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Determinants of pelvic and para-aortic lymph node metastasis in endometrial cancer and its role in tailoring lymphadenectomy

Wyznaczniki przerzutów do węzłów chłonnych miedniczych i okołoaortalnych u pacjentek z rakiem błony śluzowej trzonu macicy i ich rola w ustalaniu zakresu limfadenektomii

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Abstract

Background: The International Federation of Gynecology and Obstetrics (FIGO) decided to adopt surgical staging for endometrial cancer including systemic pelvic and para-aortic lymph node dissection in 1988; however, the extent of an optimal lymphadenectomy and which subgroup of patients would benefit are still debatable issues. The purpose of this study was to evaluate the incidence and distribution of pelvic and aortic lymph node metastases in endometrial cancer and to study various clinicopathologic variables affecting lymph node metastasis in endometrial cancer and their role in tailoring lymphadenectomy. **Methods:** This retrospective study included patients with endometrial cancer that were admitted to the Obstetrics and Gynecology Department of Shinshu University Hospital, Japan, and South Egypt Cancer Institute, Assiut University, Egypt, between June 2005 and May 2014. All patients underwent pelvic lymph node and para-aortic lymph node dissection as part of the primary surgery during the study period. Demographic and clinicopathological data were collected and analyzed in relation to pelvic lymph node and para-aortic lymph node metastasis. **Results:** Seventy-eight patients (35 patients from Japan and 43 patients from Egypt) with endometrial cancer with FIGO stage I–IV and with all histopathological cell types and tumor grades were included. Pelvic lymph node metastases were significantly correlated with advanced disease (stage III and IV), endometroid carcinoma, myometrial invasion >1/2, adnexal involvement and lymphovascular space invasion. Para-aortic lymph node metastases were significantly correlated with advanced disease (stage III and IV), myometrial invasion >1/2, adnexal involvement and lymphovascular space invasion. **Conclusion:** Our study concluded that lymphadenectomy in patients with endometrial cancer can be tailored according to risk stratification for lymph node metastasis. So, in low risk patients lymphadenectomy can be omitted to avoid operative complications.

Keywords: retrospective studies, incidence, endometrial neoplasms, lymph node excision, lymphadenectomy

Streszczenie

Wstęp: W 1988 roku Międzynarodowa Federacja Ginekologii i Położnictwa (International Federation of Gynecology and Obstetrics, FIGO) zdecydowała o przyjęciu systemu oceny zaawansowania raka błony śluzowej trzonu macicy z uwzględnieniem usunięcia węzłów chłonnych okołoaortalnych i miedniczych. Jednak zakres optymalnego zabiegu limfadenektomii oraz identyfikacja pacjentek mogących odnieść korzyści z takiego postępowania wciąż są przedmiotem dyskusji. Celem badania była ocena częstości występowania i dystrybucji przerzutów do węzłów chłonnych miedniczych i aortalnych u pacjentek z rakiem błony śluzowej trzonu macicy oraz analiza czynników kliniczno-patologicznych mogących predysponować do ich powstania, a także ich roli w ustalaniu zakresu limfadenektomii. **Metody:** Retrospektywne badanie przeprowadzono wśród pacjentek z rakiem endometrium przyjętych na Oddział Ginekologii i Położnictwa Szpitala Uniwersyteckiego Shinshu w Japonii i Instytutu Leczenia Nowotworów w Południowym Egipcie Uniwersytetu w Assiut w Egipcie w okresie od czerwca 2005 do maja 2014 roku. W badanym okresie węzły chłonne miednicze i okołoaortalne usunięto u wszystkich chorych w ramach pierwotnego leczenia. Dane demograficzne i kliniczno-patologiczne zebrano

i oceniono w oparciu o występowanie przerzutów w węzłach chłonnych miedniczych i okołoaortalnych. **Wyniki:** Do badania włączono 78 pacjentek (35 z Japonii i 43 z Egiptu) z rakiem błony śluzowej trzonu macicy w stadium FIGO I–IV z uwzględnieniem wszystkich podtypów histopatologicznych oraz stopni złośliwości histopatologicznej nowotworu. Wykazano istotną korelację między występowaniem przerzutów w węzłach chłonnych miednicy a zaawansowaniem choroby (stopień III i IV), obecnością zmian endometrioidalnych, inwazją miometrium >1/2, zajęciem przydatków i inwazją przestrzeni limfatycznej. Z kolei występowanie przerzutów w węzłach chłonnych okołoaortalnych było istotnie skorelowane z zaawansowaniem choroby (stopień III i IV), inwazją miometrium >1/2, zajęciem przydatków i inwazją przestrzeni limfatycznej. **Wnioski:** Badanie wykazało, że zakres limfadenektomii u chorych na raka endometrium można dostosować na podstawie stratyfikacji ryzyka wystąpienia przerzutów w węzłach chłonnych. U pacjentek niskiego ryzyka procedurę tę można pominąć w celu uniknięcia powikłań związanych z zabiegiem.

