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The role of paraaortic lymphadenectomy along with sentinel mapping in clinically uterine confined intermediate-high risk endometrial cancer

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Abstract

This study aimed to find out whether sentinel algorithm can be sufficient in clinically uterine confined intermediate-high risk endometrial cancer. Detailed pathology characteristics and follow-up records of the 70 intermediate-high risk endometrial cancer patients were identified. Outcomes of patients who are performed sentinel algorithm and sentinel mapping followed by systematic pelvic and paraaortic lymph node dissection were compared. All patients who had obvious extrauterine disease in preoperative and intraoperative evaluation were excluded. Sentinel mapping is performed with methilene blue and cervical injection. 66 patients were identified (sentinel algorithm group, 25; Paraaortic lymph node dissection group, 45). Paraaortic lymph node dissection group had more high grade patients (p=0.02). The mean number of lymph nodes harvested was 11.3 and 36.9, respectively, in sentinel algorithm group and paraaortic lymph node dissection group(p<0.001) and there was more lymph node metastasis in paraaortic lymph node dissection group (12% and 31,7%; p=0.07). 84% in the sentinel algorithm group and 92.7% in the paraaortic lymph node dissection group, respectively, received adjuvant therapy (p=0.02). Overall, four patients recurred within the first three year following surgery, two patients had systematic multiple metastasis and both of them died due to disease. There was no significant difference between the two groups in terms of overall survival (p = 0.252), disease specific survival (p = 0.10) and disease-free survival (p = 0.577). The mean follow-up period was calculated as 29.33 months. To date, there is no prospective study focused on whether sentinel lymphadenectomy in endometrial cancer is sufficient for management of moderate high-risk endometrial cancer and to establish the necessity of paraaortic lymphadenectomy in this patient group. Our study indicates that for clinically uterine confined intermediate-high risk endometrial cancer patients sentinel lymph node algorithm can be sufficient. Further studies are needed to confirm this finding.

Keywords: endometrial cancer, sentinel lymph node, paraaortic lymph node dissection, sentinel algorithm

1. Introduction

Although the role of lymphadenectomy in the management of EC is controversial, the role of paraaortic lymphadenectomy which is more difficult to perform with higher complication rates and requires advanced surgical ability and experience is considered more controversial (1, 2).

In recent years, the role of sentinel lymphadenectomy in gynecological malignancies has been investigated widely and is gradually taking place in the guidelines (3, 4). The main reason for this is the therapeutic effect of lymphadenectomy has not been proven in randomized controlled studies in endometrial cancer. Currently, lymphadenectomy only plays a role in tailoring the accurate adjuvant therapy (2, 5).

Patients with no or less than a half of myometrial invasion and low grade endometrial cancer have negligible risk of lymph node metastasis, however, precise definition of this group of patients is not possible preoperatively (6, 7). In the setting of systematic pelvic and paraaortic lymphadenectomy to all patients with endometrial cancer, a significant number of patients face the potential short and long term morbidities of lymphadenectomy without any survival benefit. In addition, whether this full systematic lymphadenectomy has a survival benefit in patients considered high risk for lymphatic metastasis (i.e., deep myometrial invasion, high grade lesions) is not clear. In a study comparing sentinel lymphadenectomy and systematic lymphadenectomy in the management of endometrial cancer; it was reported that the rate of metastasis detection was higher with sentinel lymphadenectomy and there was no overall survival difference between the two groups (8).

In our study, we evaluated the outcomes of patients with intermediate-high risk endometrial cancer who underwent sentinel algorithm and sentinel lymphadenectomy followed by systematic pelvic and paraaortic lymphadenectomy.

2. Materials and Methods

After approval of the Ethics Committee, the data of 179 endometrial cancer patients operated in Istanbul Prof Dr Cemil Tascioglu City Hospital and Bahcesehir University Hospital between May 2016 and November 2019 were retrospectively analyzed. The cases who had FIGO stage IIIA-IIIB-IV disease, in whom sentinel mapping had not been

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performed and those with myometrial invasion less than ½ and grade 1-2 with no lymphovascular space invasion were excluded. Additionally, the cases who had obvious lymph node metastasis in imaging were excluded. Detailed pathology characteristics and follow-up records of the 66 intermediate-high risk endometrial cancer cases were recorded. Intermediate-high risk defined as: 1) Low grade patients with myometrial invasion <1/2 and no lymphovascular space invasion, 2) High grade patients (grade 3 and non-endometrioid types) with any myometrial invasion, 3) All patients with >1/2 myometrial invasion with any grade (4).

