Original Research Article

Role of pelvic and para-aortic lymphadenectomy in epithelial ovarian cancers

Pankush Gupta[1]*, Sunesh Kumar[1], Seema Singhal[1], Jyoti Meena[1], Sandeep Mathur[2], Lalit Kumar[3]

[1]Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi, India
[2]Department of Pathology, All India Institute of Medical Sciences, New Delhi, India
[3]Department of Medical Oncology, All India Institute of Medical Sciences, New Delhi, India

*Correspondence:
Dr. Pankush Gupta,
E-mail: pksgupta2009@gmail.com

ABSTRACT

Background: Lymphadenectomy in epithelial ovarian cancers has remained a controversial subject. Lack of robust evidence on survival benefits and surgical morbidity associated questions its role in the era of adjuvant chemotherapy. The present study assessed pelvic and para-aortic lymph node removal in epithelial ovarian cancer in Indian women and tried to find clinicopathological correlation of nodal involvement and postoperative implications of lymphadenectomy.
Methods: Thirty patients with diagnosis of epithelial ovarian cancer posted for primary debulking surgery were recruited and underwent staging laparotomy along with pelvic and para-aortic lymphadenectomy. Nodal involvement was confirmed on histopathology and various parameters which could predict nodal metastasis were assessed. Patients were followed up for 12 months post-surgery.
Results: Nodal yield was ten for pelvic and four for paraaortic nodes. Pelvic node involvement was seen in 26.6% (8/30) of the patients and para-aortic in 15% (3/20) of the patients. Serous histology, higher grade, stage 3 and above, positive peritoneal cytology, omental involvement showed a higher lymph node involvement though not statistically significant. Para-aortic lymphadenectomy was associated with increased operating time, blood loss and longer hospital stay.
Conclusions: Lymphadenectomy increases morbidity and decision should be based on predictors of nodal involvement.

Keywords: Epithelial ovarian cancer, Lymphadenectomy, Para-aortic, Pelvic

INTRODUCTION

Epithelial ovarian cancer (EOC) remains the leading cause of death from gynaecological malignancy with a lifetime probability of developing the disease of one in 59.[1] The cornerstones of ovarian cancer management are surgery and chemotherapy with management being based on the tumour stage (I to IV) and/or grade (1 to 3). Higher lymph node involvement as shown by studies till now makes nodal assessment an important surgical step. Also skipping lymphadenectomy in these patients may lead to under staging as one third of patients with apparent stage 1 have microscopic stage 3 disease.[2] Some studies have also shown therapeutic role of lymphadenectomy in advanced cases.[3] With correct staging, patients with low-risk disease may be spared from undergoing cytotoxic chemotherapy.[4] Latest FIGO 2014 guidelines mandate the removal of pelvic and

paraaortic lymph nodes in patients undergoing primary debulking surgery.[5]

There is not much Indian data available to support lymphadenectomy. Moreover, most of the studies done till now are retrospective. The present study was undertaken to include removal of pelvic and paraaortic lymph nodes in women with epithelial ovarian cancers undergoing primary debulking surgery and to find the incidence of metastasis in lymph nodes. The study also tried to evaluate various risk factors which can predict lymph node metastasis and the impact of lymphadenectomy on postoperative period and overall survival.

METHODS

A prospective non randomized study was conducted in the department of obstetrics and gynecology at a tertiary care hospital from July 2015 to February 2017. A total of 30 patients fulfilling the criteria were enrolled.

Inclusion criteria

- New cases suspected to have EOC preoperatively
- Age 21-70 years
- Ability to comply with the protocol
- Adequate cardiorespiratory, renal and liver functions and who were fit to undergo surgery.

Exclusion criteria

- Patients who had already undergone surgical debulking for EOC
- Patients who had undergone chemotherapy previously for EOC
- Patients known to have other malignancies.

After undergoing a preliminary gynaecological examination and baseline investigations along with metastatic work up, all patients consenting for surgery underwent exploratory laparotomy with ascitic fluid cytology, multiple peritoneal biopsies, total abdominal hysterectomy, bilateral oophorectomy, infracolic omentectomy, pelvic±para-aortic lymphadenectomy. Para-aortic lymphadenectomy was performed upto the level of renal vessels. All intraoperative findings were noted and patients were closely monitored postoperatively till discharge and referred to Medical Oncology unit for need of chemotherapy.

