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Original Research Article

Survival and prognostic factors of lymphadenectomy in endometrial cancer: a Tunisian single center experience

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ABSTRACT

Background: Endometrial cancer (EC) is the most common pelvic gynecological cancer. The purpose of the present study is to identify histoprognostic risk factors for lymph node involvement, evaluate the impact of lymphadenectomy on relapse and overall survival and assess prognostic factors influencing the survival rates in endometrial cancer.
Methods: This was a retrospective study of 249 cases of endometrial cancer, over a period of 16 years (2000-2015). We analyzed the clinical, pathological features and outcome of our patients. Curves of overall and recurrence-free survival were performed.
Results: In our cohort, stage IA was found in 46.6% of cases, stage IB in 14.5%, stage II in 13.7%, stage IIIA in 3.6%, stage IIIB in 2%, stage IIIC1 in 8.8%, stage IIIC2 in 4.4% and stage IV in 6.4%. The histologic type (p=0.02, OR=2.702, CI [1.169; 6.25]), myometrial invasion (p<0.001, OR=4.524, CI [1.960; 10.416]), lymphovascular space invasion (p=0.047, OR=2.267; CI [1.013; 5.076]) were the only independent factors of lymph node invasion in multivariate analysis. 5-years overall and recurrence free survival was 76.3% and 81.5%, respectively. Overall survival at 5 years was 64.6% with a lymph node ratio of less than 10%, 22.2% with a lymph node ratio between 10 and 50%, and zero with a lymph node ration greater than 50% (p=0.016). By studying the number of lymph nodes removed during lymphadenectomy, survival trend to be improved when the lymph node count increased.
Conclusions: The lymphadenectomy has an incontestable diagnostic and prognostic value. Present retrospective study showed the therapeutic interest of lymph node dissection in endometrial cancers.

Keywords: Endometrial neoplasm, Lymph node excision, Prognosis, Survival

INTRODUCTION

Endometrial cancer (EC) is the most common pelvic gynecological cancer.[1] The International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system recommend a surgical staging of EC without defining the appropriate limits of each lymphadenectomy (pelvic and paraoaortic) or a cut off number of lymph node (LN) required for an optimal procedure.[2] Thus, the preoperative staging of the disease is necessary, in order to avoid an excessive surgical procedure, or on the contrary insufficient.

This evaluation aims to assess the depth of myometrial invasion in order to classify patients in stage IA or IB, stromal invasion and identify the anatomopathological predictive factors lymph node (LN) involvement (type, grade and lymphovascular space involvement, tumor size) to select eligible patients for lymphadenectomy. The procedure of pelvic and paraoaortic dissection lengthens

the operating time and therefore the time of anesthesia. As the majority of patients are obese, elderly, and have several other comorbidities, reducing the morbidity and/or mortality related to the surgery procedure must be considered.

Lymph node involvement is the most important prognostic factor in EC and the therapeutic role of lymphadenectomy is still controversial.[3,4] Optimizing the management of clinically early stages by limiting the morbidity of surgery represent a real challenge. Present study aimed to identify histoprognostic risk factors for LN involvement in endometrial cancers and to evaluate the impact of lymphadenectomy on relapse and overall survival.

METHODS

We performed a retrospective longitudinal descriptive study including 249 patients followed for endometrial cancer at the Salah Azaiz Institute during the period from January 2000 to December 2015.

Were initially excluded from this study: all cases of synchronous endometrial and ovarian carcinoma, endometrial sarcomas, and cases of metastatic disease at the initial diagnosis or those who had palliative surgery.

Characteristics of the patients (age, personal and family history, menopausal status, gestational status, parity and risk factors), clinical data (type of surgical procedure), histological data (including tumor size, type, grade, lvsi, depth of myometrial invasion, extra uterine involvement, cervical stromal invasion, number of lns and ln status) and data of adjuvant treatment were collected. for all the patients, the staging was carried out according to the classification of the International Federation of Gynecology and Obstetrics (FIGO) 2009.

Statistical analysis

The data was analyzed with SPSS software version 20. The study of the various histopronostic factors recognized as predictive in LN invasion was performed by the Chi-squared, test Mann-Whitney U and Fisher's exact tests when appropriate for univariate analyses. We included into a multivariate logistic regression analysis all variables with a p value <0.05 to determine independent predictive factors of LN involvement and calculated the odds ratios (OR) and 95% confidential intervals (CI).

