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Original Article

Role of lymphadenectomy in intermediate-risk endometrial cancer: a matched-pair study

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ABSTRACT

Objective: To assess the impact of lymph node dissection (LND) on morbidity, survival, and cost for intermediate-risk endometrial cancers (IREC).
Methods: A multicenter retrospective cohort of 720 women with IREC (endometrioid histology with myometrial invasion <50% and grade 3; or myometrial invasion ≥50% and grades 1–2; or cervical involvement and grades 1–2) was carried out. All patients underwent hysterectomy and bilateral salpingo-oophorectomy. A matched pair analysis identified 178 pairs (178 with LND and 178 without it) equal in age, body mass index, co-morbidities, American Society of Anesthesiologist score, myometrial invasion, and surgical approach. Demographic data, pathology results, perioperative morbidity, and survival were abstracted from medical records. Disease-free survival (DFS) and overall survival (OS) was analyzed using Kaplan-Meier curves and multivariate Cox regression analysis. Cost analysis was carried out between both groups.
Results: Both study groups were homogeneous in demographic data and pathologic results. The mean follow-up in patients free of disease was 61.7 months (range, 12.0–275.5). DFS (hazard ratio [HR]=1.34; 95% confidence interval [CI]=0.79–2.28) and OS (HR=0.72; 95% CI=0.42–1.23) were similar in both groups, independently of nodes count. In LND group, positive nodes were found in 10 cases (5.6%). Operating time and late postoperative complications were higher in LND group ($p<0.05$). Infection rate was significantly higher in no-LND group ($p=0.035$). There were no statistical differences between both groups regarding operative morbidity and hospital stay. The global cost was similar for both groups.
Conclusion: Systematic LND in IREC has no benefit on survival, although it does not show an increase in perioperative morbidity or global cost.

Keywords: Endometrial Neoplasms; Lymph Node Excision; Costs and Cost Analysis; Survival; Risk Factors; Morbidity

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No potential conflict of interest relevant to this article was reported.

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INTRODUCTION

Since the publication of the Gynecologic Oncology Group (GOG) study [1], the staging of endometrial cancer (EC) is based on surgical evaluation. By 1988 the International Federation of Gynecology and Obstetrics (FIGO) and GOG recommended systematic surgical procedure that included total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH&BSO), pelvic washing, and pelvic and para-aortic lymph node dissection (LND) in patients that presented risk factors including unfavorable histology and myometrial invasion [2]. The protocol stood until 2005, the year in which the American College of Obstetrics and Gynecology (ACOG) and FIGO recommended a complete surgical staging in every patient regardless of the risk factors [3]. This opinion was based on 2 retrospective studies which evidenced survival improvement in patients with EC stage I, grade 3 or more advanced tumors when the complete surgical staging was held [4,5]. However, no randomized studies supported these data. For this reason, the systematic LND has been lately a reason of debate. These doubts are more than justified considering the serious consequences and possible complications of the LND just to stratify the patient, if in fact there is no impact on the overall survival (OS). In consequence, more selective and individualized treatment regimens have been proposed in order to avoid an overtreatment. Several international guidelines already agree that patients classified as European Society of Medical Oncology (ESMO) low risk for recurrence tumors [6] could benefit from the conservative staging procedures without LND [7,8]. However, the controversy remains for tumors identified as ESMO intermediate or high-risk for recurrence. Recently a match pair retrospective study has observed the lack of prognostic value of LND in high risk EC [9], but studies analyzing intermediate-risk have not been performed.

The aim of our study was to evaluate the impact of LND on disease-free survival (DFS) in EC with intermediate-risk as primary objective; OS, morbidity, and cost as secondary end-points.

MATERIALS AND METHODS

After approval of Institutional Review Board in each participating center, we conducted a multicenter retrospective study between the years 1995 and 2013 at 6 tertiary Spanish medical centers. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement has been followed for this study. A sample of 720 women diagnosed of intermediate-risk EC (IREC) according to the guidelines of the Spanish Society of Gynecology and Obstetrics (SEGO) and ESMO (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) [6,7] were identified and their medical charts reviewed.