Biopsy specimen sent for histopathological examination were examined by a gynaecology pathologist. Samples were examined for tumor histopathology, grade and presence of metastasis in pelvic and para-aortic nodes. Patients were staged according to FIGO staging and incidence of nodal involvement was calculated.[5] Nodal metastasis was correlated on the basis of histopathology with various risk factors that could predict their involvement. All patients were followed up for 12 months postoperatively in cancer clinic and recurrences and death events were noted and impact of prognostic impact of lymph node removal was assessed.

Statistical analysis

All data analysis was carried out using statistical software STATA version 12.0. Data were expressed as frequencies and percent values. Descriptive statistics such as mean, median, Standard deviation (SD), range values and inter quartile range were calculated. Comparison of either mean values or median values between two categories was tested using Student's 't' independent test/Mann-Whitney-U test as appropriate. Frequency values between categories were compared using chi-square test/Fishers's Exact test as appropriate.

To assess significant risk factors for recurrence event and death event, univariate Cox-proportional Hazard model was fitted. For each variable included in the model, adjusted hazard ratio and it's 95% Confidence interval was computed. A two-sided probability of $p < 0.05$ was considered for statistical significance.

RESULTS

Thirty patients fulfilling the eligibility criteria were recruited. After a detailed preoperative work up patients were posted for primary debulking surgery with the aim of achieving maximum cytoreduction. Intraoperative findings and postoperative course were noted.

Base-line characteristics of study population

In the present study mean age of the patients was 47.2 years. Median age of menarche was 13 years. A total of six (20%) patients were nulliparous. Sixteen (53%) patients had attained menopause at the time of presentation. Three (10%) had a family history of ovarian cancer in first degree relatives. Four (14%) patients were found to be sterilized and one (3%) patient gave history of OCP use. Twenty-two (73%) patients presented with general symptoms like abdominal fullness and distension and six (20%) had a feeling of mass per abdomen. Average±SD BMI of the study group was 22.42±4.46 kg/m².

Preoperative work up

Preoperative work up in the form of tumor markers, cross sectional imaging, Mammography and gastrointestinal (GI) endoscopy to rule out metastasis or other primary was done. The median value of CA125 was 596 U/ml with a range of 19-6902 U/ml (Normal value <35 U/ml). The median value of CA19.9 and CEA was 8.5 U/ml and 2 ng/ml with a range of 0.58-1200 U/ml (Normal<37U/ml) and 0.83-32 ng/ml (Normal <5 ng/ml) respectively. Mammography and Upper and lower GI endoscopy was normal in all patients.

Intraoperative findings

Standard surgical technique was followed in all the patients along with pelvic±paraaortic lymphadenectomy.[6] Nineteen patients showed presence of ascites with four (13%) having more than two litres of ascites. In patients who had no ascites (n = 11), peritoneal wash cytology was taken. Tumor was unilateral in 15 (50%) patients. Fourteen (47%) patients had omental involvement out of which three patients had tumor deposit of >2 cm. Nine (30%) had deposits in pouch of douglas and bowel surface involvement was seen in nine (30%) patients. No patient in our present study had liver involvement. Taking a residual tumor of <1 cm as criteria, all patients underwent optimal debulking. Pelvic lymph nodes were removed in all 30 patients. However. paraaortic node removal was done upto renal vessels in 20 patients only. Mean±1SD operating time in all patients was 146.83±28.11 minutes with a median value of 150 minutes (range 90-195 minutes).

Pathological findings

Malignant cells were seen in peritoneal cytology of ten (33%) patients. Primary ovarian tumor was seen in 27 (90%) patients with three (10%) patients showing primary peritoneal cancer. Serous variety was the most common seen in 22 (73%) of the patients followed by endometroid type in three (10%) patients, mucinous in two (7%), clear cell in two (7%) and malignant brenner tumor in one patient. Patients with grade 3 tumors were regarded as high grade (n = 20) and 10 (33%) patients

with grade 1 or 2 tumors were clubbed as low grade tumors. Final staging of the tumor showed 16 patients (53%) belonging to FIGO stage III cancer. Nine patients had stage 1, four (14%) belonged to stage II and one patient (3%) had stage IV disease.

Incidence of lymph node metastasis

A total of 299 pelvic nodes were removed from all the patients accounting an average±1SD 10±4.3 nodes per patient. Out of 30 patients undergoing pelvic lymphadenectomy, eight (26.6%) had a total of 16 lymph nodes positive constituting two positive nodes per patient. Paraaortic nodes were removed in 20 patients and a total of 82 nodes were removed with an average±SD of 4.0±1.2 nodes per patient. Out of these 20, three (15%) patients had a total of six lymph nodes positive constituting two positive nodes per patient. Either pelvic lymph node or paraaortic lymph node or both were seen among ten (33.3%) patients (seven had positive pelvic nodes, two had positive paraaortic nodes and one had both pelvic and paraaortic node positivity.

