Lymph node dissection in intermediate and high-intermediate risk endometrial cancer

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Abstract

Introduction The aim of this study was to assess the impact of lymph node dissection (LND) on survival for patients with intermediate risk (IR) and high intermediate risk (HIR) endometrial cancer (EC). Methods Clinicopathologic features and survival data of 1294 consecutive patients who underwent primary surgical treatment for EC between 2003 and 2018 were were retrieved from the database of Hacettepe University Hospital. This study compared the overall survival (OS) and disease-free survival (DFS) among IR and HIR EC between patients with LND and no LND. Results The study population included 141 (55 %) IR, and 115 (45 %) HIR EC patients. LND was not performed in 33 (23.4%), and 31 (27%) patients in IR, and HIR EC patients, respectively. The lymph node involvement was 10.3% (n=20) among all patients. During the median follow-up of 41 months (range, 12–222), 12 (6.2 %) patients with LND, and 5 (7.8 %) patients without LND had disease recurrence (p=0.77). LND did not improve OS and DFS in IR and HIR EC patients (p=0.92, p=0.80). And the lymph node count was not associated with OS and DFS for all subsets of patients with EC grouped by recurrence risks. Discussion Without illuminating the morbidity of LND, there were no difference observed in OS and DFS between IR and HIR EC patients with LND-induced complications and no LND. With this regard, the use of sentinel lymph node procedure might be better for minimizing the possible post-operative morbidities in this selected patient groups.

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Lymph node dissection in intermediate and high-intermediate risk endometrial cancer

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Results

The study population included 141 (55 %) IR, and 115 (45 %) HIR EC patients. LND was not performed in 33 (23.4%), and 31 (27%) patients in IR, and HIR EC patients, respectively. The lymph node involvement was 10.3% (n=20) among all patients. During the median follow-up of 41 months (range, 12–222), 12 (6.2 %) patients with LND, and 5 (7.8 %) patients without LND had disease recurrence (p=0.77). LND did not improve OS and DFS in IR and HIR EC patients (p=0.92, p=0.80). And the lymph node count was not associated with OS and DFS for all subsets of patients with EC grouped by recurrence risks.

Discussion

Without illuminating the morbidity of LND, there were no difference observed in OS and DFS between IR and HIR EC patients with LND-induced complications and no LND. With this regard, the use of sentinel lymph node procedure might be better for minimizing the possible post-operative morbidities in this selected patient groups.

Key words: Endometrial cancer, Intermediate risk, High intermediate risk, Survival

What's already known about this topic?

The importance of lymph node dissection (LND) remains unclear for EC identified in intermediate (IR) and high-intermediate (HIR) risk groups

What does this article add?

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Introduction

Endometrial cancer (EC) is the most frequent gynecologic cancer, and usually diagnosed in early-stages with a favorable prognosis[1]. The standard surgical treatment for EC includes of a total hysterectomy and bilateral salpingo-oophorectomy with or without lymph node dissection (LND). The uncertainty in LND still remains due to lack of data that demonstrates a survival benefit in randomized controlled trials (RCTs) [2,3], in addition to possible complications of the LND.

A great majority of EC cases are diagnosed at earl stages. However, there is large heterogeneity regarding the histopathology and the characteristics of patients affecting prognosis and the adjuvant treatment recommendations. Different risk of recurrence in a multidisciplinary evidence-based classification for clinical practice has been established by the European Society of Medical Oncology, European Society of Gynaecological Oncology, and European Society of Radiotherapy and Oncology (ESMO-ESGO-ESTRO) for managing the

different subgroups of the disease [4]. According to this guideline early-stage endometrial cancer classified into low, intermediate, high-intermediate or high-risk for recurrence.