The overall survival (OS), loco-regional recurrence free survival (LRFS) and recurrence free survival (RFS) were established by the Kaplan-Meier method and compared by the Log-rank test in univariate analysis. Multivariate analysis was performed by the Cox regression method and identified independent factors of survival. The statistical significance level (p) was 0.05.

RESULTS

The mean age was 62 years (range: 28-95 years) and most of patients were postmenopausal (n=199, 79.9%). Demographic and clinicopathologic characteristics of the patients were summarized in Table 1.

Table 1: Demographic and clinicopathologic characteristics of the patients.

Characteristics	N=249	%
Age		
≥60	136	54.6
<60	113	45.4
Gravida (median–range)	5 (0-16)	
Parity (median–range)	4 (0-15)	
Menopause	199	79.9
Diabetes mellitus	54	21.6
Hypertension	17	28.5
Obesity	49	16.6
Stage		
I	152	61
II	34	13.7
III	47	18.9
IV	16	6.4
Histologic subtype		
Endometrioid	199	79.9
Non-endometrioid		
Serous	10	4.0
Clear cell	9	3.6
Mixted cell	3	1.2
Undifferenciated	1	0.4
Carcinosarcoma	27	10.8
Grade (for patients with endometrioid type)		
Grade 1	105	52.7
Grade 2	67	33.7
Grade 3	27	13.6
Tumor size, median (range), cm	**45 (0.9-15)**	
≤2cm	21	8.4
>2cm	119	47.8
Unknown	109	43.8
Depth of myometrial invasion		
<50%	151	60.6
≥50%	98	39.4
Lymphovascular space invasion (LVSI)		
Yes	60	24.1
No	171	68.7
Unknown	18	7.2
Stromal cervical invasion	63	25.3
Extra-uterine extension	42	16.9

Hysterectomy and bilateral oophorectomy was performed in all our patients. Lymph node surgery was performed in 92% of our patients. Pelvic lymphadenectomy (PL) was performed in 225 cases (90.3%). Paraaortic lymphadenectomy (PAOL) or biopsy was performed in 33 cases (13.2%) associated with a pelvic

lymphadenectomy in 29 cases (11.6%). Laparotomy was performed in 92.4% cases (n=230). The median duration of the surgical procedure was 180 minutes and increased by 43.4 minutes by combining a lymphadenectomy with a simple hysterectomy with bilateral adnexectomy by laparotomy.

Regarding intraoperative morbidity, 25% of our patients had intraoperatively blood transfusion and 6% of patients presented an intraoperative complication. Early postoperative complications occurred in 6.8% of our patients and 12% had late postoperative complications. The rate mortality of 2% (5 patients).

The most frequent subtype was type 1 in 79.9% of cases and type 2 was found in 20.1% of cases. For endometrioid adenocarcinomas, the most common tumor grade was grade 1 (49.7%). Grade 2 tumors were found in 33.7% of cases and grade 3 in 13.6% of cases. Vascular emboli (EV) were observed in 24.1% of cases.

Two hundred and twenty-three endometrial uterine curettage specimen (UC) were performed preoperatively. In 21 cases (9.4%), the pathological findings of the UC had failed to recognize a neoplastic lesion. We reported a discordance in the histological type between endometrial uterine curettage specimen (UC) and the final tumor examination after hysterectomy in 18 cases (8%). For endometrioid adenocarcinoma (n=116), the discordance in grade of differentiation was reported in 33 cases (28.4%) of cases (22.4% underestimation and overestimation in 6%).

Table 2: Lymph node status of the patients according to the surgical gesture.

LND	LN Status	N	Median of LN removed in LND Range
PLND	N-	174	15 (2-74)
	N+	21	10 (3-32)
	N+PL N-PA	5	15 (8-28) 14 (1-46)
	N+PL N+PA	6	20 (15-25) 15 (1-42)
	N-PL N+PA	6	18 (7-22) 4.5 (1-24)
PALND	N-PA	0	-
	N+PA	4	1.5 (1-4)

N: no lymph node involvement, N+: lymph node involvement, LND: lymph node dissection, PLND: pelvic lymph node dissection; PALND: paraoaortic lymph node dissection