In our clinic, management of all endometrial cancer cases was performed according to the algorithm in Fig. 1. For sentinel lymphatic mapping, 4 cc of methylene blue was injected into the cervix on 3-9 o'clock before the operation. Sentinel node dissection was performed first than followed by systematic pelvic lymphadenectomy with or without paraaortic lymphadenectomy according to the preoperative condition of the patients. All operations were performed by the same surgical team.

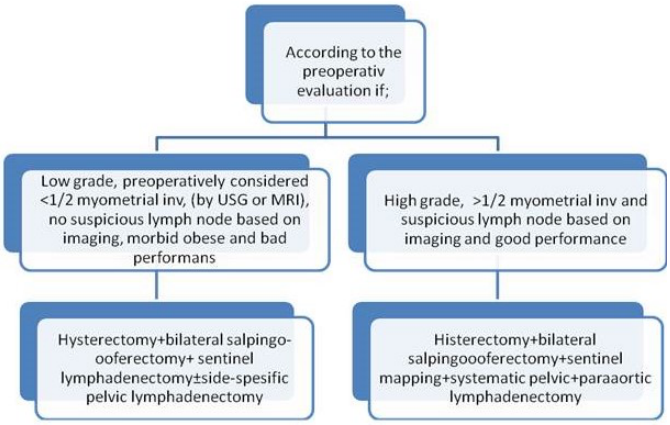

Fig. 1. Management of endometrial cancer in our clinic

All sentinel nodes are assessed by trained gynecologic pathologists. Pathologic ultra-staging includes standard lymph node assessment, which involves sectioning the SLN once along the longitudinal axis and staining it with hematoxylin and eosin to determine if it contains metastatic tumor cells. If tumor cells are identified, the lymph node is considered positive and no additional sectioning or staining is performed. However, if the initial hematoxylin and eosin is negative, further pathologic assessment—which include additional sectioning and staining of the SLN with hematoxylin and eosin and immunohistochemistry (cytokeratin stains AE1:AE3)—is performed to examine the SLN for low-volume metastatic disease. Micrometastasis is defined as a focus of metastatic tumor cells measuring >0.2 mm and ≤2 mm, whereas isolated tumor cells are defined as microscopic clusters and single cells measuring ≤0.2 mm. For the purposes of this analysis, isolated tumor cells, micrometastases, and macrometastasis were all considered node-positive.

Demographic data, pathology findings and follow-up findings were recorded. Staging was adapted according to FIGO 2009 system. Clinical, pathological and surgical features were recorded for all patients. Lymphovascular space invasion has been identified by pathologists as tumor cells on or into the wall of a capillary-like area. The presence of artificial tumor displacement is excluded. The last follow-up date, the recurrence date and the disease follow-up were recorded at the last follow-up visit. Overall survival was defined as the time from the operation dates until the death of the patient for any reason after the operation. Disease free survival was defined as the period from the operation date of the patient to the date when the recurrence was proved with pathology reports.

2.1. Statistics

Survival curves plotted by Kaplan-Meier methods and comparisons were made using log-rank Scale. Cox proportional hazards regression multivariate analysis (after univariate meanings, the relationship between survival of variables). Qualitative parameters were compared by Pearson's or Fisher's exact test. Continuous parameters compared by Student's t-test or Mann-Whitney U test. All statistical tests were two-sided and statistical significance levelis set at 0.05. Data analysis done by Versions for Windows using IBM SPSS Statistics 20.0, Armonk, NY