Słowa kluczowe: badania retrospektywne, częstość występowania, nowotwory błony śluzowej trzonu macicy, usunięcie węzłów chłonnych, limfadenektomia

INTRODUCTION

Endometrial carcinoma is the most common malignancy of the female genital tract in industrialized countries[1].

Lymphadenectomy is an important component of surgical staging of uterine corpus cancer. The ability to identify lymph nodes with metastatic involvement or other poor prognostic factors is not only prognostic, but can direct postoperative care and potentially affect survival[2]. This decision implies that both pelvic and para-aortic lymph nodes (PALN) should be assessed in all patients with endometrial cancer[3].

The Gynecologic Oncology Group (GOG)[4] established risk stratification criteria for newly diagnosed endometrial cancer. Endometrial cancer of low grade (grade 1 or 2) with endometrioid lesions confined to the endometrium (a subset of stage IA disease) is classified as low-risk endometrial cancer. The overall probability of recurrence in this group is very low (2–10%) following surgical treatment alone. There is no evidence to support benefit from adjuvant therapy for patients with low-risk or low-intermediate-risk disease. Intermediate-risk endometrial cancer is divided into low-intermediate-risk and high-intermediate risk diseases. The low-intermediate-risk group includes patients with no myometrial invasion and grade 3 disease and patients with less than 50% myometrial invasion and grade 1/2 disease. The high-intermediate-risk group includes patients with less than 50% myometrial invasion and grade 3 disease, patients with myometrial invasion ≥50% and grade 1/2 disease, and patients with stage IIA disease and grade 1/2 disease. Intermediate-risk patients have increased risk of locoregional relapse in the presence of high risk factors, but overall they are at low risk of distant metastases. As such, these women benefit most from adjuvant treatment. High-risk endometrial cancer includes stage III disease, regardless of histology or grade, and uterine serous carcinoma or clear cell carcinoma of any stage. Given their high risk of relapse and death from endometrial cancer, women with high-risk endometrial cancers often receive adjuvant chemotherapy. However, the optimal regimen and the role that radiotherapy has to improve survival outcomes are unclear.

Omission of complete lymphadenectomy is possible in selected cases in which the risk of lymph node spread is low, in other words, in low-risk cancer. The definition of low-risk in corpus cancer is controversial; however, taking many reports into consideration, we regard grade 1 or 2 endometrioid corpus cancer with myometrial invasion ≤50% and no intraoperative evidence of macroscopic disease as low-risk[5].

A refined classification of low risk, intermediate risk and high-intermediate risk has been introduced in ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer. A definition of risk groups to identify patients at risk of recurrence who may benefit from adjuvant therapy has been devised by the consensus panel[6].

The need for a complete staging procedure in patients with grade 1 disease is debated. Fifteen to twenty-five percent of women with preoperative grade 1 histology will demonstrate postoperative uterine features suggesting the risk for metastatic disease. Surgical staging in patients presenting with grade 1 endometrial cancer significantly impacts postoperative treatment decisions in 21–29% of patients. Therefore, patients presenting with apparent early-stage endometrial cancer, even preoperative grade 1 cancer, should be counseled regarding the likelihood of adverse features including extrauterine disease[7].

In this study, our objectives were to evaluate the incidence and distribution of pelvic and aortic lymph node metastases in endometrial cancer and to study various clinicopathologic variables affecting lymph node metastasis in endometrial cancer and their role in tailoring lymphadenectomy.