According to FIGO 2009 classification, stage IA was found in 46.6% of cases, stage IB in 14.5%, stage II in 13.7%, stage IIIA in 3.6%, stage IIIB in 2%, stage IIIC1 in 8.8%, stage IIIC2 in 4.4% and stage IV in 6.4%. The median number of removed LN was 15 (range: 1-74). Forty-one (17.9%) patients had lymph node metastasis. We divided the patients into 4 groups according the number of retrieved NRLN: no lymphadenectomy in 20 cases (8%), 1-8 LN in 41 cases (16.5%); 9 and 16 LNs in 101 cases (40.6%) and more than 16 LNs: 87 patients (34.9%). Lymph nodes ratios were divided into 3 groups: <10%, 10%-50%, and more than 50% in 46.4%, 39.3% and 14.3% of the cases, respectively.

The median number of pelvic removed LN was of 15 (range: 2-74). Among the patients who had a PL, 32 (12.8%) had lymph node metastases and the median number of involved LNs was 2 (range: 1-16).

The median number of paraaortic removed LN was 8 (range: 1-46) with 16 cases of LN involvement (6%). Isolated paraaortic LN involvement was found in five cases (2%). The median number of metastatic LN was 3 (range: 1-13). Simultaneous pelvic and paraaortic LN involvement was reported in 54.5% of patients. Table 2 summarizes lymph node status.

Table 3: Univariate analysis of correlation between prognostic factors and LN metastasis.

Prognostic factors	N- (%)	N+ (%)	P
Depth of myometrial invasion			
≥50%	61 (66.3)	31 (33.7)	P<0.001
<50%	127 (92.7)	10 (7.3)	
Histologic type			
Type 1	161 (86.1)	26 (13.9)	P=0.001
Type 2	27 (64.3)	15 (35.7)	
Grade			
G1	88 (93.6)	6 (6.4)	P=0.001
G2	52 (82.5)	11 (17.5)	
G3	16 (64)	9 (36)	
LVSI			
Yes	34 (63)	20 (37)	P<0.001
No	138 (87.9)	19 (12.1)	
Stomal cervical invasion			
Yes	37 (62.7)	22 (37.3)	P<0.001
No	151 (88.8)	19 (11.2)	
Extra-uterine extension			
Yes	17 (44.7)	21 (55.3)	P<0.001
No	171 (89.5)	20 (10.5)	
Tumor size			
≤2 cm	18 (90%)	2 (10%)	P=0,13
>2 cm	79 (76%)	25 (24%)	

N: no lymphe node involvement; N+: lymph node involvement

Brachytherapy and external radiotherapy were performed in 77% (n=188) and 37.7% (n=94%) of the cases respectively. Adjuvant chemotherapy were administrated in 7.9% (n=19) of the cases. After a median follow-up of 38.5 months (range: 1-185), 169 patients (67.9%) were in clinical remission. Locoregional recurrence occurred in 26 patients (10.4%) with a median time of relapses of 17 months. Metastatic relapses occurred after a median delay of 16 months in 12.4% of cases.

Univariate analysis of the predictive factors of LN involvement revealed that the depth of myometrial invasion (p<0.001), histologic type (p=0.001), LVSI (p<0.001), extra-uterine extension (p<0.001), grade (p=0.001) and stromal cervical invasion (p<0.001) were significantly associated to lymph node involvement (Table 3). In multivariate analysis, histologic type (p=0.02, OR=2.702, CI [1.169; 6.25]), myometrial invasion (p<0.001, OR=4.524, CI [1.960; 10.416]) and LVSI (p=0.047, OR=2.267; CI [1.013; 5.076]) were the only independent factors of LN invasion.

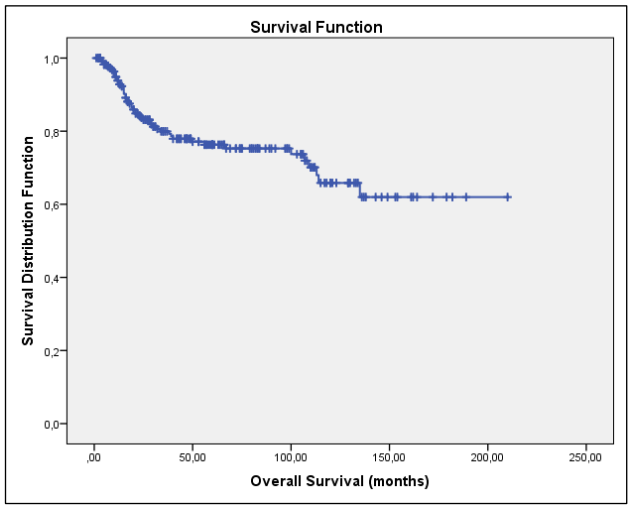

Figure 1: Kaplan-Meier curves of overall survival for patients with EC.