Fig. 1 shows a flow chart of subjects and reasons for withdrawal. We excluded 6 (0.8%) out of 720 patients who did not undergo surgery as primary treatment because of severe morbidity prior to surgery. These patients were treated with progestin or radiotherapy. We excluded 66 (9.1%) cases with follow-up less than 12 months.

Patients with enlarged lymph nodes (LNs), as noted on computed tomography (CT) scan or magnetic resonance imaging (MRI), were included in the study. The remaining 648 (90%) cases were analyzed using a case-matched method to obtain equal cohorts of patients respect to age, body mass index (BMI), pre-surgical co-morbidities, American Society of Anesthesiologists (ASA) score, myometrial invasion and surgical approach to assess short-

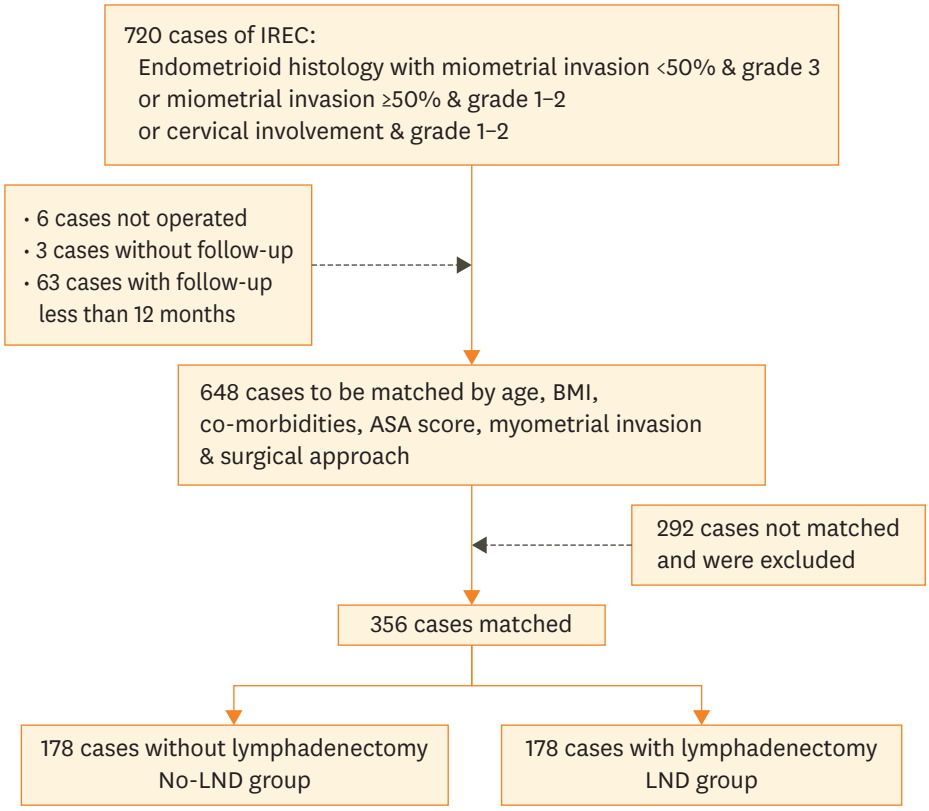

Fig. 1. Chart flow of election of cases in paired match selection.
ASA, American Society of Anesthesiologist; BMI, body mass index; IREC, intermediate-risk endometrial cancer; LND, lymph node dissection.

term surgical and oncological outcomes regarding the performance or not of any kind of LND (pelvic or pelvic and para-aortic LND). Finally, a total of 356 (49.4%) patients (178 matched pairs) were included in the final comparison.

All patients underwent TAH&BSO. Pelvic or pelvic and para-aortic LND were performed at institution discretion based on surgical team experience. The same oncological team in each center performed all surgical interventions. All patients were managed following the guidelines approved by the SEGO, which considered recommended but not mandatory the performance of LND for IREC cases.

Preoperatively, mechanical bowel preparation could be carried out, and prophylactic antibiotics and low molecular weight heparin always administered. Intravenous fluids were maintained until patients tolerated oral fluids, usually within first 24 hours after the surgery. Foley catheter was usually removed the day after the surgery. Serum hemoglobin levels were routinely obtained within 24 hours after the procedure. Patients were discharged home if they demonstrated ability to ambulate independently, tolerated a regular diet, had stable vital signs and pain was under control.

