ORIGINAL RESEARCH

DOI: 10.5336/jcog.2024-102726

Tumor Burden of Non-bulky Metastatic Lymph Nodes in Endometrial Cancer: A Retrospective Cohort Study

Alper SEYHAN[a], İpek YILDIZ ÖZAYDIN[b], Merve KONAL[c], Özgür AKBAYIR[c]

[a]Adnan Menderes University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Aydın, Türkiye
[b]Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Pathology, İstanbul, Türkiye
[c]Prof. Dr. Cemil Taşcıoğlu State Hospital, Clinic of Obstetric and Gynecology, İstanbul, Türkiye

ABSTRACT Objective: Evaluation of the diagnostic superiority of systematic lymphadenectomy in endometrial cancer cases in conditions of sentinel lymph node (SLN) dissection cannot be performed. **Material and Methods:** The file records of 853 patients with endometrial cancer were reviewed in the gynecological oncology clinic of Kanuni Sultan Süleyman Hospital between 2008 and 2020. Thirty nine endometrial cancer patients with lymph node involvement were selected to study. Pelvic and paraaortic lymph node counts, positive lymph node ratios, metastatic lymph node sizes and percentages of tumor infiltration in lymph nodes were defined. Clinicopathological variables, including the categorical data, were analyzed as a descriptive method. **Results:** Grossly suspicious lymph nodes were observed in 46.2% of the patients. While 54.4% of metastatic lymph nodes were <1 cm (non-palpable), 12% of them <5 mm. In 17.9% of patients, all dissected metastatic lymph nodes were <1 cm (non-palpable). **Conclusion:** In clinics that can not performed SLN procedure in endometrial cancer, extent of lymphadenectomy may vary as a systemic lymphadenectomy or selective palpable lymph node excision depends on surgeon preference and patient morbidity. With comprehensive lymphadenectomy, occult lymph node metastasis can be detected and adding adjuvant chemoradiotherapy allows the patients to be given better survival rates in Stage IIIc disease.

Keywords: Endometrial neoplasms; lymphatic metastasis; neoplasm staging

Endometrial cancer (EC) is the most common gynecological cancer, accounting for 5-6% of all female cancers. At the time of diagnosis, 75% of the cases are clinically seen in the early stage. The most important prognostic factor is the stage at the time of diagnosis. Lymph node involvement is one of the most important factors changing the stage and prognosis. Tumor metastasis is mostly seen in lymph nodes. Lymph node involvement rates increase in the presence of deep myometrial invasion, adnexal involvement, and extrauterine pelvic and abdominal metastases. While there was no benefit of lymphadenectomy in the low-risk group (superficial endometrial invasion, Grade I-II endometrioid histology, lymphovascular space invasion (LVSI) negative or focal) during the pre- and intraoperative evaluation, lymph node involvement rates increase with the presence of high-risk findings (Grade-III or non endometrioid histology, deep myometrial invasion, LVSI positive). According to Creasman et al., pelvic lymph node involvement was observed in %9 and paraaortic lymph node involvement was observed in %5 of cases.[1] The radicality of lymphadenectomy may vary according to the surgeon and clinical approach. Palpable lymph nodes excision, sentinel lymph node (SLN) mapping or systematic total lymphadenectomy can be chosen in surgical staging procedure. Excision of palpable lymph nodes is a common surgical procedure in order not to increase surgical complications like lymph

TO CITE THIS ARTICLE:
Seyhan A, Yıldız Özaydın İ, Konal M, Akbayır Ö. Tumor burden of non-bulky metastatic lymph nodes in endometrial cancer: A retrospective cohort study. JCOG. 2024;34(2):67-72.

Correspondence: Alper SEYHAN
Adnan Menderes University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Aydın, Türkiye
E-mail: naseyhan@adu.edu.tr

Peer review under responsibility of Journal of Clinical Obstetrics & Gynecology.