MATERIAL AND METHODS

Study design and patients

This retrospective study included patients with endometrial cancer that were admitted to the Obstetrics and Gynecology Department of Shinshu University Hospital, Japan, and South Egypt Cancer Institute of Assiut University, Egypt,

between June 2005 and May 2014. In this study, tumor grading was performed according to the World Health Organization grading system[8] and tumor staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 criteria[9]. Demographic and clinicopathological data collected from the institutional databases included each patient's age at surgery, type of surgical procedure, tumor stage, tumor type, tumor grade, depth of myometrial invasion, lymphovascular space invasion (LVSI), cervical invasion, adnexal involvement, lymph node swelling, number of pelvic and aortic lymph nodes removed, number of metastatic lymph nodes, and distribution of metastatic lymph nodes. The data were collected after approval from the ethics committee of Shinshu University Hospital and South Egypt Cancer Institute. Written informed consent was obtained from all patients.

The inclusion criteria were as follows: i) patients with endometrial carcinoma with FIGO stage I–IV, ii) all histopathological cell types and tumor grades and iii) a surgical procedure that was performed via laparotomy, which included total hysterectomy or hysterectomy and bilateral salpingo-oophorectomy with pelvic and PALN dissection as part of the primary surgery.

The exclusion criteria were as follow: i) patients with comorbidities that prevented surgical procedure, ii) patients that did not undergo lymph node dissection or did not have enough clinicopathological data, iii) when selective lymph node sampling was not considered to be lymph node dissection, and iv) patients who had radiotherapy or chemotherapy before surgical intervention.

Preoperative workup

All patients were subjected to careful preoperative diagnosis and staging through:

- clinical assessment: including history and examination (general, abdominal and pelvic);
- laboratory assessment: including routine investigations and tumor markers;
- histopathological assessment: including biopsy from the lesion if possible (e.g. dilatation and curettage);
- imaging studies to assess tumor location, staging, and to exclude distant metastases.

Procedures

All patients underwent pelvic lymph node (PLN) and PALN dissection as part of the primary surgery during the study period. Pelvic lymphadenectomy included complete vessel skeletonization from all lymph node bearing fat tissue from the caudal to medial circumflex femoral artery to the aortic bifurcation including: the common iliac, external iliac, internal iliac, obturator, medial suprainguinal (deep inguinal), lateral suprainguinal, parametrial, and sacral lymph node. Para-aortic lymphadenectomy included skeletonization of the nodes lateral to the vena cava, intercaval–aortic nodes, and nodes lateral to the aorta from the bifurcation of the aorta to the level of the left renal vessels above and below the inferior mesenteric artery (IMA) (Fig. 1). Although there is no consensus among gynecologic oncologists and pathologists with regard to the definition of an "adequate" lymphadenectomy, our cutoff number of dissected lymph nodes was ≥20 for PLN and ≥10 for PALN. Intermittent venous calf compression was used intraoperatively and early mobilization was encouraged postoperatively. All postoperative pathology specimens were reviewed and confirmed by a dedicated pathologist. The patients who underwent surgery prior to 2009 were restaged according to the FIGO 2009 criteria[2].

Surveillance

All patients who achieved complete remission or had no evidence of disease following initial treatment were followed-up for postoperative complications every three months for two years, every six months for the next three years, and then annually. The patients will continue to be followedup until the disease recurs or mortality occurs.

Statistical analysis

The statistical analysis was performed using Chi-square and Fisher's exact probability tests to determine statistically significant differences in distribution patterns of lymphatic spread with different variables associated with endometrial cancer. All statistical analyses were performed using STATA v.12 (STATA Corp., Texas, USA). A p-value <0.05 was considered significant.