Route of surgery depended on the surgical team and institution experience. Due to its influence in morbidity outcomes, match paired controls were also selected for this variable. External beam radiotherapy (EBRT), brachytherapy and chemotherapy were selectively used postoperatively depending on the Institutional Tumor Board decision, as well as patients'

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follow-up. These data were also included in the match-pair analysis. The presence of recurrence, type of therapies, and patient status were collected during the patient's follow-up.

The cost analysis was performed using economic data provided by the economical department of each center. The value for each item analyzed was the median cost in euros of the participating centers. All costs with regards to surgery (including Robotic Da Vinci Surgical System and laparoscopy towers with an amortization over 7 years), human resources, the use of surgical instruments, the operating room per minute, and cost of conversion to other surgical routes. The hospitalization cost included the hospital stay and expenses resulting from complications, blood transfusions, intensive care unit stay, and re-operations. We did not include adjuvant treatment and societal costs.

For the statistical analysis, after obtaining the matched pairs cohorts, differences between the study groups (178 cases with LND vs. 178 cases with no-LND) were analyzed. Continuous variables were expressed as median and range, and were compared using the t-test in normal distributions or the Mann-Whitney test in non-parametrical distributions. Discrete variables were represented with absolute frequencies and percentages, and they were compared by a chi-squared test or the Fisher's exact test in case of small cell comparisons. Receiver operating characteristic (ROC) curve was calculated to analyze the relation between the number of nodes removed and nodes status to identify the cut-off predicting the number of nodes removed to find an affected node. For survival analysis, Cox's method was used to assess which factors were directly associated with survival. Multivariate modeling using Cox's proportional hazard models, including the significant variables in univariate analysis, was performed to obtain a subset of independent predictors of DFS and OS. Hazard ratio (HR) with 95% confidence interval (CI) was calculated. The Kaplan-Meier method was used to estimate the survival distribution in the study groups. The log-rank test was used to calculate the statistical signification between the groups in relation to disease recurrence and death. All statistical tests were 2-sided and statistical significance was defined as p-value less than 0.05. All computations were performed using STATA Statistics/Data Analysis version 11.2 (StataCorp LP, College Station, TX, USA).

RESULTS

A total of 356 patients (178 matched pairs) with IREC were included in the study. The lymphadenectomy group (LND group) included 178 patients who underwent TAH&BSO and LND. In the no-lymphadenectomy group (no-LND group), 178 matched patients underwent only TAH&BSO.

Patient's characteristics, preoperative findings, pathology and therapeutic details are shown in **Table 1**. Both surgical groups were similar in all variables, except in FIGO stage.

In the LND group, the median number of nodes removed was 15 (range, 1–65): 16 nodes for pelvic LND (range, 1–34) and 6 nodes for para-aortic LND (range, 1–42). In 67 cases (37.6%) the total nodal count was ≥18, and in 10 patients (5.6%) positive nodes were observed. All cases with pelvic positive nodes had a para-aortic LND, but para-aortic metastases were detected only in 1 case.

Adjuvant treatment was not added in 78 patients (21.9%). The complications derived from surgery, advanced age, co-morbidities, and refusal of consent were the reasons for not