By considering the benefit-to-harm ratio, guidelines recommend considering omission of LND for patients with low-risk early-stage EC[5,6], and LND for high-risk EC is obviously prioritised as beneficial for survival [7]. However, the importance of lymph node dissection (LND) remains unclear for EC identified in intermediate (IR) and high-intermediate (HIR) risk goups[8]. Although the roles of LND are guiding adjuvant treatment planning by assessing the extend of disease, and removing apparent or occult metastatic lymph nodes for a therapeutic utility[9]. Previous studies pointed out that LND in IR and HIR EC reduced the risk of pelvic recurrences, but overall survival (OS) benefit was not reported [10,11].

In the present study, in a cohort of EC patients, we aimed to evaluate the prognostic difference between EC patients with or without performing LND to reveal the necessity of LND in the management of IR and HIR.

Materials and Methods

The data of 1294 consecutive patients who underwent primary surgical treatment for EC between 2003 and 2018 were retrieved from the computerized database at Hacettepe University Hospital, Turkey included to this study. A total of 258 patients were diagnosed as IR and HIR EC using the ESMO-ESGO-ESTRO classification were identified and their datas were retrospectively reviewed [8]. These criteria are related three pathological risk factors including grade 2 or 3 histology, the presence of LVSI and deep myometrial invasion. The patients were considered as IR as if they have; endometrioid histology with myometrial invasion <50% and histological grade 3; or myometrial invasion [?]50% and grades 1–2; or cervical involvement and grades 1–2. And patients were accepted as HIR if they have: age above 70 years with a risk factor, age between 50 and 69 years with two, and age above 18 years with three risk factors.

All patients underwent total hysterectomy and bilateral salphingoopherectomy (TH+BSO), peritoneal washing and pelvic ± para-aortic lymph node dissection (LND) was performed in selected cases. Patients were divided into two groups up to performing LND. Patients with non-endometrioid histology, synchronous epithelial ovarian cancer, patients who had undergone sentinel lymph node procedure, missing medical and pathological report were excluded from the study. It was described as adequate at least 10 lymph nodes for pelvic LND, and 5 lymph nodes for para-aortic LND. Patients were categorized according to lymph node counts, and the choice of 20 pelvic lymph nodes as the discrimination point in our study warrants further discussion. This threshold number is consistent with the mean and median number of lymph nodes removed during surgical staging in our patient population. Patients beyond these criteria were excluded from the study (Figure 1).

Collected data included patients' age, body mass index (BMI), co-morbidities, primary tumor size, myometrial invasion (MI), histological grade, LVSI, stage of primary EC, the surgical procedure, adjuvant treatments, date of diagnosis, date of last follow-up or death, date of disease recurrence and its' localizations. BMI was defined as the body mass in kilograms divided by the square of the body height in meters. Co-morbidities were consist of hypertension, diabetes, cardiovascular, and pulmoner diseases. The largest diameter of the tumor considered as primary tumor size. The surgical specimens were examined by gynecologic pathologists, and the grading was determined by standard FIGO criteria. LVSI is defined as the presence of tumor in lymphatic and/or vascular spaces within the uterine myometrium[12]. All tumors were staged according to the revised 2009 FIGO staging system.

SPSS (Statistical Package for Social Sciences for Windows, Armonk, NY: IBM Corp.) version 22.0 was used for the recording and analysis of data. Correlation of variables between groups was assessed using Chi-square or Fisher Exact test in the case of categorical data and using the Student t-test for quantitative variables. Survival probability was studied by the Kaplan–Meier method and the equality of survival curves was tested by the log-rank test. Disease-free survival (DFS) was calculated from the date of treatment start until recurrence or death from any cause. Overall survival (OS) was defined as the time elapsed between date of diagnosis and date of death, or last follow-up. A p-value of less than 0.05 was considered to be statistically significant and all statistical tests were two-sided.

Committee permission was not sought due to the retrospective design of the study. However, all participants signed an informed consent which forgives the institution to utilize their data.