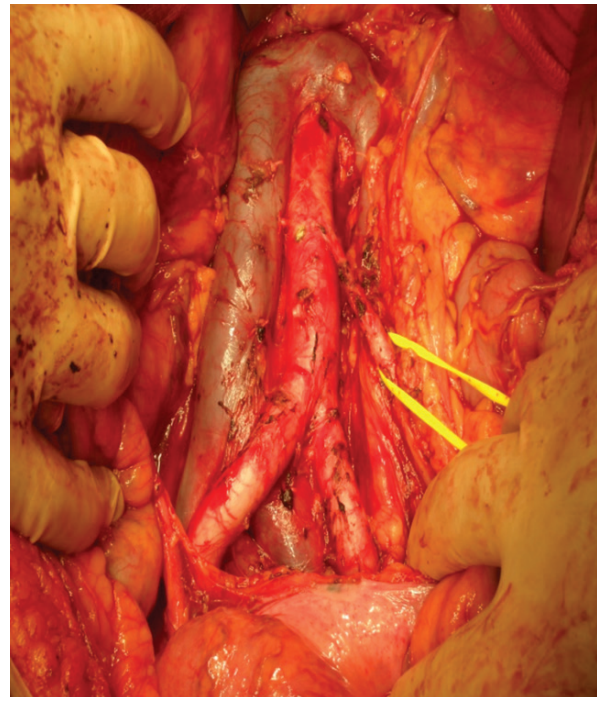

Fig. 1. Para-aortic lymphadenectomy in endometrial cancer

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RESULTS

A total of 120 patients with endometrial cancer were treated at the Obstetrics and Gynecology Department of Shinshu University Hospital, Japan, and South Egypt Cancer Institute of Assiut University, Egypt, between June 2005 and May 2014. We excluded 15 patients with comorbidities that prevented surgical procedure, 13 patients that did not undergo lymph node dissection or did not have enough clinicopathological data, 10 patients with selective lymph node sampling not considered to be lymph nodes dissection and 4 patients who had undergone radiotherapy or chemotherapy before surgical intervention. Seventy-eight patients (35 patients from the Obstetrics and Gynecology Department of Shinshu University Hospital, Japan, and 43 patients from South Egypt Cancer Institute of Assiut University, Egypt) with endometrial carcinoma with FIGO stage (I–IV), with all histopathological cell types and tumor grades, were included in the study. The mean age at the time of surgery was 56.8 years. The most frequent stage was stage III in 34 patients (43.5%). Then, stage I was observed in 32 patients (41%), and stage II and IV, in 6 patients each (7.6%). Endometroid carcinoma was the most common pathology and was observed in 68 patients (87.1%), serous carcinoma and carcinosarcoma in 4 patients each (5.1%) and clear cell carcinoma in 2 patients (2.5%). The most common tumor grade was grade 3 (48.7%), followed by grade 1 and grade 2 (30.7% and 20.5%, respectively). Myometrial invasion >1/2 was observed in 51.3% of patients while ≤1/2 myometrial invasion was seen in 38.4% of patients; there were 8 patients (10.2%) with no invasion. Cervical invasion was detected in 24 patients (30.8%), while adnexal metastasis was encountered in 16 patients (20.6%). LVSI was diagnosed in 42 patients (53.9%) (Tab. 1).

A mean of 24 PLN (range 11–50) and 17 PALN (range 5–35) were removed per patient. Positive lymph node metastasis was diagnosed in 32 patients (41%), 18 of them with pelvic and PALN metastasis (23%), 8 patients with PLN metastasis only (10.3%) and 6 patients with isolated PALN metastasis (7.7%). The distribution of the positive pelvic and aortic lymph node groups is detailed in Tab. 2.

PLN metastases were significantly correlated with advanced disease (stage III and IV), endometroid carcinoma, myometrial invasion >1/2, adnexal involvement and LVSI (Tab. 3). PALN metastases were significantly correlated with advanced disease (stage III and IV), myometrial invasion >1/2, adnexal involvement and LVSI (Tab. 4).

DISCUSSION

Lymphadenectomy is currently one of the most controversial topics in discussions on the management of endometrial cancer. Since the FIGO introduced surgical staging of endometrial cancer in 1988, essential questions have remained unanswered, including the extent of optimal lymphadenectomy and which subgroup of patients would benefit.

Variable	Frequency	Percent (%)
Histopathologic type:		
• endometroid adenocarcinoma	68	87.1
• serous carcinoma	4	5.1
• clear cell carcinoma	2	2.5
• carcinosarcoma	4	5.1
Tumor grade:		
• grade 1	24	30.7
• grade 2	16	20.5
• grade 3	38	48.7
Myometrial invasion:		
• no	8	10.2
• <1/2	30	38.4
• >1/2	40	51.2
Cervical invasion:		
• negative	54	69.2
• positive	24	30.8
Adnexal involvement:		
• negative	62	79.4
• positive	16	20.6
Lymphovascular space invasion (LVSI):		
• negative	36	46.1
• positive	42	53.9

Tab. 1. Histopathologic data of endometrial carcinoma

Variable	No. of patients	Percent (%)
Lymph node metastasis:		
• negative	46	59
• positive pelvic nodes	8	10.3
• positive para-aortic nodes	6	7.7
• positive pelvic and aortic nodes	18	23
Positive node group:		
• pelvic lymph nodes:		
- external iliac	10	38.4
- internal iliac	20	67.9
- common iliac	8	30.7
- obturator	16	61.5
- parametrial	2	7.6
- presacral	2	7.6
- suprainguinal	2	7.6
• aortic lymph nodes:		
- pre-aortic (infra- and supramesentric)	12	66.6
- precaval (infra- and supramesentric)	6	33.3
- para-aortic (infra- and supramesentric)	4	22.2
- para-aortic inframesentric	6	33.3
- para-aortic supramesentric	4	22.2
- pre-aortic inframesentric	2	11.1
- precaval supramesentric	2	11.1