Table 1. Patient's demographics and pathologic details in match-paired IREC

Characteristics	Lymphadenectomy (n=178)	No lymphadenectomy (n=178)	p-value*
Age (yr)	71.0 (37–86)	71.0 (40–91)	0.431
BMI (kg/m^2)	30.0 (19–47)	30.1 (21–49)	0.355
Associated diseases†	133 (74.7)	133 (74.7)	>0.999
ASA score			>0.999
I–II	57 (32.0)	57 (32.0)	
III–V	54 (30.4)	54 (30.4)	
Unknown	67 (37.6)	67 (37.6)	
Years from menopause	20.0 (0–50)	20.0 (0–56)	0.252
Parity	2.0 (0–7)	2 (0–8)	0.464
Pre-surgical hemoglobin (mg/L)	13.4 (9.4–15.9)	13.1 (10.0–16.2)	0.550
Histologic subtype			0.502
Endometrioid pure	174 (97.8)	170 (95.5)	
With mucinous differentiation	1 (0.6)	2 (1.1)	
With squamous differentiation	3 (1.7)	6 (3.4)	
Histological grade			0.890
G1	76 (42.7)	80 (44.9)	
G2	83 (46.1)	80 (44.9)	
G3	20 (11.2)	18 (10.1)	
Myometrial invasion			>0.999
<50%	28 (15.7)	28 (15.7)	
≥50%	150 (84.3)	150 (84.3)	
FIGO stage			0.005
I	166 (93.3)	175 (98.3)	
II	2 (1.1)	3 (1.7)	
III	10 (5.6)	0 (0)	
VI	0 (0)	0 (0)	
Tumor size (cm)	3.0 (0.2–8.0)	3.0 (0.5–7.0)	0.265
Surgical approach			>0.999
Laparotomy	145 (81.9)	145 (81.9)	
Laparoscopy or robotic-assisted laparoscopy	32 (18.1)	32 (18.1)	
Lymphadenectomy			-
Pelvic only	141 (79.2)	-	
Pelvic and paraaortic	37 (20.8)	-	
Adjuvant treatment			0.653
None	36 (20.2)	42 (23.6)	
Irradiation	129 (72.5)	126 (70.8)	
Chemotherapy	1 (0.6)	2 (1.1)	
Irradiation and chemotherapy	12 (6.7)	8 (4.5)	
Follow-up in alive (mo)	58.1 (12.0–235.9)	67.4 (12.4–275.5)	0.684

Data are shown as median (range) or cases (%).
ASA, American Society of Anesthesiologist; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; IREC, intermediate-risk endometrial cancer.
*The t-test in variables with normal distribution, Mann-Whitney test for the others continuous variables, and χ^2 test or Fisher's test in discrete variables.
†Includes hypertension, diabetes, lung, and heart diseases.

receiving it. In the 10 patients with positive nodes, EBRT was used as adjuvant treatment in 4, chemotherapy alone in 1 patient, and combined chemo-radiotherapy in 5 patients.

1. Follow-up and survival analysis

After a median follow-up of 61.7 months (range, 12.0–275.5), 55 (15.4%) women presented a relapse and 56 (15.7%) women deceased. Among relapsed patients, at last contact, 12 were alive free of disease, 19 were alive with disease, and 24 died. Among patients deceased, 25 women were death disease-related, 26 death of other disease, and 6 unknown. In the LND group, 5 out of 10 patients with positive LNs and 26 out of 168 with negative LNs experienced relapse. The median of LNs dissected in cases with negative LNs were 14 (1–37) in relapse and 13 (1–61) in non-relapse group (p=0.795), and in cases with positive LNs: 18.5 (18–19) in relapse and 23.5 (9–30) in non-relapse (p=0.552), respectively.

Table 2. Recurrence and mortality in IREC

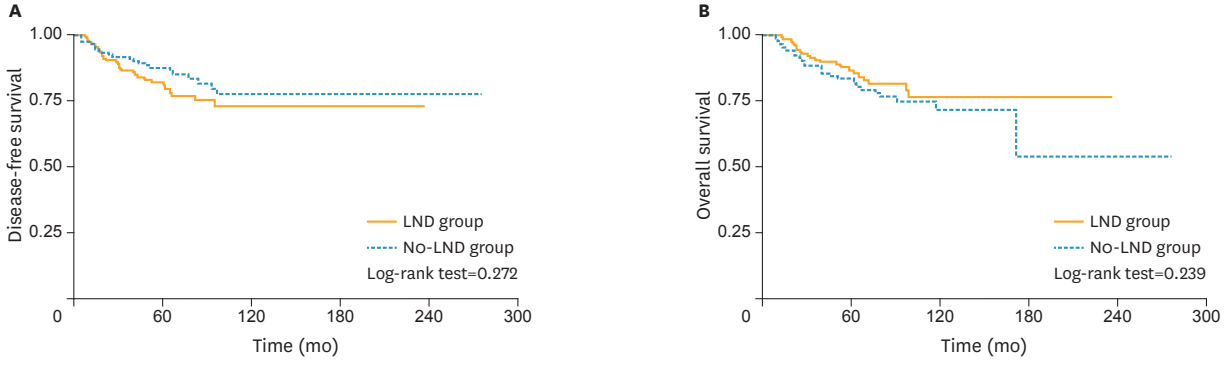
Characteristics	Lymphadenectomy (n=178)	No lymphadenectomy (n=178)	p-value
Recurrence	31 (17.4)	24 (13.5)	0.293
Site of recurrence			0.306
Pelvis	7 (3.9)	10 (5.6)	
Nodes*	6 (3.4)	3 (1.7)	
Spread†	18 (10.1)	11 (6.2)	
Decrease	23 (12.9)	33 (18.5)	0.145
Cause of decrease			0.028
Dead for tumor	15 (8.4)	10 (5.6)	
Dead for other causes	6 (3.4)	20 (11.2)	
Cause unknown	2 (1.1)	3 (1.7)	