Received: 12 Mar 2024 ***Received in revised form:*** 22 May 2024 ***Accepted:*** 27 May 2024 ***Available online:*** 31 May 2024

edema, major vascular bleeding, infectious morbidities, especially in clinics where SLN application cannot be performed. However, in the various studies, 56% of endometrial carcinoma cases, metastatic lymph node sizes were found less than 10 mm.[2] From this point of view in our study, we analyzed the effectiveness of selective lymphadenectomy for only palpable lymph nodes by making a detailed examination of metastatic lymph nodes (MLN) in terms of their size.

MATERIAL AND METHODS

In our study, the file records of 853 patients who were found to have endometrial carcinoma as a result of endometrial biopsy and underwent surgical procedures in the gynecological oncology clinic of Kanuni Sultan Süleyman Hospital between 2008 and 2020 were reviewed (Figure 1). This study was approved by Clinical Research Ethics Committee of Healthy Science University-Kanuni Sultan Süleyman Research and Training Hospital with a protocol number of 91 and date of May 11, 2022. The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. Patients with endometrioid and non-endometrioid histology were analyzed. Patients who had been treated for a different malignancy in the last 5 years, presence of synchronous malignancy, presence of non-epithelial uterine tumor, presence of neoadjuvant treatment, insufficient pathological records, and patients who did not undergo lymphadenectomy or sampled less than 10 pelvic and/or paraaortic lymph nodes were excluded from the study. All surgical procedures were performed by the same gynecologic oncologists, and pathological evaluations were performed by the same gyneco-pathologists with at least 10 years of experience. Intraoperative frozen-section examination was performed in all cases. Pelvic and paraaortic lymphadenectomy was performed in the presence of non- endometrioid or Grade 3 histology, and/or deep myometrial or cervical invasion. Only bilaterally pelvic lymphadenectomy was performed for patients with Grade 1 or 2, superficial myometrial invasion, tumor diameter larger than 2 cm. No pelvic lymph node dissection was performed if the tumor diameter is less than 2 cm in this subgroups of patients. Systematic lymphadenectomy is preferred over selective lymphadenectomy in our gynecological oncology clinic. Lymphadenectomy radicality may vary depending on the patients' comorbidity factors such as high body mass index and anesthesia-related morbidities. Preoperative evolution of the myometrial invasion was performed by transvaginal ultrasonography and magnetic resonance imaging. Tumor grade was determined by paraffine section of curettage material preoperatively. Both uterus and cervix were analyzed intraoperatively by frozen section in respect of tumor grade and cervical/myometrial invasion. Decision of lymph node dissection is made according to the result of frozen section and preoperative analysis. Lymph node dissection was performed whenever indication of lymph node dissection was seen in frozen section and/or preoperative evaluation of the patients to minimized undertreatment risk.

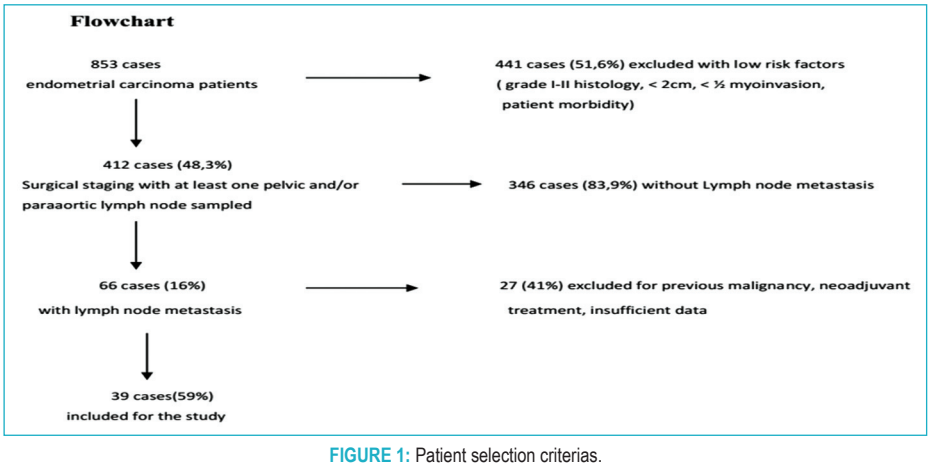

FIGURE 1: Patient selection criterias.