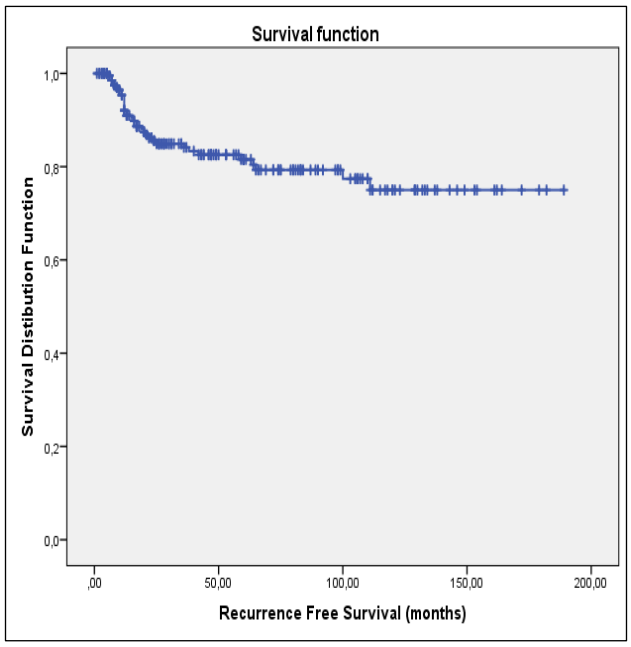

Figure 2: Kaplan-Meier curves of RFS for patients with EC.

The OS rate was 76.3% at 5 years and 65.8% at 10 years (Figure 1). The 5 and 10 years RFS were 81.5% and 77.4%, respectively (Figure 2).

Table 4: Correlation between LN status and survival.

Variables	5-years RFS		5-years OS	
	%	p	%	p
PLND				
N+	55.2	0.03	49.3	<0.001
N-	86.2		83.1	
PALND				
N+	33.3	0.028	20.5	0.004
N-	76.1		65.7	
LNR				
<10%	61	0.174	64.6	0.016
10-50%	25		22.2	
>50%	0		0	
Number of LN removed				
0	68.8	0.416	65	0.404
1-8	76		65.9	
9-16	80.7		80.1	
≥17	89.2		80.5	

LN: lymph node; PLND: Pelvic lymphadenectomy; PALND: Para-aortic lymphadenectomy; LNR: lymph node ratio

Table 5: Univariate analysis of correlation between clinicopathologic factors and survival.

Variables	5-years OS		5-years RFS	
	%	p	%	p
Age				
<60	80.8	0.024	85.7	0.131
≥60	71.7		76.8	
Stage				
I	87.7	<0.001	90.4	<0.001
II	73.2		73.8	
III	53.9		61.7	
IV	30.9		35	
Tumor size				
≤2cm	86.5	0.189	92.9	0.422
>2 cm	66.9		79.2	
Histologic type				
1	84.9	<0.001	87.5	0.001
2	34.9		47.8	
Grade				
1/2	88.7	<0.001	88.4	0.078
3	55.7		76.3	
Myometrial invasion				
<50%	83.2	0.003	87.8	0.042
≥50%	67.4		71.2	
LVSI				
No	82.6	<0.001	84.2	0.006
Yes	51.2		70.4	
Extrauterine invasion				
No	81	0.001	85.1	0.12
Yes	62.1		69	
LN status				
Negative	84.7	<0.001	87.8	<0.001
Positive	42.4		49.8	

The rate of OS and RFS at 5 years significantly decreased from 84.7% and 87.8% to 42.4% and 49.8%, respectively in case of lymph node involvement. The 5-years OS decreased from 83.1% to 49.3% in case of pelvic lymph node involvement and from 65.7% to 20.5% in cases of paraaortic LN invasion. The lymph node ratio (LNR) was inversely proportional to the OS. The 5-years OS was 64.6% in patients with LNR less than 10%, 22.2% with an LNR between 10 and 50%, and zero if the LN ratio exceeded 50%. The 5-year OS was 65% for patients without LN dissection, 65.9% for patients with 1to 8 removed LN, 80.1% in cases of 9 to 16 removed LN and 80.5% for a number of LN greater than or equal to 17.