Results

A total of 256 patient postoperatively diagnosed with IR and HIR endometrioid type EC were included to study. The study population included 141 (55 %) and 115 (45 %) patients identified as IR and HIR EC, respectively. Among IR EC patients, 94 (66.6%) had underwent pelvic and para-aortic lymphadenectomy (PPLND), 14 (9.9%) had pelvic lymphadenectomy (PLND) and lymphadenectomy was not performed in remaining 33 (23.4%) cases. In HIR EC patients, 73 (63.5%) had underwent PPLND, 11 (9.5%) had underwent PLND, and 31 (27%) patients had no lymphadenectomy. The mean number of pelvic lymph nodes removed in LND group was 25.7±11.8. Among IR EC patients with LND, 36.7% (n=32) patients had [?] 20 pelvic lymph nodes, and the remaining had more than 20 pelvic lymph nodes. While these figures were 38.1 % (n=32) and 61.9 % (n=52), respectively in HIR EC patients with LND (p=0.19). Figure 1 shows the flow of patients through the study design.

The demographics and clinicopathologic characteristics of the whole cohort are shown in Table 1. Mean (range) patients' age was 61.1+-9.7 (range, 27-86) years and the mean BMI was 29.1+-7.9 kg/m^2. The comorbidities was detected in 122 (47.6%) patients. Tumors larger than 3 cm were seen in 30.4% (n=78) of all patients. Eighty-two patients (32%) had <50% MI and the remaining 174 (68%) had [?] 50 % MI. One hundred thirty-seven patients (53.5%) had grade 1, 63 (24.6%) had grade 2, and 56 (21.9%) had grade 3 endometrioid EC. Presence of LVSI was identified in 63 (25%) patients. For the 195 IR and HIR EC patients who had undergone LND, the rate of lymph node involvement was 10.3% (n=20). Adjuvant treatment was not received in 103 patients (40.2%). Remaining 153 (59.8%) patients recieved adjuvant treatment including radiotherapy (50.5%, n=129), chemoradiotherapy (6.2%, n=16), and chemotherapy (3.1%, n=8). Four (1.6%), 3 (1.2%), and 10 (3.9%) patients experienced local, pelvic and distant recurrences, respectively (Table 1).

Comparisons between EC patients with LND and no LND groups are summarized in Table 2. Patients with LND were significantly younger with a mean age of 60.3+-9.8 years compared to the patients with no LND group with a mean age of 63.4+-10.8 years ($p < 0.05$). The BMI was significantly lower in LND group. The rate of comorbidities in patients with EC was significantly lower in the LND group ($p < 0.05$). There were no notable differences between other comparisons including tumor size (p=0.73), EC risk group (p=0.13), FIGO stages (p=0.21) and grade (p=0.68), LVSI (p=0.43) and adjuvant treatments (p=0.22) among both groups. During the median follow-up of 41 months (range, 12–222), 12 (6.2 %) patients with LND, and 5 (7.8 %) patients without LND had disease recurrence (p=0.77).

Survival analysis showed a 5-year OS of 86.7% in the LND group, and 84.2% in the no LND group (log-rank test=0.39), Kaplan-Meier analysis revealed a similar 5-year DFS in the LND group compared to the no LND group (81.5% vs. 82.9%, respectively; log-rank test=0.13). LND did not improve OS and DFS in IR and HIR EC patients (p=0.92, p=0.80) (Figure 2). Moreover, LND did not improve OS and DFS in either the IR and HIR group of patients, separately (p= 0.87, p=0.84; p=0.95, p=0.63).

Table 3 showed the cox proportional-hazards models of OS and DFS among IR and HIR EC. Patients were categorized according to pelvic lymph node counts into three groups as no lymph node group, lymph nodes [?]20 and lymph nodes > 20. The lymph node count was not associated with OS and DFS for all subsets of patients with EC grouped by recurrence risks.