TABLE 1: Characteristics of metastasis in lymph nodes.

	n
Metastatic lymph node counts	
Pelvic nodes	90
Paraaortic nodes	35
	Mean (range)
Metastatic lymph nodes, n	
Pelvic	3.53 (0-26)
Paraaortic	3.7 (0-15)
Diameter of LNM, mm	11.5 (0.2-40)
% tumoral invasion of LN	76.9 (4-100)
<1 cm metastatic LN	83.2 (11.1-100)
1-2 cm metastatic LN	67.6 (10.5-100)
>2 cm metastatic LN	74 (4-100)
Metastatic node diameter, n (%)	
<5 mm	15 (12)
5-10mm	53 (42.4)
>10 mm	57 (45.6)
Patients with LNM, n (%)	
Only non palpable (<1 cm)	7 (17.9)
Others	32 (82.1)

LNM: Lymph node metastasis.

Hysterectomy and bilateral salpingoopherectomy without lymphadenectomy were performed in 441 out of 853 patients due to low risk factors or patients' commorbidities. Pelvic and/or paraaortic lymphadenectomy was performed in 412 patients. In 66 patients, pelvic and/or paraaortic lymph node involvement was detected. However, considering the exclusion criteria, 27 patients with lymph node involvement were excluded (Figure 1). By evaluating the pathology reports, pelvic and paraaortic lymph node counts, positive lymph node ratios, metastatic lymph node sizes and percentages of tumor infiltration in lymph nodes were calculated (Table 1). Positive lymph node ratio was calculated by looking at the total number of removed pelvic and paraaortic lymph nodes and the number of lymph nodes with metastasis (Table 2). Cut-off values of 1 and 2 cm were determined as a definition of palpable and bulky lymph nodes, respectively. MLN were grouped as <5 mm, 5-10 mm, >10 mm in size, and the presence of metastases in palpable and non-palpable lymph nodes was evaluated.

Statistical analyses were applied using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA), while clinicopathological variables, including the categorical data, were analyzed as a descriptive method.

RESULTS

Thirty-nine cases with lymph node metastasis (LNM) positive patients characteristics were presented in Table 2. The median age of the patients was found to be 60.9 years. Non-endometrioid, Grade 1, Grade 2, and Grade 3 histology were detected in 18 (46.1%), 4 (10.2%), 10 (25.6%), and 7 (17.9%) patients, re-

TABLE 2: Patient characteristics.

Age, mean (range)	**60.9 (41-84)**
	Patient no (%)
Histology	
Grade 1	4 (10.2)
Grade 2	10 (25.6)
Grade 3	7 (17.9)
Non-endometrioid	18 (46.1)
Cervical involvement	
Yes	13 (33.3)
No	26 (66.7)
Myometrial invasion	
<%50	9 (23.1)
>%50	30 (76.9)
Peritoneal washing	
-	30 (76.9)
+	9 (23.1)
Lenfovascular space invasion	
-	2 (5.1)
+	37 (94.9)
Tumor diameter	
<2 cm	2 (5.1)
2-4 cm	19 (48.7)
>4 cm	18 (46.1)
Nodal dissection	
Pelvic only	7 (17.9)
Paraaortic only	0 (0)
Pelvic and paraaortic	32 (82.1)
Grossly suspucious nodes	
No	21 (53.8)
Yes	18 (46.2)
Lymph node counts, n	Mean
Pelvic node count	25,3 (8-56)
Paraaortic node count	16.6 (0-35)
Pelvic and paraaortic node count	41.5 (8-77)
Lymph node ratio	Patients no (%)
<10	23 (58.9)
10-50	13 (33.3)
>50	3 (7.8)