Table 4 summarize the effect of LN metastasis, LNR and number of LN removed on OS, DFS and RFS.

Table 6: Multivariate analysis of correlation between clinicopathologic factors and survival.

Variable		HR	95% CI	p
5-years OS	STAGE I/II versus III/IV	8.268	3.54-19.31	<0.001
	GRADE ½ versus 3	3.344	1.355-8.252	0.009
5-years RFS	STAGE I/II versus III/IV	3.185	1.477-6.865	0.003
	Histologic type 1 versus 2	3.907	1.747-8.739	0.001

Univariate analysis revealed that the age (0.024), FIGO stage (<0.001), histological Type 2 (<0.001), high tumor grade for endometrioid adenocarcinoma (<0.001), myometrial invasion greater than 50% (0.003), LVSI (<0.001), extrauterine extension (p=0.001) and LN involvement (p<0.001) were prognostic factors of OS (Table 5). In multivariate analysis, the histological (p<0.001, HR= 8.268, CI [3.54-19.31]) and FIGO stage (p = 0.009, HR=3.344, CI [1.355-8.252]) were the only independent factors (Table 6).

DISCUSSION

EC is in the most of the cases confined in the uterus, with an excellent prognosis.[5] LN metastasis has been described as the most important prognostic factor in presumed early staged EC.[6] Morice and al reported a decrease in the 5 years disease free survival from 90% to 60-70% in case of pelvic LN metastasis and 30-40% in case of paraoaortic LN metastasis.[5] In the present study the 5-years RFS decreased from 86.2% to 55.2% in case of pelvic LN involvement and from 76.1% to 33.3% in case of paraoaortic LN metastasis.

Akbayir and al reported that the prevalence of pelvic LN involvement in EC was 10.1%.[7] The prevalence rate was 9% in the study published by chi et al.[8] In the study of Muallem and al, the prevalence of pelvic and para-aortic LN metastasis were 11.3% and 16.1%, respectively.[9] In our results the prevalence of pelvic LN metastasis was 12.8% and 6% in paraoaortic area.

Several authors have tried to estimate the number of LN that should be removed in the LN dissection to improve surgical staging and therapeutic management.

In a large series of 12, 333 women with EC, Chan and al showed that lymphadenectomy (pelvic with or without paraoaortic LN dissection) improved the OS of high and intermediate risk patients.[10] In fact, the 5-years disease-specific survivals was improved with a higher number of resected lymph nodes and increased from 75.3% to 86.6% in case of 1 LN removed to more than 20. However, LN dissection did not improve the survival of low-risk patients.

These findings were confirmed by another study published by Lutman et al.[11] The results showed an increase of both of overall and progression-free survivals when pelvic lymphadenectomy removed exceeded 12 LN for patients with stage I/II EC with poor histologic prognostic factors (type 2/grade 3).This study did not show a significant association between the number of lymph nodes removed during lymphadenectomy and survival in patients with EC grade 1/2 (low risk). Aburustum and al, suggested that the removal of 10 lymph nodes or more was associated to a better survival.[12] In the present study, the 5-year OS of patients without LN dissection was 65%, 65.9% for patients with 1 to 8 removed LN, 80.1% in cases of 9 to 16 removed LN and 80.5% for a number of LN greater than or equal to 17.

Nodal ratio is defined as the number of involved nodes divided by the total number of lymph nodes removed. This new setting could help to evaluate the nodal tumor burden and spread and the quality and extend of lymphadenectomy.

Polterauer and al. showed that patients with a LN ratio less than or equal to 10 %,> 15-50% and> 50% had a 5-year overall survival of 79%, 61%, and 36%, respectively. In multivariate analysis, LN ratio was an independent predictive factor of overall and progression free survivals.[13] In the present study, the 5-years OS was 64.6% in patients with LNR less than 10%, 22.2% with a LNR between 10 and 50%, and zero if the LN ratio exceeded 50%.

The discordance in the depth myometrial infiltration and the histologic grade between definitive and preoperative histopathological examination may lead to difficulty in the selection of the group of patients with low risk of recurrence.[14,15] For endometrioid adenocarcinoma we reported a discordance in the histological type in 18 cases, and a discrepancy in the grade of differentiation in 28.4% of cases (22.4% underestimation and overestimation in 6%).