Data are shown as cases (%).
IREC, intermediate-risk endometrial cancer.
*Recurrence in nodes as first localization. †Recurrence in 2 or more sites, or distant metastases.

The site of recurrence was similar in both study groups; however, deaths due to other diseases were significantly more common in the no-LND group compared to LND group (**Table 2**). Patients with recurrence were treated surgically with resection in 9 cases (16.4%); in 5 cases (9.1%) adjuvant chemotherapy was administrated; 3 (5.4%) patients received radiotherapy as unique treatment; 23 (41.8%) patients were treated with chemotherapy alone; and 4 (7.3%) with concurrent chemoradiation. Eleven (20%) patients did not receive any treatment, and palliative care was used.

In the LND group, a ROC curve was calculated to determine the number of nodes predicting node involvement, regardless the lymphatic area dissected. The curve showed that 18 or more nodes was the best cut-off to detect positive nodes, with a sensitivity of 68.3% and specificity of 67.4% (area under the curve=0.525; 95% CI=0.45–0.60). This value was considered as a satisfactory LND in survival analysis.

Survival analysis shown a 5-year DFS of 79.5% in the LND group, and 87.4% in the no-LND group (log-rank test=0.272). Kaplan-Meier curves for DFS did not show a significant benefit for LND (**Fig. 2A**). Cox's univariate analysis identified chemotherapy (p=0.002) and advanced FIGO stage (p=0.025) as predictor factors of recurrence. Advanced FIGO stage (III–IV) (HR=8.63; 95% CI=3.60–20.70; p<0.001) was the unique independent factor of recurrence in



No. at risk						
LND group	178	66	16	2	1	0
No-LND group	178	82	16	2	1	0

No. at risk						
LND group	178	73	17	2	1	0
No-LND group	178	85	19	2	1	0

Fig. 2. DFS (A) and OS (B) in patients with IREC.
DFS, disease-free survival; IREC, intermediate-risk endometrial cancer; LND, lymph node dissection; OS, overall survival.

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Table 3. Univariate analysis of DFS and OS using Cox's model