Postoperative course

Average±1SD blood loss was 535±234.5 ml with a range of 100-1200 ml with 22 (73%) patients receiving blood transfusion in postoperative period. Six patients (20%) had Clavien Dindo grade 1 complications and grade 2 and grade 3 complications were seen in two patients each. Average±1SD hospital stay was 5.3±1.08 days with a range of 4-8 days.[7]

Table 1: Correlation of lymph node positivity with various parameters.

Variable	Sample size	Node positive (n = 10)	Node negative (n = 20)	p-value
Age (years) (Mean±SD)	30	46.3±17.5	47.6±11	0.798
CA125 (U/ml)	30	919	369	0.245
Tumor volume (ml)	30	1000	756	0.99
Laterality				
Unilateral	15	3 (20%)	12 (80%)	0.398
Bilateral	12	5 (41%)	7 (59%)	
Cytology				
Negative	20	5 (25%)	15 (75%)	0.231
Positive	10	5 (50%)	5 (50%)	
Stage				
I-II	9	0 (0%)	9 (100%)	0.013
III-IV	21	10 (47.6%)	11 (52.4%)	
Grade				
Low	10	3 (30%)	7 (70%)	0.995
High	20	7 (35%)	13 (65%)	
Histology				
Non serous	8	2 (25%)	6 (75%)	0.682
Serous	22	8 (36%)	14 (64%)	
Omental involvement				
Absent	16	5 (31.25%)	11 (68.75%)	0.990
Present	14	5 (35.7%)	9 (64.3%)	

*For age mean values taken and for CA125 and tumor volume median values taken.

Correlation of various factors with lymph node positivity

The various clinical and pathological parameters were correlated with lymph node positive and negative cases and are shown in Table 1.

Correlation with Imaging modality

Imaging findings (CECT) were compared with intraoperative findings and were correlated in terms of tumor volume, presence of ascites, lymph nodes and presence of deposits. Correlation between tumor volume on imaging and intraoperative findings was significant with positive correlation (r = 0.879; p <0.001). Positive predictive value (PPV) of imaging for ascites estimation was 100% and negative predictive value (NPV) was 68.8%. PPV of imaging for assessment of nodal status was 60% and NPV was 72% with a sensitivity of 30% compared to specificity of 90%. Presence of deposits on imaging compared to intraoperative assessment showed a PPV of 81.8% and NPV of 63.2%.

Impact of para-aortic lymphadenectomy on various parameters

Patients in which both pelvic and para-aortic lymph nodes were removed, operating time was 159±22.4 minutes compared to those in which only pelvic was removed 121±19.2 minutes and there was statistically significant difference (p <0.001). Mean±SD blood loss of 585±249.7 ml was seen where both group of nodes were removed and patients (n=10) with only pelvic group removed had blood loss of 435±170ml. However, the difference was not statistically significant (p=0.099). Comparing transfusions, patients undergoing only pelvic lymphadenectomy had a significantly lesser transfusions (mean: 0.5±0.97) compared to patients undergoing both pelvic and paraaortic lymph node removal (mean:1.75±0.96; p = 0.002). Eight (40%) patients had Clavien Dindo grade 1-3 complications in pelvic±paraaortic group compared to only two complicated cases in pelvic group but the observation was not statistically significant (p = 0.419). Difference in hospital stay was also not significant (p = 0.816).

Follow up

Twenty-two patients received postoperative chemotherapy. Five patients were kept under observation and two patients were lost to follow up. One patient expired before initiation of chemotherapy. Out of 22 patients receiving postoperative chemotherapy, 19 patients received 6 cycles of carboplatin and paclitaxel (TP), two patients received 3 cycles of TP combination and one patient received 10 cycles of Capecitabine. Patients were followed up for 12 months. At 12 months follow up, 24 patients were in remission, two had recurrence, two were lost to follow up and two patients had expired. Both patients with recurrence had received

