Some surgeons advocate the potential benefit of complete pelvic and para-aortic lymph node dissection (LND), while others question the necessity of para-aortic LND. However, LN metastasis is known to be a major predictor of prognosis for EC [1]. While demonstrating the value of LN dissection, the staging system for EC showed a transition from clinical staging to surgical staging in 1988 [2], and the 2009 revised staging system has further sub-stages according to pelvic and/or para-aortic LN metastasis [3]. There is still a debate on the extent of LND in surgical management of EC. A survey about the practice patterns among gynecologic oncologists showed that the majority of surgeons perform low para-aortic (to the level of inferior mesenteric artery) dissection, while only one in ten incorporated para-aortic dissection to the level of renal vessels [4]. EC patients, which require LND, can precisely be determined using preoperative endometrial biopsy and intraoperative frozen section study [5]. The aim of this study is to determine the necessity and the extent of para-aortic LND for surgical treatment of endometrioid type EC.

## Materials and Methods

Using the computerized database of a tertiary care hospital in Ankara, the authors identified all cases of endometrioid type EC patients that had been surgically treated between March 2007 and February 2015. Only patients who had eight or more dissected pelvic LNs were included in the analysis to achieve the satisfactory LN count according to the previous studies [6]. The patients were stratified according to the modified Mayo Clinic risk criteria. According to these criteria, the authors identified each patient as low risk or high risk for extra-uterine disease spread on final pathology reports. Low risk criteria for nodal disease were identified as grade 1 or 2 endometrioid type disease, equal or less than 1/2 myometrial invasion (MI) and greatest tumor diameter equal or less than 2 cm [7]. Total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) was performed if the patient had low risk criteria according to preoperative and intraoperative findings; otherwise a systematic surgical staging procedure was performed with pelvic and para-aortic LN dissection. Anatomical landmarks for para-aortic LN dissection were: renal vessels for cranial border, aortic bifurcation for caudal border and gonadal vessels for lateral borders. Pelvic LNs were collected from three regions each side: common iliac, obturator, and external iliac. Patients were staged according to FIGO classification, which was revised in 2009. Patient characteristics and clinical features were identified. FIGO grade, size, MI, adnexal and cer-

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Table 1. — *Patient characteristics and clinical features.*

Patient and tumor characteristic	Number of patients (N)	(%)
Age	247	100
Median: 59, mean: 58.7, range: 28-82		
Tumor type		
Endometrioid	247	100
FIGO Stage		
1a	119	48.2
1b	55	22.3
2	23	9.3
3a	9	3.6
3b	5	2.0
3c1	12	4.8
3c2	18	7.2
4	6	2.4
FIGO Grade		
Grade 1	143	57.9
Grade 2	74	30
Grade 3	30	12.1
Myometrial invasion		
Confined to the endometrium	7	2.8
< 1/2	134	54.3
≥ 1/2	106	42.9
Peritoneal cytology		
Negative	230	93.1
Positive	17	6.9
Adnexal involvement		
Negative	232	93.9
Positive	15	6.1
Cervical involvement		
Negative	193	78.1
Positive	54	21.9
Glandular		
Stromal	17	31.4
	37	68.5
LVSI		
Negative	184	72.7
Positive	69	27.3
Mean dissected pelvic nodes (range)	40 (10-110)	
Mean dissected para-aortic nodes (range)	18 (7-58)	
Mean tumor diameter (range)	4.2cm (1-13 cm)	

247 patients had complete surgical staging with systematic pelvic and para-aortic LND. LVSI: lymphovascular space invasion.

Table 2. — *Lymph node status of the patients.*

		Para-aortic LN metastasis		Total
		Negative	Positive	
Pelvic LN metastasis	Negative	215	6	221
	Positive	13	13	26
Total		228	19	247

LN: lymph node.

vical involvement, lymphovascular space invasion, LN status, peritoneal cytology status, and disease stage were identified. Data were analyzed by the SPSS computer software (version 22). The authors obtained the institutional review board approval for this study.