Discussion

This study was powered to determine the impact of LND on survival for IR and HIR EC, and it concluded that there were no differences observed between patients in whom LND were performed and those in whom LND were not performed with respect to 5-year Kaplan-Meier estimates of OS, and DFS were statistically insignificant. Additional analysis, particularly for IR and HIR EC groups was performed to determine whether these estimates will converge or continue to diverge. Our results were in line with the previously

published two RCTs [2,3]. These RCTs revealed that LND in EC had only a diagnostic role to guide the adjuvant treatments such as radiotherapy and chemotherapy without providing a survival benefit.

These RCTs concluded that the routine systematic pelvic LND cannot be performed for therapeutic purposes in primary surgery for early-stage EC patients [2,3]. The main critique of RCTs was the presence of high percentage of EC patients with either low-risk or advanced disease. Nevertheless, the administration rates of adjuvant treatments are similar among LND and no LND groups. Our study diverges from many studies with investigating IR and HIR EC groups by excluding the remaining subgroups of EC. Besides, the present study had an equal proportion of administering adjuvant treatments among LND and no LND groups.

Moreover, to conduct a stratified analysis, we investigate the impact of lymph node count on survival. Our results revealed that the count of pelvic lymph nodes were not predictors of IR and HIR EC outcomes. Contrary to our findings, Lutman et al. showed that pelvic lymph node count was found to be a prognostic factor in high grade EC patients. Further analysis revealed a total of 12 or more pelvic lymph nodes was a predictor for survival in early staged HIR EC patients[13]. The putative therapeutic benefit of increasing the number of dissected lymph nodes may be attributed to accurate stage assignment and subsequent use of adjuvant therapies in node-negative EC[14]. The reason for the inconsistency of previous results with our study might be the high proportion of utilizing adjuvant treatments in the no LND group than its expected[15,16]

There were limited number of studies particularly focusing on postoperatively assessed IR EC patients. Coronado et al. found that LND has no any survival benefit in IR EC without increasing in perioperative morbidity or mortality [17]. Moreover, L. Bougherara et al. also reported that survival benefit was not improved in IR EC patients by performing lymphadenectomy without excluding the nodal positive patients [11]. Our results are consistent with these two studies by showing LND in IR EC patients has no benefit on survival. However, the SEPAL study concluded that performing complete LND has a survival benefit for EC patients at intermediate risk that is corresponding to IR and HIR according to ESMO-ESGO-ESTRO classification[18].

Contrary to our findings, some retrospective studies showed a therapeutic role of an adequate LND in HIR EC patients[9,13,19]. The main suggestions for the benefits of survival were the suggested that the adequate LND might provide survival benefit by the removing of occult lymph node metastases. While the present study was not designed to evaluate for the presence of occult metastases, the removal of possible occult metastases does not appear to be clinically useful for IR and HIR EC. The inconsistency of our results might be explained with the risk of LN involvement in IR and HIR EC appears lower than some relevant previous studies[19,20], with a rate of 10.3%. But larger-scale prospective studies are needed to evaluate the oncologic safety of omitting LND in HIR EC.

Some studies considered that the patients with no LND were more likely to have nodal recurrence than the patients with LND in IR and HIR EC[18-20], but our results did not support this finding. Regarding HIR EC patients, a recent French national retrospective study showed that unstaged patients had more nodal recurrence than surgically staged patients [19]. However, a recently performed a retrospective matched pair study, which included 178 diagnosed of IR EC, showed the number and the site of recurrence was similar in LND and no LND groups [17].

The limitation of the present study are the retrospective design and the lack of evaluating the risks of LND. Without illuminating the morbidity of LND, there were no difference observed in OS and DFS between IR and HIR EC patients with LND-induced complications and no LND. The results of the present study were similar with many published studies including two RCTs in highly stratified EC risk groups with lymph node counts. Considering the systematic nodal staging is associated with higher morbidity [21], with this regard, we believe that the use of sentinel lymph node procedure might be better for minimizing the possible post-operative morbidities in this selected patient groups.

Conflict of Interest

The authors have no conflicts of interest.

Author contribution

Data curation: UA, MG.