chemotherapy. One patient expired after completing chemotherapy and one before chemotherapy initiation. CA125 values of all but two patients were noted and were compared with preoperative values irrespective of whether they received adjuvant therapy or not (Figure 1).
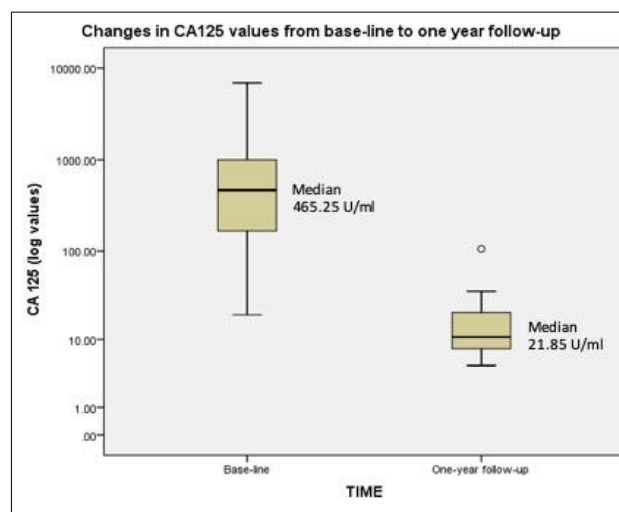

Figure 1: Box-plots comparing preoperative and 12 months follow up CA125. The length of the box represents the interquartile range (50% of the data), whiskers represent the 5 and 95% quartiles. The line across the box is the median value of CA125. Outliers are depicted by dots beyond the whiskers.

Three patients had recurrence at 12 months follow up out of which one patient expired. All patients with recurrence were compared with variables that could have been associated with recurrences and only history of familial cancer was found to be significantly associated with recurrence (p <0.01). Apart from that serous histology and high tumor grade were also associated with increased chances of recurrence though not statistically significant.

Two patients had expired at follow up and comparing variables to death events, higher tumor grade, advanced stage, positive peritoneal cytology and positive lymph node status was found to have higher correlation with deaths but was not statistically significant.

DISCUSSION

Ovarian cancer is best managed by surgery followed by chemotherapy. Lymphadenectomy as a part of surgical staging has been studied since 80s, evidence is still conflicting in its role in primary debulking. Moreover, not many studies have included Indian women and their response to treatment protocols. So current study tried to look into the lymph node metastasis in Indian women undergoing primary debulking surgery for ovarian tumors, problems associated intraoperatively and postoperatively, its clinicopathological correlation and its impact on survival.

In the present study the mean age of presentation was 47 years which is lesser as compared to previous studies where the age was above 50 which could be attributed to less usage of oral contraceptives in Indian females which have a significant oncoprotection.[8-10] Goff et al found symptoms like pelvic/abdominal pain, urinary urgency/ frequency, increased abdominal size/bloating or a feeling of fullness when present for <1 year for more than 12 days a month to be suspicious of carcinoma ovary.[11] In our study also, 73% of the patients presented with similar complaints.

Nodal yield in a previous study by Pereira et al was 24.6 for Pelvic and 13.1 for Paraaortic nodes.[12] Roscigno in an attempt to find the number of nodes needed to be removed to detect metastasis showed that 13 nodes yielded 90% probability to detect >1 positive node and removal of 8 nodes had 75% probability.[13] In our patients pelvic nodal yield was 10 which appears an adequate number though the paraaortic nodal yield of four was less. The incidence of pelvic node involvement was 26.6% (8/30) and paraaortic node involvement was seen in 15% (3/20) patients. The incidence was lower compared to earlier reports owing to small sample size.[14-16]

Presence of lymph node metastasis can be predicted by various factors. CA125 levels being one such factor has been validated at a cut off value of 740 U/ml to predict nodal involvement though we did not find any such trend.[16] In our study serous histology, higher grade, stage 3 and above, positive peritoneal cytology, omental involvement showed a higher lymph node involvement though not statistically significant .This corroborated with previous studies showing similar findings.[15,17,18]

Cross sectional imaging is most frequently used modalities for lymph node assessment. Sensitivity of CT varies from 43% (ovarian and cervical neoplasms) to 65% (cervical neoplasm), and its rate of precision varies from 67% (endometrial neoplasm) to 90% (cervical neoplasm).[19-21] The sensitivity of magnetic resonance imaging (MRI) for the detection of metastatic lymph nodes varies from 38% (ovarian cancer) to 73% (cervical cancer).[22,23] Whereas its specificity varies from 58% (ovarian cancer) to 93% (cervical cancer).[24,25] In our study also lymph node assessment on cross sectional imaging (CECT) was compared to positive lymph nodes and was seen that out of five patients showing lymph node involvement on imaging three had positive nodes on final pathological examination (60%) and out of 25 patients who had no lymphadenopathy on imaging, 18 patients (72%) had negative nodes on final examination. So imaging was found to have a sensitivity of 30% compared to specificity of 90% for lymph node assessment.