## Results

Three hundred eighty-six patients were surgically treated at the present institution between March 2007 and February 2015 with the diagnosis of endometrioid type EC. All patients had endometrioid type EC according to the final pathological result. Two hundred forty-seven patients had high risk factors for extra-uterine disease; thus, complete surgical staging was performed to this group. The remaining 139 patients had low risk criteria and excluded from analysis. Among low risk patients, 108 of them had completely staged, while 21 had TAH-BSO with peritoneal washing. Patient characteristics and clinical features are shown in Table 1. The median follow-up time was 35 months (minimum two months, maximum 97 months). Twenty-six patients (10.5%) died of disease during the follow-up period. The median age of the patients was 59 (ranging 28 to 82) years. The median dissected pelvic LN counts were 40 (range 10-110) respectively. The median dissected para-aortic LN counts were 18 (range 7-58) respectively. Two hundred fifteen patients (215/247, 87%) had negative nodes, while remaining 32 (12.6%) patients had pelvic and/or para-aortic LN metastasis. Two patients with LN metastasis were identified to have Stage 4 disease according to final pathology report. Thirteen patients (13/32, 40.6%) had only pelvic LN involvement (Stage 3C1), 19 patients (19/32, 59.4%) had either pelvic and/or para-aortic LN involvement (Stage 3C2), and six patients (6/32, 18.6%) had isolated para-aortic LN involvement. Among these six patients, four patients had only one positive isolated para-aortic lymphatic metastasis (Table 2). Other two patients had four metastatic para-aortic LNs. Isolated para-aortic LN metastases were only inframesenteric in three patients, only supramesenteric in two patients, while remaining patient had both infra- and supramesenteric LNs involved. Detailed clinical characteristics of patients with isolated para-aortic LN metastasis are shown in Table 3.

## Discussion

Some authors suggest routine LND in the setting of adequate surgical staging of EC. However, therapeutic role of systematic LND, optimal LN counts to be dissected, and the extent of the procedure is a main concern among gynecologic oncologists.

Cragun *et al.* reported slightly improved survival among

Table 3. — Detailed characteristic of patients with isolated para-aortic lymph node metastasis.

Patient characteristics	Pat.1	Pat.2	Pat.3	Pat.4	Pat.5	Pat.6
Age	56	67	64	70	64	70
FIGO Stage	IIIC2	IIIC2	IIIC2	IIIC2	IIIC2	IIIC2
FIGO Grade	2	3	1	2	3	3
LVSI	Positive	Positive	Positive	Positive	Positive	Positive
Tumor size (cm)	5	4.5	4	6	4.5	5
MI depth	≥1/2	≥1/2	≥1/2	≥1/2	≥1/2	≥1/2
Dissected pelvic LN	32	20	32	64	24	51
Dissected PA LN	15	12	16	23	23	55
Metastatic PA LN count	4	4	1	1	1	1
LN metastasis localization	Infra+supra mesenteric	Infra-mesenteric	Infra-mesenteric	Infra-mesenteric	Supra-mesenteric	Supra-mesenteric
Peritoneal cytology	Negative	Negative	Negative	Negative	Negative	Positive
Adnexal involvement	Negative	Negative	Negative	Negative	Negative	Positive
Cervical involvement	Absent	Absent	Absent	Present, stromal	Absent	Absent
Ca-125 (IU/ml)	6	36	26	73	14	73
Adjuvant therapy	CT	CT	EBRT+CT	CT	EBRT+CT	CT
Follow up (months)	13	13	12	88	3	86
Recurrence	None	None	None	Yes	None	None
Status	Alive WD	Alive WD	Alive WD	Alive with disease	Alive WD	Alive WD

LVSI: lymphovascular space invasion; MI: myometrial invasion; PA: para-aortic; LN: lymph node; CT: chemotherapy; EBRT: external beam radiation therapy; WD: without disease.

poorly differentiated EC patients who underwent systematic pelvic LND (more than 11 dissected pelvic nodes), but same survival benefit could not be demonstrated in the patients with selective para-aortic LN and with FIGO Grade 1/2 tumors [8]. Similar results were reported by Lutmanet *et al.* and Chan *et al.* that demonstrated some survival benefit only in patients with non-endometrioid and Grade 3 endometrioid tumors [9, 10].