spectively. Cervical stromal invasion was detected in 13 (33.3%), while outer half of myoinvasion was detected in 30 (76.9%) patients. Peritoneal washing positivity and LVSI positivity were detected in 9 (23.1%), and 37 (94.9%), respectively. Tumor sizes were >4 cm, 2-4 cm, and <2 cm 29 (74.4%), 5 (12.8%), and 5 (12.8%) patients, respectively. When the characteristics of the dissected lymph nodes were detailed; gross suspicious lymph nodes were observed in 18 (46.2%) of the patients. Mean lymph node counts were found to be 25.3, 16.6, and 41.5 in the pelvic, paraaortic, and pelvic-paraaortic groups, respectively. Considering the characteristics of MLN, 68 (54.4%) of MLNs were <1 cm (non-palpable) while 15 (12%) of MLN<5 mm in diameter. In 7 (17.9%) of patients, all dissected MLNs were <1 cm (non-palpable). It was considerable that 3 of 7 patients had isolated paraaortic LNM. The mean number of MLNs was 3.53 and 3.7 in the pelvic and paraaortic groups, respectively. Tumor infiltration rate in MLNs was 76.9%. Lymph node ratios less than 10%, between 10-50%, and more than 50% were found in 23 (58.9%), 13 (33.3%), and 3 (7.8%) patients, respectively. In Table 3, histologic tumor characteristics were compared with nodal metastasis (pelvic and/or paraaortic) status. In this data, only pelvic node positivity was detected in 8 of 9 patients (88.8%) with inner half myoinvasion group. But significant detail should be emphasized that paraaortic lymph nodes dissection were performed in only 4 of 9 patients (44.4%) in this group.

DISCUSSION

The indication and extent of lymphadenectomy in EC cases is a controversial issue. There is no gold standard approach about the extent of lymphadenectomy, number of lymph nodes should be removed, and upper boundary of paraaortic lymphadenectomy, yet. In recently published European Society of Gynecologic Oncology guideline, lymphadenectomy can be omitted in low risk group of EC patients (Grade I-II, LVSI (-), <1/2 myoinvasion, <2 cm tumor diameter).[3] Comprehensive lymph node staging should be performed in patients with high-intermediate-risk or high-risk disease, yet the role of systematic lymphadenectomy is still controversial. This uncertainty is due to the results of two randomized controlled trials emphasized that lymph node dissection in EC patients is not associated with survival benefit.[4,5] In contrast, retrospective several studies have shown longer survival in patients who underwent pelvic and para-aortic lymphadenectomy, especially in high risk group for recurrence.[6,7] When the balance between the complications, morbidities, and survival benefits

TABLE 3: Lymph node metastasis according to risk factors.

	Only pelvic	Only paraaortic	Pelvic and paraaortic	Total
Grade				
I	3 (75)	0 (0)	1 (25)	4
II	6 (60)	2 (20)	2 (20)	10
III	4 (57.2)	1 (14.3)	2 (28.5)	7
Non-endometrioid	6 (33.3)	2 (11.2)	10 (55.5)	18
Myometrial invasion				
<%50†	8 (88.8)	1 (11.2)	0 (0)	9
>%50	9 (30)	6 (20)	15 (50)	30
LVSI				
No	1 (50)	1 (50)	0 (0)	2
Yes	16 (43.3)	7 (18.9)	14 (37.8)	37
Tumor diameter				
<2 cm	2 (100)	0 (0)	(0)	2
2-4 cm	9 (47.3)	2 (10.5)	8 (42.2)	19
>4 cm	6 (33.3)	5 (27.7)	7 (39)	18

†In this group, paraaortic lymphadenectomy was not performed in 5 of 9 patients; LVSI: Lymphovascular space invasion.

of systematic pelvic and paraaortic lymphadenectomy and SLN mapping and biopsy were evaluated, SLN mapping and biopsy is an acceptable alternative to systematic lymphadenectomy without treatment and survival disadvantages.[8]