Characteristics	DFS*		OS†	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (lineal increment per year)	0.99 (0.97–1.02)	0.883	1.06 (1.03–1.09)	<0.001
Lymphadenectomy				
No	1.00	-	1.00	-
Yes	1.34 (0.79–2.28)	0.282	0.72 (0.42–1.23)	0.723
No. nodes removed				
No lymphadenectomy	1.00	-	1.00	-
<18 nodes	0.53 (0.24–1.14)	0.525	1.13 (0.42–3.01)	0.805
≥18 nodes	0.66 (0.30–1.44)	0.298	1.15 (0.42–3.12)	0.793
Adjuvant treatment				
No	1.00	-	1.00	-
Yes	1.48 (0.44–4.95)	0.525	0.94 (0.31–2.85)	0.918
Type of adjuvant treatment				
None	1.00	-	1.00	-
Irradiation	2.00 (0.85–4.70)	0.112	1.02 (0.54–2.02)	0.903
Chemotherapy	12.31 (2.45–61.82)	0.002	2.70 (0.35–21.06)	0.344
Irradiation and chemotherapy	2.13 (0.53–8.52)	0.286	-	-
Histological subtype				
Endometrioid	1.00	-	1.00	-
Mucinous	-	-	0.05 (0.0–100)	0.721
Squamous	0.67 (0.09–4.85)	0.670	0.05 (0–43.35)	0.397
Histological grade				
G1	1.00	-	1.00	-
G2	1.33 (0.76–2.32)	0.319	1.54 (0.86–2.76)	0.141
G3	1.18 (0.45–3.13)	0.732	2.84 (1.33–6.06)	0.007
Myometrial invasion				
<50%	1.00	-	1.00	-
≥50%	0.79 (0.40–1.57)	0.506	0.66 (0.35–1.24)	0.195
FIGO stage				
I–II	1.00	-	1.00	-
IIIC	8.64 (3.30–20.69)	<0.001	2.36 (0.74–7.56)	0.201
Tumoral size (cm)				
≤2	1.00	-	1.00	-
>2	2.23 (0.92–5.40)	0.076	2.00 (0.93–4.31)	0.076

Multivariate analysis included all variables with p-value less than 0.10.
CI, confidence interval; DFS, disease-free survival; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; OS, overall survival.
*An independent variable of recurrence in the multivariate analysis was advanced FIGO stage (HR=8.63; 95% CI=3.60–20.70; p<0.001). †Independent variables of mortality in the multivariate analysis were the age (linear increment per year HR=1.06; 95% CI=1.03–1.09; p<0.001) and the grade 3 (HR=2.52; 95% CI=1.10–5.76; p<0.029).

the multivariate analysis (**Table 3**); while LND did not show statistical significance (p=0.272), regardless of the nodal count. Nodal recurrences were not significantly different among groups (6 in LND group vs. 3 in no-LND; p=0.306) (**Table 2**). In the 6 nodal recurrences of the LND group, 4 were located in the pelvis (in 1 of these patients the pelvic nodes were positive at surgery and in other 3 was concomitant with liver metastases) and 2 in the para-aortic area (in the context of disseminated disease in both cases).

Kaplan-Meier plots showed a similar 5-year OS in the LND group compared to the no-LND group (86.8% vs. 83.4%, respectively; log-rank test=0.239) (**Fig. 2B**). In the Cox's univariate analysis, the factors associated to lower OS were age (p<0.001), and the histological grade 3 (p=0.057). Age (linear increment per year HR=1.06; 95% CI=1.03–1.09; p<0.001) and the grade 3 (HR=2.52; 95% CI=1.10–5.76; p<0.029) were the only independent factors influencing OS in multivariate analysis (**Table 3**).

When we stratified by adjuvant treatment, the LND was not associated with DFS and OS neither in the group with adjuvant treatment (HR=1.26; 95% CI=0.68–2.33; p=0.466 for DFS

and HR=0.69; 95% CI=0.36–1.32; p=0.267 for OS, respectively), nor in the non-adjuvant treatment group (HR=1.34; 95% CI=0.22–8.01; p=0.752 for DFS and HR=0.48; 95% CI=0.15–1.61; p=0.236 for OS, respectively).

2. Morbidity and cost analysis

Perioperative outcomes are shown on **Table 4**. The median operating time was significantly longer in the LND group. The hemoglobin drop trended to be higher in the LND group (p=0.056). Rate of early postoperative complications (<30 days) was similar in both groups. However, infections, defined by any infection or fever detected in postoperative period, was significantly higher in the no-LND group. The late postoperative complications (≥30 days from discharge) were significantly higher in the LND group. Lymphocyst and lower-limb lymphedema were the most common findings.