Tab. 2. Incidence and distribution of lymph node metastasis in endometrial carcinoma

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In our study, a mean of 24 PLN (range 11–50) and 17 PALN (range 5–35) were removed per patient with endometrial cancer. While, in the study of Geisler et al.[10], the mean number of pelvic nodes removed was 22 (range 6–51) and the mean number of PALN removed was 6 (range 2–47).

Positive lymph node metastasis was diagnosed in 32 patients (41%) with endometrial carcinoma, 23% of them with pelvic and PALN metastasis, 10.3% with PLN metastasis only and 7.7% with PALN metastasis only. Morrow et al.[11] reported that, in the Gynecologic Oncology Group study, PALN metastasis was found in 48 (5.4%) of 895 patients with endometrial carcinoma. Other reports[7] have shown positive PALN metastasis in 5.5 to 14.6% of patients with stage I endometrial carcinoma.

Regarding the distribution of the positive pelvic lymph node groups, the most commonly involved groups were internal iliac and obturator groups (67.9% and 61.5%, respectively). The same results have been reported by Matsumoto et al.[12] and P2 group stating that the internal iliac, external iliac and obturator lymph nodes were most commonly affected by metastasis (89%). This also agrees with reports that address the routes of lymphatic dissemination in endometrial cancer, which have suggested that the principal connections are between the uterine corpus and the external iliac and obturator basins (ACOG practice bulletin)[13]. In the aortic area, most of our patients with positive lymph nodes below the IMA also had positive nodes above the IMA that would have escaped detection if the dissection had been limited to the lower node basins. Thus, the node-bearing tissue between the IMA and the renal vessels is important for assessment of the extent of disease and for determination of overall treatment plan. So, para-aortic lymphadenectomy should be extended up to the level of the renal veins for endometrial cancer; this is in line with the results of Odagiri et al.[14]. Isolated PALN metastasis was noticed in 6 patients (7.7%). Therefore, a direct route may exist from the corpus to the para-aortic node-bearing basins by the lymphatic channels adjacent to the gonadal vessels within the infundibulopelvic ligament[15]. If the pelvic nodes were negative, para-aortic dissection was performed because of the presence of other high-risk factors, such as tumor histology or grade, adnexal metastasis, or suspicious nodes on exploration[16].

Variables	Cases with PLN metastasis		*p*-value
	Yes	No	
Tumor stage:			
• stage I and II	0	38	**<0.001***
• stage III and IV	26	8	
Histologic type:			
• endometroid carcinoma	16	52	**<0.001****
• non-endometroid carcinoma	10	0	
Tumor grade:			
• grade I and II	10	30	NS*
• grade III	16	22	
Myometrial invasion:			
• no	2	6	**<0.001***
• ≤1/2	0	30	
• >1/2	24	16	
Cervical invasion:			
• negative	12	22	NS*
• positive	14	10	
Adnexal involvement:			
• negative	16	46	**0.005***
• positive	10	6	
Lymphovascular space invasion (LVSI):			
• negative	2	34	**<0.001***
• positive	24	18	

* Chi-square test was used to compare the difference in proportions.
** Fisher's exact test was used.
NS – not significant.

Tab. 3. Clinicopathologic variables in relation to PLN metastasis in endometrial cancer

Variables	Cases with PALN metastasis		*p*-value
	Yes	No	
Tumor stage:			
• stage I and II	0	38	**<0.001***
• stage III and IV	24	10	
Histologic type:			
• endometroid carcinoma	18	50	NS**
• non-endometroid carcinoma	6	4	
Tumor grade:			
• grade I and II	10	30	NS*
• grade III	14	24	
Myometrial invasion:			
• no	2	6	**<0.001***
• ≤1/2	2	28	
• >1/2	20	20	
Cervical invasion:			
• negative	12	22	NS*
• positive	12	12	
Adnexal involvement:			
• negative	14	48	**0.002***
• positive	10	6	
Lymphovascular space invasion (LVSI):			
• negative	6	30	**<0.01***
• positive	18	24	

* Chi-square test was used to compare the difference in proportions.
** Fisher's exact test was used.
NS – not significant.