The risk of LN dissemination depends on the primary tumor characteristics. In fact, Mariani and al reported a prevalence of lymph node metastasis of 16% in endometrioid type witch increase to 40% in non-endometrioid type of EC.[16]

Muallem and al demonstrated that high grade in endometrioid carcinoma was associated with 5 times more risk to had lymph node involvement and suggested that deep myometrial invasion (>50%) increased 5 times and 14 times the risk of pelvic and paraaortic lymph node invasion, respectively.[9] Toptaş and al reported that peritoneal cytology, omental involvement and adnexal involvement were correlated to the risk of lymph node dissemination.[17]

In the present study, the depth of myometrial invasion, histologic type, LVSI, extra-uterine extension, high grade, and stromal cervical invasion were identified as the most predictive factors of LN involvement in univariate analysis. Histologic type, myometrial invasion, and LVSI were the only independent factors of LN invasion. Solmaz and al, reported that LVSI and stromal cervical invasion were independent predictors factors of lymph node involvement.[18] A cut off of 2cm of tumor size was not correlated with LN metastasis. These finding were in line with the conclusions of Widschwendter et al and Akbayir et al.[19,7]

Several studies tried to establish monograms to identify patients with clinically early stage EC at risk of developing LN metastases, but only few of them had external validation.[20-28] However, a recent consensus paper of new risk group classification system was recently published by the 3 European societies: (ESMO, ESGO, and ESTRO) and is currently accepted by most surgical teams.[29] This European consensus could limit the extent of lymphadenectomy and would theoretically reduce morbidity for low risk EC; and provide a complete staging information for more accurately guide for adjuvant therapy for patients with high and intermediate risk group.

Our study has some limitations. Firstly, it is a retrospective and uni-centric study. Secondary, therapeutic indications predate the new recommendations since our work included patients managed in the early 2000s. In addition, the studied population was very heterogeneous, ranging from the earliest stage of endometrial cancer to the most advanced stage.

Future perspective

Sentinel lymph node (SLN) technique has been suggested as a reliable technique for predicting metastatic regional lymph nodes in early stage EC in order to avoid the morbidity of the systemic lymphadenectomy. Two main results must be assessed to determinate the interest of the sentinel lymph node. First, can this SLN technique be a reasonable procedure between complete pelvic and paraaortic lymphadenectomy and the absence of lymph node dissection?

In the FIRES trial published recently, sensitivity of detection of LN metastasis was 97.2%, with a negative predictive value of 99.6% (in all histology subtypes and grade). The false-negative rate was approximately 3%.[30] Touhami and al, demonstrated that the risk of metastasis in non SLN in case of positive SLN was 35% and significantly correlated to the size of the SLN (cut-off 2 mm).[31]

Secondary, sentinel node method can identify "low-volume lymph node metastases" as the ultra-staging of the targeted SLN detect micrometastasis and isolated tumor cells.[20] In a French multicenter study including 304 patients with low or intermediate risk EC, metastatic LN were detected in 16% in case of SLN procedure while the rate of detection decreased to 5% with standard lymphadenectomy.[32] This findings modified the indications of adjuvant treatment by adding external radiotherapy in case of detection of micrometastasis and suggesting brachytherapy or a simple follow-up in case of their absence. The real impact of these micrometastases whether on patient survival or on the indication of adjuvant treatment remains unknown. More prospective randomized trials should be done to predict the prognostic impact of these “low-volume lymph node metastasis”.

Heterogeneous nature of EC was confirmed by The Cancer Genome Atlas research group. The researchers identified molecular subgroups according to molecular genetic diversity in 4 subclasses. This new molecular classification aimed to establish an optimal and personalized therapeutic approach in order to indicate lymphadenectomy in the high risk group and to ovoid morbidity of overtreatment in low risk group.[33] In an ongoing PORTEC 4a trial, patients with stage I high-risk CE are randomized to two arms: the first arm indicating to the patients a personalized adjuvant treatment according to the recommendations based on an analysis of the molecular markers, the second arm indicating adjuvant treatment according to recommendations based on clinicopathological characteristics.

CONCLUSION

These findings highlight the fact that LN metastasis were an important prognostic factor in EC and lymphadenectomy had therapeutic effect.

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