The effect of lymph node metastasis on long term survival has been widely studied. Burghardt et al found survival rate of 51%, 56% and 18% in patients with no, one or more than one positive node respectively and lymphadenectomy if done showed higher survival.[26,27] However a recent trial has confirmed that patients where intraabdominal macroscopically complete resection is done and lymph nodes both before and during surgery are normal, no increase in overall or progression-free survival is seen than no lymphadenectomy and is associated with a higher incidence of postoperative complications.[28] We had two recurrences and two patients died in a follow up of 12 months and lymph node metastasis was positively correlated with recurrences (p = 0.99) and death events (p = 0.570) suggesting lymphadenectomy to be performed in suspicious nodes only leaving normal looking nodes behind though survival benefits could not be assessed in our study due to small sample size.

While assessing the impact of paraaortic lymphadenectomy on operative variables, it was seen that paraaortic lymphadenectomy was significantly associated with longer operating time, more blood loss followed by more number of blood transfusions and longer hospital stay as shown previously.[29] The mean hospital stay in our study was shorter than the previous ones as ERAS protocol was strictly followed and patients were mobilized early and discharged.[30]

The strength of our study is that it is one of the very few studies conducted in the field of ovarian cancer in Indian population which can guide us further in surgical tolerance in this subset of patients. The study also suffered from a few limitations, small sample size and lesser nodal yield being most important.

CONCLUSION

Lymphadenectomy in ovarian cancer is associated with increased morbidity. Decision for removal of nodes should be taken judiciously based on different parameters shown to predict lymph node involvement and patient's ability to tolerate such aggressive treatment considering lack of survival benefits from removal of normal looking nodes.

REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. Cancer Statistics, 2008. CA Cancer J Clin. 2008;58(2):71-96.
2. Morice P, Joulie F, Camatte S, Atallah D, Rouzier R, Pautier P, et al. Lymph node involvement in epithelial ovarian cancer: analysis of 276 pelvic and paraaortic lymphadenectomies and surgical implications. J Am Coll Surg. 2003;197(2):198-205.