3. Results

Hystopathologic characteristics of 66 patients who were defined as intermediate-high risk for recurrence are detailed in Table 1. Sentinel node was detected in at least one side in 57 cases (86.4%), and bilateral sentinel nodes were found in 45 cases (68.2%). Lymphatic metastasis was detected in 16 (24.2%) cases, 10 of these cases were isolated tumor cell metastasis (15.1%), 2 of cases were micrometastasis (3%) and 4 were macrometastasis (6%). Seven (10.6%) patients did not receive adjuvant therapy after the operation or received only Intracavitary Radiotherapy, 35 (53%) patients received external beam radiotherapy and Intracavitary Radiotherapy, 24 (36.4%) patients received chemotherapy and radiotherapy combined. The mean follow-up period was calculated as 29.33 months. 41 patient underwent sentinel lymphadenectomy followed by pelvic and paraaortic lymphadenectomy, while 25 patients underwent only pelvic lymphadenectomy according to sentinel algorithm. The clinicopathologic characteristics of the patients between two groups were compared in Table 2. There was no statistically significant difference between two groups for mean age, body mass index, FIGO stage, tumor size, depth of myometrial invasion, lymphovascular space invasion, cervical stromal invasion, the detection rate of sentinel node and follow-up time. However, patient with high grade tumor were higher in paraaortic lymph node dissection group (p=0.02). Additionally, patients in paraaortic lymph node dissection group received more adjuvant therapy (92.7% vs. 84%, p=0.02).

Table 1. Clinicopathologic characteristics of the all cases

Charachteristics	n=66
age (median)	61 (40-87)
Bmi(median)	30.09 (19.53- 50.67)
hystologic type	
Endometrioid	53 (80.3%)
Non-endometrioid	5 (7.6%)
Carcinosarcom	8 (12.1%)
Mean lymph node count	27.2 (17.4%)
Mean pelvic lymph node count	17.3 (±8.2)
Mean paraaortic lymph node count	15.8 (±10.1)
Grade	
1	13 (%20)
2	27 (%41.5)
3	25 (%38.5)
FIGO Stage	
IA	9 (%13.6)
IB	36 (%54.5)
II	5 (%7.6)
IIIC1	11 (%16.7)
IIIC2	5 (%7.6)
myometrial invazion	
<1/2	11 (%16.7)
>1/2	55 (%83.3)
LVSI	
Negative	51 (%77.3)
Positive	15 (%22.7)
Cervical stromal inv	
Negative	59 (%89.4)
Positive	7 (%10.6)
Sentinel mapping	
None	9 (%13.6)
Unilateral	12 (%18.2)
Bilateral	45 (%68.2)
Lymph node metastasis	16 (%24.2)
Isolated Tumor Cell	10 (%15.1)
Micrometastasis	2 (%3)
Macrometastasis	4 (%6)
Isolated paraaortic metastasis (n=45)	2 (%4.4)
Adjuvant Treatment	
none or ICRT	7 (%10.6)
EBRT+ICRT	35 (%53)
RT+Chemotherapy	24 (%36.4)
Follow-up time (Month)	25.35 (5-47)

The average number of lymph nodes removed in the paraaortic lymph node dissection group was significantly higher than that of sentinel algorithm group (36.9 and 11.3 respectively; p = 0.001) and patients in paraaortic lymph node dissection group had more lymphatic metastasis. However the difference was not statistically significant (31.7% vs. 12%, p = 0.07) (Table 3). In patients in whom paraaortic lymph node dissection performed, 12 had pelvic lymph node metastasis. Among 12 patients, 3 (25%) had also paraaortic lymph node metastasis. In addition, 2 (4.9%) cases had isolated paraaortic metastasis.

Overall, four patients recurred within the first three year following surgery, two patients had systematic multiple metastasis and both of them died due to disease. One of the other two patients had a pelvic nodal recurrence and second patient had a vaginal cuff recurrence. Both patients are treated with chemotherapy following secondary surgery.