Supervision: CS, NO.

Writing – review & editing: UA, MG.

Investigation: UA, CS, NO.

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Figure Legends

Figure 1. Chart flow of election of endometrial cancer who were accrued into the study

Figure 2. Overall survival (A) and Disease-free survival (B) of IR and HIR EC patients

Characteristics	**Value, n (%)**
Age (years), mean±standard deviation	61.1±9.7
BMI (kg/m^2), mean±standard deviation	29.1±7.9
Co-morbidities	
Yes	122 (47.6)
No	134 (52.4)
Tumor size (cm)	
>3	78 (30.4)?¿?
3	168 (69.6)
Myometrial invasion	
<50%	82 (32)?¿?
50%	174 (68)
FIGO Grade	
Grade I	137 (53.5)
Grade II	63 (24.6)
Grade III	56 (21.9)

Characteristics	Value, n (%)
LVSI	
Yes	64 (25)
No	194 (75)
Lymphadenectomy	
Pelvic	25 (9.7)
Pelvic and para-aortic	165 (64.5)
None	66 (25.8)
Lymph Node Involvement	
No	175 (89.7)
Yes	20 (10.3)
Adjuvant Treatment	
None	103 (40.2)
Radiotherapy	129 (50.5)
Chemoradiotherapy	16 (6.2)
Chemotherapy	8 (3.1)
Recurrences (n)	
No	239 (93.3)
Total recurrences	17 (6.7)
Vaginal/ local	4 (1.6)
Pelvic	3 (1.2)
Distant	10 (3.9)

Table 1. Clinicopathologic characteristics, demographics, and outcomes of study cohort (n=256)

Table 2. Comparision of demographical and pathological features of patients with intermediate and high-intermediate risk endometrial cancer

	LND-Group, n(%)	No LND-Group, n(%)
Characteristics		
Age (years), mean±standard deviation	60.3±9.8	63.4±10.8
BMI (kg/m^2), mean±standard deviation	28.3±7.8	31.7±8.1
Additional Disease		
Yes	90 (46.1)	38 (59.3)
No	105 (53.9)	26 (40.7)
Tumor size (cm)		
>3	57 (29.2)	21 (32.8)
3	138 (70.8)	43 (67.2)
Risk Groups		
Intermediate	108 (55.3)	33 (51.6)
High-intermediate	84 (44.7)	31 (48.4)
FIGO Stage		
Stage IA	55 (28.2)	21 (32.8)
Stage IB	114 (58.5)	40 (62.6)
Stage II	6 (3.1)	3 (4.6)
Stage III	20 (10.3)	NA
Grade		
I–II (Low-grade)	153 (78.4)	49 (76.5)
III (High-grade)	42 (21.6)	15 (23.5)
LVSI		

	LND-Group, n(%)	No LND-Group, n(%)
Yes	45 (23)	18 (28.1)
No	150 (77)	46 (71.9)
Adjuvant Treatment		
None	89 (45.6)	28 (43.7)
Radiotherapy	101 (51.8)	33 (51.6)
Chemotherapy	2 (1.1)	1 (1.6)
Chemoradiotherapy	3 (1.5)	2 (3.1)
Recurrences (n)		
No	183 (93.8)	59 (92.2)
Yes	12 (6.2)	5 (7.8)
NA: Not available, BMI: Body Mass Index	NA: Not available, BMI: Body Mass Index	NA: Not available, BMI: Body M

Table 3 . Influence of pelvic lymph node count on overall and progression-free survival among HIR EC subgroups.

	Disease-free survival
	HR
IR EC	
No LND-Group	1.14
LND-Group	
[?]20 Lymph node	1.08
>20 Lymph node	0.95
HIR EC	
No LND-Group	0.88
LND-Group	
[?]20 Lymph node	1.32
>20 Lymph node	0.87
The number of dissected lymph nodes less than 12 was considered as no LND.	The number of dissected lymph nodes less

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