3. Berek JS. Lymph node-positive stage IIIC ovarian cancer: a separate entity? Int J Gynecol Cancer Off J Int Gynecol Cancer Soc. 2009;19 Suppl 2:S18-20.
4. Mikami M. Role of lymphadenectomy for ovarian cancer. J Gynecol Oncol. 2014;25(4):279-81.
5. Prat J. FIGO's staging classification for cancer of the ovary, fallopian tube, and peritoneum: abridged republication. J Gynecol Oncol. 2015;26(2):87-9.
6. Trimbos B, Timmers P, Pecorelli S, Coens C, Ven K, van der Burg M, et al. Surgical staging and treatment of early ovarian cancer: long-term analysis from a randomized trial. J Ntl Cancer Inst. 2010;102(13):982-7.
7. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187-9.
8. Baek SJ, Park JY, Kim DY, Kim JH, Kim YM, Kim YT, et al. Stage IIIC epithelial ovarian cancer classified solely by lymph node metastasis has a more favorable prognosis than other types of stage IIIC epithelial ovarian cancer. J Gynecol Oncol. 2008;19(4):223-8.
9. du Bois A, Reuss A, Harter P, Pujade-Lauraine E, Ray-Coquard I, Pfisterer J. Potential role of lymphadenectomy in advanced ovarian cancer: a combined exploratory analysis of three prospectively randomized phase III multicenter trials. J Clin Oncol. 2010;28(10):1733-9.
10. Beral V, Doll R, Hermon C, Peto R, Reeves G. Collaborative group on epidemiological studies of ovarian cancer. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet Lond Engl. 2008;371(9609):303-14.
11. Goff BA, Mandel LS, Drescher CW, Urban N, Gough S, Schurman KM, et al. Development of an ovarian cancer symptom index: possibilities for earlier detection. Cancer. 2007;109(2):221-7.
12. Pereira A, Magrina JF, Rey V, Cortes M, Magtibay PM. Pelvic and aortic lymph node metastasis in epithelial ovarian cancer. Gynecol Oncol. 2007;105(3):604-8.
13. Roscigno M, Shariat SF, Freschi M, Margulis V, Karakiewizc P, Suardi N, et al. Assessment of the minimum number of lymph nodes needed to detect lymph node invasion at radical nephroureterectomy in patients with upper tract urothelial cancer. Urology. 2009;74(5):1070-4.
14. Yavuzcan A, Baloglu A, Cetinkaya B. The investigation of the factors affecting retroperitoneal lymph node metastasis in stage IIIC and IV epithelial ovarian cancer. Arch Gynecol Obstet. 2009;280(6):939-44.
15. Powless CA, Aletti GD, Bakkum-Gamez JN, Cliby WA. Risk factors for lymph node metastasis in apparent early-stage epithelial ovarian cancer: Implications for surgical staging. Gynecol Oncol. 2011;122(3):536-40.
16. Zhou J, Sun J-Y, Wu S-G, Wang X, He Z-Y, Chen Q-H, et al. Risk factors for lymph node metastasis in ovarian cancer: Implications for systematic lymphadenectomy. Int J Surg. 2016;29:123-7.
17. Ulker V, Kuru O, Numanoglu C, Akbayır O, Polat I, Uhri M. Lymph node metastasis in patients with epithelial ovarian cancer macroscopically confined to the ovary: review of a single-institution experience. Arch Gynecol Obstet. 2014;289(5):1087- 92.
18. Ayhan A, Gultekin M, Taskiran C, Celik NY, Usubutun A, Kucukali T, et al. Lymphatic metastasis in epithelial ovarian carcinoma with respect to clinicopathological variables. Gynecol Oncol. 2005;97(2):400-4.
19. Mitchell DG, Hill MC, Hill S, Zaloudek C. Serous carcinoma of the ovary: CT identification of metastatic calcified implants. Radiology. 1986;158(3):649-52.
20. Tempany CM, Zou KH, Silverman SG, Brown DL, Kurtz AB, McNeil BJ. Staging of advanced ovarian cancer: comparison of imaging modalities- report from the radiological diagnostic oncology group. Radiology. 2000;215(3):761-7.
21. Bipat S, Glas AS, van der Velden J, Zwinderman AH, Bossuyt PMM, Stoker J. Computed tomography and magnetic resonance imaging in staging of uterine cervical carcinoma: a systematic review. Gynecol Oncol. 2003;91(1):59-66.
22. Yang WT, Lam WW, Yu MY, Cheung TH, Metreweli C. Comparison of dynamic helical CT and dynamic MR imaging in the evaluation of pelvic lymph nodes in cervical carcinoma. AJR Am J Roentgenol. 2000;175(3):759-66.
23. Reinhardt MJ, Ehritt-Braun C, Vogelgesang D, Ihling C, Högerle S, Mix M, et al. Metastatic lymph nodes in patients with cervical cancer: detection with MR imaging and FDG PET. Radiology. 2001;218(3):776-82.
24. Ricke J, Sehouli J, Hach C, Hänninen EL, Lichtenegger W, Felix R. Prospective evaluation of contrast-enhanced MRI in the depiction of peritoneal spread in primary or recurrent ovarian cancer. Eur Radiol. 2003;13(5):943-9.
25. Kim SH, Kim SC, Choi BI, Han MC. Uterine cervical carcinoma: evaluation of pelvic lymph node metastasis with MR imaging. Radiology. 1994;190(3):807-11.
26. Burghardt E, Girardi F, Lahousen M, Tamussino K, Stettner H. Patterns of pelvic and paraaortic lymph node involvement in ovarian cancer. Gynecol Oncol. 1991;40(2):103-6.
27. Gao J, Yang X, Zhang Y. Systematic lymphadenectomy in the treatment of epithelial ovarian cancer: a meta-analysis of multiple epidemiology studies. Jpn J Clin Oncol. 2015;45(1):49-60.
28. Harter P, Sehouli J, Lorusso D, Reuss A, Vergote I, Marth C, et al. A Randomized Trial of Lymphadenectomy in Patients with Advanced

Ovarian Neoplasms. N Engl J Med. 2019;380(9):822-32.

29. Maggioni A, Benedetti Panici P, Dell'Anna T, Landoni F, Lissoni A, Pellegrino A, et al. Randomised study of systematic lymphadenectomy in patients with epithelial ovarian cancer macroscopically confined to the pelvis. Br J Cancer. 2006;95(6):699-704.

30. Nelson G, Dowdy SC, Lasala J, Mena G, Bakkum-Gamez J, Meyer LA, et al. Enhanced recovery after surgery (ERAS®) in gynecologic oncology - Practical considerations for program development. Gynecol Oncol. 2017;147(3):617-20.