Table 2. Clinicopathologic characteristics of the both groups

Charachteristics	Pelvic only (n=25)	palnd+pelvic (n=41)	p value
Age (y)	62.08	60.8	0.62
BMI	33.5	30.4	0.06
FIGO Stage			0.15
IA	4 (16%)	5 (12.2%)	
IB	16 (64%)	20 (48.8%)	
II	3 (12%)	2 (4.9%)	
IIIC1	2 (8%)	9 (22%)	
IIIC2	-	5 (12.2%)	
Tumor Grade			**0.02**
1	7 (29.2%)	6 (14.6%)	
2	13 (54.2%)	14 (34,1%)	
3	4 (16.7%)	21 (51.2%)	
Tumor Size(mm)	43.4	44.1	0.87
MyometrialInvazion			
<1/2	4 (16)	7 (17,1)	0.91
>1/2	21 (84)	34 (82.9)	
LVSI			0.30
Neg	21 (%84)	30 (%73.2)	
Poz	4 (%16)	11 (%26.8)	
CervicalStromalInv			0.59
Neg	23 (92%)	36 (87.8)	
Poz	2(8%)	5 (12.2)	
Sentinel Mapping			0.06
None	6 (24)	3 (7.3)	
Unilateral	6 (24)	6 (14.6)	
Bilateral	13 (52)	32 (78)	
AdjuvantTherapy			0.02
None	4 (16)	3 (7.3)	
RT	17 (68)	18 (43.9)	
RT+Chemo	4 (16)	20 (48.8)	
Follow-upTime	26.28	24.68	0.58

Table 3. Nodal assesment paterns of both groups

	Sentinel algorthim (n=25)	pelvic+paraaortic lymphadenectomy (n=41)	p value
Number of pelvic node retrieved	11.3	36.9	**0.001**
Presence of lymph node metastasis			0.07
Neg	22 (88)	28 (68.3)	
Poz	3 (12)	13 (31.7)	
Location of Metastatic Lymph Node			0.17
pln-/paln-	22 (88)	27 (65.9)	
pln+/paln-	3 (12)	9 (22)	
pln+/paln+	0	3 (7.3)	
pln-/paln+	0	2 (4.9)	

In univariate analysis, none of the risk factors was related to recurrence and death. Additionally, paraaortic lymph node dissection was not related to recurrence or death.

Table 4. Univariate analysis of factors associated with overall survival based on all 66 patients

Characteristics	Univariate analysis	
	HR (%95 CI)	P
Age	1.10 (1.01-1.19)	0.801
BMI	0.83 (0.68-1.00)	0.544
FIGO Grade		0.261
1	Reference	
2	0.41 (0.02-6.66)	
3	1.03 (0.1-10.19)	
FIGO Stage		0.64
I	Reference	
II	3,34 (0.34-32.44)	
III	1.09 (0.11-10.62)	
Cerical Stromal Invasion		0.33
no	Reference	
yes	2.04 (0.22-18.33)	
LVSI		0.077
no	Reference	
yes	1.26 (0.13-11.53)	
Presence of Paraaortic lymphadenectomy		0.252
No or Paraaortic LND not performed	Reference	
Yes	0.94 (0.15-5.65)	
Adjuvant therapy		0.649
None or only ICRT	Reference	
EBRT+ICRT		
Chemotherapy+EBRT+ICRT		

In Kaplan Meier analysis, there was no significant difference between the two groups in terms of overall survival (p = 0.252), disease specific survival (p = 0.10) and disease-free survival (p = 0.577) (Fig. 2).

4. Discussion

Lymphadenectomy remains a controversial issue in the surgical management of endometrial cancer. The risk of lymph node involvement in high risk endometrial cancer is between the ranges of 16-37.8 %, (8, 9, and 10). At least 62, 2 % of patients with the high risk uterine factors underwent unnecessary lymphatic dissection. Two randomized controlled studies on this subject report that lymphadenectomy has no therapeutic effect in endometrial cancer. However, the most criticized parts of the studies were that omission of paraaortic lymph node dissection and the low number of removed lymph nodes. On the other hand, sentinel lymphadenectomy has been introduced recently in the management of endometrial cancer in order to detect metastatic lymph nodes with the highest accuracy and to decide the most appropriate adjuvant therapy and it is recommended in NCCN guidelines (3). Although it is thought that lymphadenectomy has no therapeutic effect in the low-risk endometrium cancer group, the role of lymphadenectomy in patients with intermediate-high risk endometrial cancer has not been clarified yet (8).