Isolated para-aortic LN metastasis was found to be 1.6% among all endometrioid type EC in the patients with satisfactory pelvic LN dissection by Abu-Rustum *et al.* [11], slightly lower than the present results. In present study, we found six isolated para-aortic LN metastasis among 247 (2.4%) endometrioid type EC patients. Even if this incidence seems to be relatively lower, we found 32 patients to be node-positive among 247 endometrioid type EC patients, and six of them (18.6%) had isolated para-aortic LN metastasis. In this retrospective cohort, a substantial proportion of high risk patients were composed of Grade 1 tumors with < 1/2 MI (total of 91 patients, data not shown). None of these patients had nodal disease in the final pathology. If we exclude these patients in addition to former low-risk patients, isolated para-aortic LN metastasis ratio for the remaining 156 higher risk patients would be 3.8%. In Abu Rustum *et al.*'s paper, the authors did not clearly define the LND indications and they stated that during the study period, the management of EC changed among practitioners, particularly in regards to the role of lymphadenectomy [11]. In their retrospective cohort, some proportion of the patients might have low risk factors for

nodal disease and this explains their relatively lower isolated para-aortic LN metastasis ratios. At the same time, they defined a satisfactory LND count for pelvic region as minimum seven LNs, but not for the para-aortic region, and their median dissected para-aortic LN counts were only five (range, 1-32). Isolated para-aortic nodal recurrence is relatively uncommon for EC and it is found that only 6% of all recurrences in EC are isolated para-aortic recurrences in patients with surgically staged EC patients [12]. However, but it can be argued that significant proportion of EC patients with para-aortic LN involvement had deep MI and LVSI, therefore recurrences are mostly seen loco-regionally.

In 2001, Mariani *et al.* suggested that isolated para-aortic LN metastasis was probably a late and uncommon event in EC patients [13]. In the light of these retrospectively designed studies, the value of para-aortic LND can be demonstrated in high-grade endometrioid tumors and non-endometrioid histologic subtypes. In spite of these findings, half of the patients with isolated para-aortic LN metastasis in the present study, had Grade 1 or 2 endometrioid disease. The common features of the patients were that all of them had LVSI in histopathologic sections and tumors had more than 1/2 MI.

The other point of controversy is the number of dissected para-aortic LNs. In the present study, the mean dissected para-aortic LN was 18 and it is satisfactory compared to similar studies in the literature [11]. In four of six patients with isolated para-aortic LN metastasis had only one positive para-aortic LN and mean dissected para-aortic LN

count of these four patients was 29.

The first prospective randomized studies are published in 2008 and 2009 by ASTEC study group [14] and Benedetti Panici *et al.* [15], respectively, but these studies are criticized for low numbers of dissected pelvic LNs and patient selection criteria [16-19]. In the setting of these studies, the value of systematic para-aortic LND could not be properly demonstrated, but the authors emphasized the value of para-aortic LND in regards of proper surgical staging to define appropriate adjuvant therapy regimen.

In a recent prospective study, Kumar *et al.* found the incidence of isolated para-aortic LN metastasis 3% of patients (11 of 351 patients) with negative pelvic LNs [20]. At the same time, they reported that if isolated para-aortic LN metastasis is present, it is more likely to involve high para-aortic region (67%). In present study, we found 50% of the isolated para-aortic LN metastasis involved the high para-aortic region (supramesenteric). The study population consisted of uniformly staged, large cohort of "at risk" EC patients. "At risk" was defined as FIGO Grade 2/3 disease, non-endometrioid histologic types, more than 1/2 MI in frozen section, and tumors larger than 2 cm. However, the present study population is similar except that the authors only included endometrioid type EC. There is less debate on performing systematic LN dissection for non-endometrioid types in the literature.

Significant proportion of gynecologic oncologist limit LND to pelvis or perform a selective or limited para-aortic LND in surgical management of EC [21]. In the present study population, 19 patients had para-aortic LN involvement among 32 patients (59.3%). In the setting of this result, we believe that it is not questionable to perform para-aortic LND in the presence of risk factors for nodal spread. Another controversial issue is the extent of para-aortic LND. In the present retrospective cohort, three out of six isolated para-aortic LN metastasis (50%) affected high para-aortic region and this instance had been issued in the previous studies [20].

In conclusion, we advocate the value of para-aortic LND in surgical management of EC, and retroperitoneal LND should not be limited to pelvic nodes, a systematic para-aortic dissection up to left renal vein should be performed in patients with at least one risk factor for nodal disease.

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