Tab. 4. Clinicopathologic variables in relation to PALN metastasis in endometrial cancer

With regard to the FIGO stage and lymph node metastasis, our results confirmed that pelvic or PALN metastasis in advanced stage (III and IV) was significantly more frequent than in early stage carcinoma (I and II), which means that lymph node metastases increased in parallel to the increase in local extension of the disease. This is consistent with Hirahatake et al.[17] who reported that the incidence of PLN and PALN metastasis significantly increased with the progression of the stage of endometrial carcinoma. Similarly, Feuer and Calanog[18] reported that the incidence of PALN metastasis in endometrial carcinoma increased as the disease progressed.

In our study, PLN metastases were significantly correlated with increased tumor stage, endometroid type carcinoma, increased myometrial invasion, adenexal involvement and LVSI. PALN metastases were significantly correlated with increased tumor stage, increased myometrial invasion, adnexal involvement and LVSI. Geisler et al.[10] reported that the depth of myometrial invasion at the time of final pathology was correlated with nodal positivity ($p < 0.001$). This correlation applied not just to global nodal positivity, but also to para-aortic nodal positivity. Kamura and Jeon[19] found that variables most significantly correlated with PLN metastasis were clinical stage, myometrial invasion, cervical invasion and adnexal metastasis, while Nomura et al.[20] reported that the presence of para-aortic lymph node metastasis was related to the tumor grade, myometrial invasion, pelvic lymph node metastasis, vascular space invasion, cervical involvement, and adnexal metastasis. Our findings are in accordance with previous studies that involved more than 100 patients[21–25].

In contrast to other studies[26,27], our results showed that PLN and PALN metastases were more common with grade 3 tumor than grade 1 and 2. Although it is not statistically significant, tumor grade is considered an important factor in the risk stratification of endometrial cancer patients.

GOG #33 showed that there was no case with nodal metastasis in the low-risk group defined as having no myometrial invasion, grade 1 endometrioid histology, and no intraperitoneal disease[11]. Mariani et al.[28] confirmed a low-risk group with grade 1 to 2 endometrioid histology, depth of invasion of ≤50%, and tumor size of ≤2 cm. They concluded that lymphadenectomy does not bring benefit in patients in the low-risk group (so-called Mayo criteria). Milam et al.[29] also demonstrated that these criteria led to a rate of nodal metastasis of only 0.8% in the low-risk group of the Mayo criteria. However, all of these criteria depend on surgicopathologic findings. There have been only a few studies that aimed to establish preoperative risk assessment for predicting lymph node metastasis in endometrial cancer[30,31]. Our results are consistent with these studies and may help to establish a risk stratification system based on preoperative and operative parameters to tailor surgery and reduce the rate of unnecessary lymphadenectomies.

Frozen-section analysis may represent a safe and effective method of risk stratification in endometrial carcinoma. High-risk features indicating metastatic disease on frozen sections were defined by high grade (grade 3), >50% MI, LVSI, and adnexal or cervical involvement[32,33]. However, if frozen-section analysis is not available or if it is not reliable, findings of preoperative imaging studies (magnetic resonance imaging) and preoperative endometrial sampling associated with intraoperative tumor size, are alternative methods for risk stratification and help to identify patients who may benefit from comprehensive surgical staging.

The current work encountered some weak points; such as the small sample size and the retrospective nature. However, it possessed some strong points as we studied a well annotated retrospective cohort of patients, regardless of which risk group they are in, with clearly defined clinical, demographic, and pathologic variables along with distinct study outcomes. Hence, we recommend prospective, larger cohorts and multicentric studies for better delineation of such variables.

CONCLUSION

Our study concluded that lymphadenectomy in patients with endometrial cancer can be tailored according to risk stratification for lymph node metastasis. So, in low-risk patients (endometroid carcinoma, myometrial invasion ≤50%, no adnexal invasion or LVSI) lymphadenectomy can be omitted because of low risk of lymph node metastasis to avoid operative morbidities and complications. These findings are to be supported by larger cohorts and multicentric prospective studies. Also, novel prognostic factors (tumor size and DNA ploidy) and techniques (sentinel lymph node biopsy) should be examined to avoid unnecessary lymphadenectomy.

Conflict of interest

Authors disclose no conflict of interest.

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