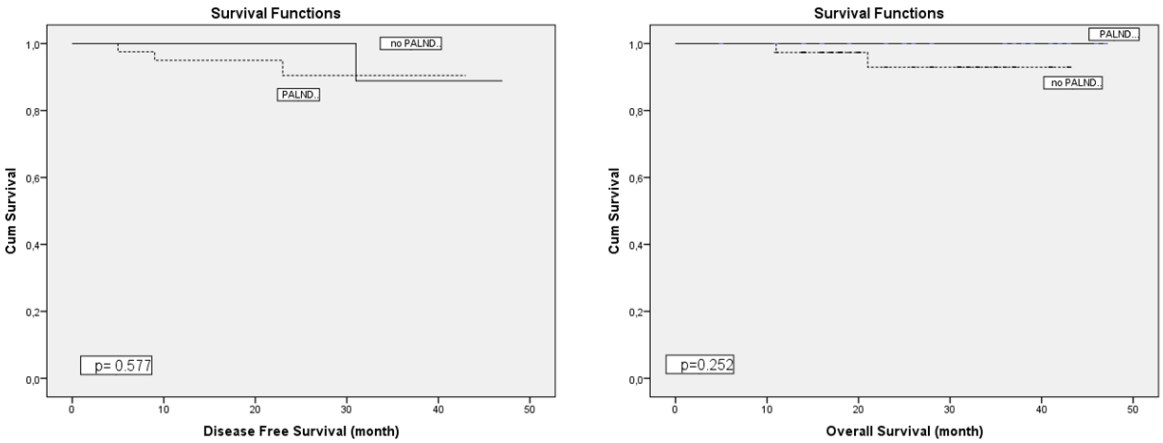

Fig. 2. The comparison of overall survival, disease specific survival and disease free survival between group

Previously published data supports the efficacy and oncologic safety of sentinel lymphadenectomy algorithm in endometrioid endometrial cancer with limited myometrial invasion, but few reports have evaluated its efficacy and safety in the setting of deeply invasive endometrioid histology, (6, and 7).

In the SEPAL study, one of the most comprehensive studies investigating the role of efficacy of paraaortic lymphadenectomy in the management of intermediate-high risk endometrial cancer, it was reported that paraaortic lymphadenectomy had a positive effect on survey, (1). Furthermore, Mariani et al. evaluated patients who had pelvic lymphatic metastasis with or without paraaortic lymph node dissection and revealed that paraaortic lymphadenectomy improved 5-year progression free survival and overall survival suggesting a therapeutic benefit of paraaortic lymph node dissection (11).On the contrary, Schlappea et al.; compared the outcomes of the sentinel algoritm versus systematic pelvic + paraaortic lymph node dissection approaches in the management of high-intermediate risk endometrial cancer and found no difference between the two groups in terms of overall and disease free survival,(8).

The findings in our study indicate that paraaortic lymph node dissection does not contribute to mean overall survival and disease free survival in patients with intermediate-high risk endometrial cancer and clinically uterine confined. We performed systematic lymphadenectomy after sentinel lymphadenectomy and we added paraaortic lymph node dissection in 64.2% of the cases. The number of patients with lymphatic metastasis was 16 (24%) and among these patients

only 4 patients had macrometastasis. We excluded all patients with suspicious node in preoperative imaging and intraoperative evaluation. This low rate of macrometastasis and inefficiency of systematic lymph node dissection may be due to this selection of patients.

The rate of isolated paraaortic lymph node metastasis in endometrial cancer has been reported as 2-5% in the studies conducted in the literature bears the concern that these cases can be skipped with the sentinel algorithm, (9, 12,13). In our study, isolated paraaortic metastasis was detected in 2 (4.9%) cases. Both metastasis were low volume and were in the sentinel nods. In literature there are some studies conducted to resolve this concern by detecting paraaortic sentinel node with fundal injection in addition to cervical injection, (14).

Concern about the sentinel algorithm, 35% of cases having pelvic metastasis have also paraaortic metastasis and these metastatic nodes are missed, (15). In our study, paraaortic metastasis was detected in 25% of cases with pelvic lymphatic metastasis. However, the clinical significance of metastatic paraaortic nodes that are not excised is unknown, when these cases receive adjuvant therapy.