The estimated costs (in euros), of the surgical procedures are shown in **Table 4**. There were no significant differences between the study groups with respect to the surgical treatment,

Table 4. Perioperative morbidity and estimated cost in euros of lymphadenectomy for IREC

Characteristics	Lymphadenectomy (n=178)	No lymphadenectomy (n=178)	p-value*
Surgical time (min)	140.0 (80–330)	99.5 (40–200)	<0.001
Estimated blood loss (mL)	210.0 (45–1,000)	200.0 (60–600)	0.249
Drop of hemoglobin (g/dL)	2.1 (0.4–4.9)	1.8 (0.1–7.8)	0.056
Transfusion rate	6 (3.4)	10 (5.6)	0.306
Surgical morbidity†	37 (20.8)	44 (24.7)	0.376
Length of hospital stays (day)	7.0 (2–33)	7.0 (1–30)	0.352
Overall complications	36 (20.2)	48 (26.9)	0.134
Intraoperative	6 (3.4)	9 (5.1)	0.429
Bowel/ureter injury	2	1	>0.999
Vascular injury	4	1	0.371
Bowel injury	0	3	0.248
Early postoperative	30 (16.9)	39 (21.9)	0.227
Clavien-Dindo classification			0.548
I–II	22	31	
III–IV	8	8	
Type of complication			
Infections‡	12	24	0.035
Vaginal cuff dehiscence	2	0	0.498
Thromboembolic disease	2	1	>0.999
Ileus	6	4	0.750
Heart/renal insufficiency	1	2	>0.999
Hematoma	5	6	>0.999
Other§	2	2	>0.999
Late postoperative	9 (5.1)	1 (0.6)	0.019
Lymphocyst	2	0	0.498
Lower-limb lymphedema	7	1	0.067
Readmittance	8 (4.5)	8 (4.5)	>0.999
Reintervention	7 (3.9)	6 (3.4)	>0.999
Cost in euros			
Surgical cost‖	1,223.3 (427.0–4,803.4)	1,116.8 (417.2–4,453.1)	0.624
Hospitalization cost¶	3,063.3 (1,120.4–17,413.4)	3,546.3 (635.2–14,308.7)	0.665
Global cost**	4,710.7 (2,049.5–11,686.7)	4,438.7 (2,047.2–13,684.4)	0.217

Data are shown as median (range) or cases (%).
LDN, lymph node dissection; IREC, intermediate-risk endometrial cancers.
*The t-test in variables with normal distribution, Mann-Whitney test for the others continuous variables and χ^2 test or Fisher's test in discrete variables. †Surgical morbidity was defined as presence of one or more of the following situations: transfusion, estimated blood loss >400 mL, surgical time >240 minutes or intraoperative complication. ‡Infection includes wound, urinary and/or, respiratory infections, and isolated fever. §Other complications include in LDN group a glycemic decompensation, hypertensive encephalopathy; and in no-LDN group acute psychosis and digestive hemorrhage. ‖Surgical cost include cost of technical recourses (7 years of amortization), personal, instruments used, cost of operating room, complications, and conversions to others surgical approaches. ¶Hospitalization cost include days of hospital stay, complications, transfusions, and need of unit care. **Global cost include all cost measured.

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hospitalization related costs or global costs. The mean cost to identify one patient with positive nodes among the 178 patients who underwent any type of lymphadenectomy was 83,850.5€.

DISCCUSSION

The benefit in DFS and OS of lymphadenectomy in IREC is still very controversial and there is no consensus among international scientific societies. This study did not found any benefit for survival in these types of tumors. The ACOG recommends the comprehensive surgical staging as an initial management of EC [11]; whereas others institutions suggest an individually adjusted LND approach [12]. The recently published thorough European consensus of the 3 societies of European Society for Radiotherapy and Oncology (ESTRO), European Society of Gynecologic Oncology (ESGO), and ESMO again do not clarify the surgical staging in patients with IREC [8].

There are just 2 prospective randomized studies analyzing the role of LND in EC [13,14]. Both, Benedetti Panici group and ASTEC study concluded that there was apparently no survival benefit of LND neither in low risk nor intermediate/high risk EC. However, there are no prospective randomized studies that assess expressly the role of LND in IREC. The main drawback of the A Study in the Treatment of Endometrial Cancer (ASTEC) was the absence of systematic para-aortic LND performance in the LND group, the low mean number of nodes retrieved, and the mathematical model used in the analysis [15,16]. These results were verified by a Cochrane group meta-analysis [17], and suggested the need of studies for intermediate-risk patients.