In many instutions where SLN mapping and biopsy cannot be performed due to technical and financial inadequacies, selective lymph node sampling for only palpable lymph nodes can be performed as a part of surgical procedure in high-intermediate or high risk group of EC patients. With this approach, many surgeons purpose to minimize the complications and morbidities due to the lymphadenectomy up to the renal vessels. Missed diagnosis of metastatic but non-palpable lymph nodes is the main concern of selective lymphadenectomy. Because detection of LNM in EC is of vital importance in diagnosing advanced stage disease and making adjuvant treatment decision. In this study, grossly suspicious lymph nodes were detected only in 46.2% of patients with lymph node metastases and when the metastatic nodes were evaluated, 54.4% of them were detected under 10 mm. As a notable finding, in 7 of 39 (17.9%) patients, all metastatic nodes were detected to be under 10 mm (non-palpable). Ayhan et al. reported similar results as MLNs were smaller than or equal to 10 mm in 36.1% patients.[2] When the cut-off value of MLN diameter was taken as ≤2 mm (micrometastasis) or >2 mm (macrometastasis), only micrometastasis were detected in 29% of patients in Mariani et al.'s study.[9] These results demonstrated the diagnostic necessity of systemic lymphadenectomy in detecting MLN in EC patients with high risk features in clinics where SLN algoritm can not be applied. In addition to this reality, SLN algoritm with ultrastaging procedure seems more sensitive in detecting micrometastasis and isolated tumor cells.

It has been demonstrated in other malignancies, including breast and ovarian cancer, that the number of positive nodes is correlated with patients outcome.[10] In EC, studies reported that high number of MLNs were associated with worse prognosis and the removal of increasing number of MLNs improved prognosis.[11,12] In contrast to these studies, Multinu et al. reported that the extent of lymphadenectomy does not significantly affect outcomes in patients with non-bulky MLN, especially in paraaortic areas. In addition to this reality, comprehensive lymphadenectomy may not be sufficient for lymphatic dissemination. They suggest that postoperative chemotherapy plus extended field radiotherapy in Stage IIIc EC patients are likely to at least partially treat any microscopic lymphatic metastases that may have remained after a more limited lymphadenectomy. Type of adjuvant therapy has a critical role in prognosis of patients with non-bulky LNM. Combined chemoradiotherapy provides better survival outcomes than radiotherapy alone.[13] But they noted that, comprehensive lymphadenectomy may provide survival benefit for patients with bulky lymph nodes.[14]

Many pathological parameters were well defined in EC closely related with prognosis. Among the patients with LNM; ratios of LVSI positivity, deep myometrial invasion, and tumor diameter larger than 4 cm were detected to be significantly higher than other prognostic risk factors (Table 2). Similar results were detected by Polterauer et al.[15] In their study, deep myometrial invasion and LVSI positivity rates were detected to be 66.7% and 69.9% in patients with MLN, respectively, while peritoneal washings positivity, cervical involvement, and adnexal involvement were detected at lower rates as 11.6%, 39.8%, and 19%, respectively.

Surgical approach in Stage IIIc EC with bulky lymph nodes is still a controversial issue. Although there is no clear definition of a "bulky lymph node" for gynecologic malignancies, it generally refers to a swelling of ≥2 cm. In different gynecologic malignancies, especially in cervical carcinoma, removal of bulky nodes seems to provide a survival benefit. Several studies reported that, removal of bulky nodes is important as it provides pathological evidence and reduces the higher doses radiotherapy complications.[14,16]

CONCLUSION

In recent years, SLN mapping and biopsy procedures were commonly performed in many gynecologic oncology clinics in order to define LNM and stage of disease. But in too many clinics, pelvic and/or paraaortic lymphadenectomy for staging of EC are

performed because of technical and financial inadequacy. Extent of lymphadenectomy may vary as a systemic lymphadenectomy or selective palpable lymph node excision depends on surgeon preference and patient morbidity. Results of this study and many others emphasized that, advanced stage disease with occult LNM can only be detected with comprehensive lymphadenectomy and this allows the patients to be given adjuvant treatment. So, better survival results can be achieved with systematic lymphadenectomy in EC patients with non-palpable lymphatic involvement.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Alper Seyhan, Özgür Akbayır;* ***Design:*** *Alper Seyhan;* ***Control/Supervision:*** *Alper Seyhan;* ***Data Collection and/or Processing:*** *Alper Seyhan, Merve Konal, İpek Yıldız Özaydın;* ***Analysis and/or Interpretation:*** *Özgür Akbayır;* ***Literature Review:*** *Alper Seyhan;* ***Writing the Article:*** *Alper Seyhan, Merve Konal;* ***Critical Review:*** *Alper Seyhan;****References and Fundings:*** *Merve Konal;* ***Materials:*** *Alper Seyhan.*