The limitations of our study are that it's retrospective nature and that the group undergoing paraortic lymphadenectomy received statistically significantly more adjuvant therapy. Eighty four percent of the patients in sentinel algorithm group and 92.7% of the patients who underwent systematic lymphadenectomy received adjuvant therapy and 48% of the patients in this latter group received chemotherapy in addition to radiotherapy.

To date, there is no prospective study focused on whether sentinel lymphadenectomy in endometrial cancer is sufficient for management of moderate high-risk endometrium cancer and the necessity of paraaortic lymphadenectomy in this patient group. Our study indicates that for clinically uterine confined intermediate-high risk endometrial cancer patients sentinel lymph node algorithm can be sufficient. Further studies are needed to confirm this finding.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

References

1. 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: 1165–72
2. The writing committee of behalf of the ASTEC study group. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 2009; 373: 125−36.
3. Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, et al. Uterine Neoplasms, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2018;16:170–99.
4. Colombo N, Creutzberg C, Amant F, Bosse T, Martin AG, Ledermann J, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol 2015;117:mdv484.
5. Benedetti Panici P, Basile S, Maneschi F, Lissoni AA, 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;100:1707–16.
6. Zahl Eriksson AG, Ducie J, Ali N, McGree ME, Weaver AL, Bogani G, et al. Comparisonof a sentinel lymph node and selective lymphadenectomy algorithm in patients with endometrioid endometrial carcinoma and limited myometrial invasion. Gynecol Oncol 2016;140:394–9.
7. Papadia A, Gasparri ML, Siegenthaler F, Imboden S, Mohr S, Mueller MD. FIGO stage IIIC endometrial cancer identification among patients with complex atypical hyperplasia, grade 1 and 2 endometrioid endometrial cancer: laparoscopic indocyanine green sentinel lymph node mapping versus frozen section of the uterus, why get around the problem? J Cancer Res Clin Oncol 2017;143:491–7.
8. Schlappea BA, Weaverb AL, Duciea JA, Eriksson AGZ, Dowdy SC, Cliby WA, et al. a Multicenter study comparing oncologic outcomes between two nodal assessment methods in patients with deeply invasive endometrioid endometrial carcinoma: a sentinel lymph node algorithm versus a comprehensive pelvic and paraaortic lymphadenectomy. Gynecol Oncol 2018 November ; 151(2): 235–242
9. Mariani A, Dowdy SC, Cliby WA, Gostout BS, Jones MB, Wilson TO, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. Gynecol Oncol 109 (2008) 11–18.
10. Karalok A, Turan T, Basaran D, Turkmen O, Kimyon GC, Tulunay G, et al. Lymph Node Metastasis in Patients With Endometrioid Endometrial Cancer Overtreatment Is the Main Issue. Int J Gynecol Cancer 2017;00: 00Y00
11. Mariani A, Webb MJ, Galli L, Podratz GC. Potential Therapeutic Role of Para-aortic Lymphadenectomy in Node-Positive Endometrial Cancer. Gynecol Oncol 2000;76:348–56.
12. Kumar S, Podratz KC, Bakkum-Gamez JN, Dowdy SC, Weaver AL, McGree ME, et al. Prospective assessment of the prevalence of pelvic, paraaortic and high paraaortic lymph node metastasis in endometrialcancer. Gynecol Oncol 2014;132:38–43.
13. Nasioudis D, Holcomb K, Incidence of isolated para-aortic lymph node metastasis in early stage endometrial cancer. Eur J Obstet Gynecol Reprod Biol. 2019 Nov;242:43-46
14. Ruiz R, Gorostidi M, Jaunarena I, Goiri C, Aguerre J, Lekuona A. Sentinel Node Biopsy in Endometrial Cancer With Dual Cervical and Fundal Indocyanine Green Injection. Int J Gynecol Cancer 2018 Jan;28(1):139-144(
15. Fotopoulou C, El-Balat A, du Bois A, Sehouli J, Harter P, Muallem MZ, et al. Systematic pelvic and paraaortic lymphadenectomy in early high-risk or advanced endometrial cancer Arch Gynecol Obstet. doi:10.1007/s00404-015-3746-6