In the present study, the results can be limited because systematic LND including pelvic and para-aortic dissection was not carried out in all patients, and the number of para-aortic nodes removed was lower when compared with other studies [18]. Although, no minimum nodal counts have been established so far, some publications that focus on pelvic lymphadenectomy suggest that removal at least 10 pelvic nodes is needed to show a survival improvement [19]. Lutman et al. [20] suggested the excision of 12 LNs to improved survival in patients of intermediate/high-risk EC. A systematic review analyzed data from 2 randomized controlled trials (RCTs) and 7 observational studies, involving 16,995 patients with EC, showed that the efficacy of systematic LND, defined as removal of at least 10 LNs, resulted in improved OS in patients with intermediate/high-risk EC. The same group recently analyzed 476 patients with intermediate/high-risk EC and concluded that removing as many pelvic nodes as possible is required to warrant accurate nodal staging and improve survival [21]. Additionally, in our study the number of positive LN cases was low (10 cases), and probably a larger study could be needed to address those differences.

LND in intermediate/high-risk EC has been also studied in numerous retrospective trials, showing controversial results in relation to its survival benefit [22,23]. Our group recently performed a retrospective matched pair study, which included 194 (97 pairs) diagnosed of high-risk EC, finding no benefit in DFS and OS of LND [10]. Similarly, differences between pelvic and para-aortic LND compared to pelvic LND alone have been studied, again with controversial results [18,24]. The Survival Effect of Para-aortic Lymphadenectomy in Endometrial Cancer (SEPAL) study concluded that para-aortic LND had survival benefits for patients with intermediate/high-risk EC compare to pelvic LND alone [18]. However, the no-LND group was not reported, which could bias its final conclusions. Although, the role of para-aortic LND is established in the case of high-risk tumors, it remains to be determined in intermediate-risk tumors [25].

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An additional value of LND in EC could be the impact on the adjuvant treatment modification, specifically radiation therapy. In these sense, the nodal metastases have been described as independent prognostic factor of survival, that it is why need to be explored surgically, supporting systematic LND [26]. However, other studies suggested that surgical nodal evaluation could be unnecessary [10,27]. In our study, no impact on adjuvant treatment was observed.

In our study, we observed a low rate of perioperative complications and morbidity in the LND group. Nevertheless, we noted a significant difference between the 2 groups regarding late postoperative complications as lymphocyst and lower-limb lymphedema. These findings were previously observed in other studies [10,28]. The infection rate was significantly higher in the no-LND group, probably due to the same factors that could have the impact on the decision to not perform LND, such as clinical characteristic of the patients and associated diseases. In addition, we considered infection not only the related ones with the surgical wound, but whatever sign of infection, included isolated fever.

Finally, the cost effectiveness study could also argue for the implementation of LND. There were no significant differences between the 2 analyzed groups with respect to the surgical treatment, hospitalization related costs or global costs. These results concur with studies in high-risk EC [10] but not in low-risk EC [28]. Other authors, however, suggested that a selective LND strategy based on a preoperative prediction model is shown to be more cost-effective than routine LND for EC [17]. The differences are probably due to the inclusion of different risk tumors and the differences in National Health Service budgets. More prospective trials are needed, performing specific analyzes for each risk group to establish the efficiency of LND in EC.

This study has some drawbacks that must be considered. Although the matched pair analysis is the best way to study a retrospective cohort, this is not a randomized trial and its results have a limited evidence. On the other hand, the exclusion of 45% of cases could have caused the loss of cases with recurrence or death that could affect the survival, and the low LN count could have induced the omission of some cases with positive LN. However, the presented study has a strength due to a matched-pair design that reduces the bias in the patient selection, creating homogenous and comparable groups for the main features, that could alter the election of the LND and survival.

In conclusion, LND in IREC have no influence in DFS or OS rates. However, the role of the type of LND and its biological impact need to be further explored. LND did not increase early morbidity or costs, but it may present higher late postoperative complications rate. Considering the low rate of positive nodes found in this type of tumors and lack of benefit, LND cannot be recommended systematically, but it could be an option when the adjuvant treatment has to be planned. In absence of prospective randomized trials, the present study contributes to refocus the surgical management for patients with IREC.

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