REFERENCES

1. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer. 1987;60(8 Suppl):2035-41. [Crossref] [PubMed]
2. Ayhan A, Tuncer ZS, Tuncer R, Yüce K, Küçükali T. Tumor status of lymph nodes in early endometrial cancer in relation to lymph node size. Eur J Obstet Gynecol Reprod Biol. 1995;60(1):61-3. [Crossref] [PubMed]
3. Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer. 2021;31(1):12-39. [Crossref] [PubMed]
4. ASTEC study group; Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet. 2009;373(9658):125-36. Erratum in: Lancet. 2009;373(9677):1764. [Crossref] [PubMed] [PMC]
5. Benedetti Panici P, Basile S, Maneschi F, Alberto Lissoni A, Signorelli M, Scambia G, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst. 2008;100(23):1707-16. [Crossref] [PubMed]
6. Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. Lancet. 2010;375(9721):1165-72. Erratum in: Lancet. 2010;376(9741):594. [Crossref] [PubMed]
7. Abu-Rustum NR, Iasonos A, Zhou Q, Oke E, Soslow RA, Alektiar KM, et al. Is there a therapeutic impact to regional lymphadenectomy in the surgical treatment of endometrial carcinoma? Am J Obstet Gynecol. 2008;198(4):457.e1-5; discussion 457.e5-6. [Crossref] [PubMed]
8. Rossi EC, Kowalski LD, Scalici J, Cantrell L, Schuler K, Hanna RK, et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 2017;18(3):384-92. [Crossref] [PubMed]
9. Mariani A, Webb MJ, Rao SK, Lesnick TG, Podratz KC. Significance of pathologic patterns of pelvic lymph node metastases in endometrial cancer. Gynecol Oncol. 2001;80(2):113-20. [Crossref] [PubMed]
10. Weir L, Speers C, D'yachkova Y, Olivotto IA. Prognostic significance of the number of axillary lymph nodes removed in patients with node-negative breast cancer. J Clin Oncol. 2002;20(7):1793-9. [Crossref] [PubMed]
11. Chan JK, Kapp DS. Role of complete lymphadenectomy in endometrioid uterine cancer. Lancet Oncol. 2007;8(9):831-41. [Crossref] [PubMed]
12. Chan JK, Urban R, Cheung MK, Shin JY, Husain A, Teng NN, et al. Lymphadenectomy in endometrioid uterine cancer staging: how many lymph nodes are enough? A study of 11,443 patients. Cancer. 2007;109(12):2454-60. [Crossref] [PubMed]
13. Multinu F, Ducie JA, Eriksson AGZ, Schlappe BA, Cliby WA, Glaser GE, et al. Role of lymphadenectomy in endometrial cancer with nonbulky lymph node metastasis: Comparison of comprehensive surgical staging and sentinel lymph node algorithm. Gynecol Oncol. 2019;155(2):177-85. [Crossref] [PubMed] [PMC]
14. de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, et al; PORTEC study group. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19(3):295-309. Erratum in: Lancet Oncol. 2018;19(4):e184. [PubMed] [PMC]
15. Polterauer S, Khalil S, Zivanovic O, Abu-Rustum NR, Hofstetter G, Concin N, et al. Prognostic value of lymph node ratio and clinicopathologic parameters in patients diagnosed with stage IIIC endometrial cancer. Obstet Gynecol. 2012;119(6):1210-8. [Crossref] [PubMed]
16. Tohyama A, Murakami M, Yoshino K. Strategies for the treatment of cervical cancer with bulky pelvic lymph nodes: an overview of the current evidence. J UOEH. 2020;42(4):317-25. [Crossref] [PubMed]