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Creating a risk model to determine paraaortic lymph node involvement in endometrial carcinoma

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Aim: To define a high-risk group for paraaortic (PA) lymph node metastasis among endometrial carcinoma patients.

Materials and methods: Prognostic factors determining PA lymph node metastasis were defined. Using these factors in different combinations, 14 risk groups were formed. A patient with at least one of these factors was considered as high-risk for PA lymph node metastasis.

Results: This study included 152 patients. Of these patients, 18 had tumors in the PA region. Lymphovascular space invasion (LVSI) and pelvic lymph node metastasis were independent prognostic factors for PA lymph node involvement. In the risk modeling system, pelvic lymph node metastasis was an important factor in predicting PA lymph node status, and in groups where this factor was included for risk modeling, PA lymph node involvement was significantly increased in high-risk patients. Best results were obtained with the risk group model (group 10) involving cell type, LVSI, serosal spread, adnexal metastasis, and pelvic lymph node as prognostic factors. In this group sensitivity was 94%, specificity was 53.7%, and negative and positive predictive values were 98.6% and 21.5%, respectively. According to this model, 52% of all patients were in the high-risk group.

Conclusion: Group 10 seemed to include the guiding properties for a decision on paraaortic lymphadenectomy and it was possible to reduce unnecessary paraaortic lymphadenectomies by 50%.

Key words: Endometrial cancer, paraaortic lymph node metastasis

Introduction

Endometrial carcinoma has been staged surgically since 1988 according to International Federation of Gynecology and Obstetrics (FIGO) criteria. However, the extent of surgery, whether a lymphadenectomy should be done or not, and the extent of lymphadenectomy are controversial points.

Pelvic and paraaortic (PA) lymphadenectomy is known to increase morbidity and mortality (1,2). In cases of grade 1 endometrioid tumor with less than half myometrial invasion and no cervical invasion or adnexal spread, it is known that this procedure is not associated with an increase in survival rates (3). Patients considered as high-risk for lymph node metastasis undergo both pelvic and PA lymphadenectomies; however, the extent of lymphadenectomy is not clearly defined. In selected patients, is pelvic lymphadenectomy alone enough, or should PA lymphadenectomy be added? If PA lymphadenectomy is indicated, where should the limit of the procedure be, the inferior mesenteric artery or the left renal vein? If PA lymphadenectomy is to be a part of the surgery, it needs to be done up to the level of the renal vein. Mariani et al. showed that 77% of patients with pelvic lymph node metastasis

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also had metastatic lymph nodes superior to the level of the inferior mesenteric vein and that in more than half of these patients lymph node metastasis was only at these sites (4). Other studies also demonstrated similar results (5,6).

The main point of discussion should be the necessity of PA-region lymphadenectomy. Under which surgical circumstances should we add PA lymphadenectomy to the surgical procedure, and is it associated with an increase in survival rates? These are unclear issues. It was shown in multivariate analysis that pelvic lymph node metastasis, cell type, presence of lymphovascular space invasion (LVSI), patient age, tumor grade, depth of myometrial invasion, and cervical invasion were determining factors for PA lymph node metastasis (7–12). However, when these studies are evaluated individually, it can be seen that one or more of these factors is found to be significant while the others are not, or vice versa. For example, in a study by Yokoyama et al., tumor grade and myometrial invasion were significant risk factors for PA lymph node metastasis while LVSI was not (11). For that reason, using only one risk factor to argue for the necessity of PA lymphadenectomy will lead to unnecessary morbidity or inadequate treatment.

It is known that in 45%–67% of patients with pelvic lymph node metastasis, there is tumoral spread in the PA region (4,5,7,10). Reported rates of isolated PA lymph node metastasis range between 0% and 8% (6,8,10–14). It was proposed that routine addition of PA lymphadenectomy to pelvic lymphadenectomy was not associated with a significant advantage in terms of survival (10,15). For these reasons, it seems rational to define high-risk patients who will benefit from PA lymphadenectomy and form risk groups.

In our previous study we showed that the risk model including the existence of pelvic lymph node metastasis, nonendometrioid cell type, LVSI, adnexal spread, and serosal involvement could predict PA metastasis in endometrial carcinoma (16). In the current study, risk models were created based on the previous study to predict PA-region metastasis. The efficiencies of these groups in predicting PA metastasis were evaluated. We aimed to create risk models predicting the necessity for PA lymphadenectomy.

Materials and methods

Patients were staged according to FIGO 1988 criteria. We performed surgical staging for patients whose intraoperative frozen pathology revealed endometrial tumor with cell types other than endometrioid adenocarcinoma, tumor grade 2 or 3, ≥1/2 myometrial invasion, and tumor size greater than 2 cm. Patients diagnosed to have grade 3 tumor or high-risk cell types preoperatively underwent surgical staging without intraoperative histologic evaluation.

In the present study, the data of 152 patients with a sufficient pathology report who underwent systematic lymphadenectomy up to the level of the renal vein with the removal of at least 15 pelvic and 10 PA lymph nodes were analyzed retrospectively.

The incidence of PA lymph node metastasis and prognostic factors determining metastasis were determined. The influence of clinicopathologic factors on PA lymph node metastasis was examined using the chi-square test. Statistical power of factors was examined using multivariate logistic regression analysis and statistical analysis was performed using SPSS 17.0. The cut-off for statistical significance was set at $P < 0.05$. By using different combinations of these factors, 14 risk groups were formed (Table 1). Statistical results and data from the literature about prognostic factors determining PA lymph node metastasis were taken into consideration when creating these risk groups.

Patients with at least one of the factors used to define the risk groups were accepted as having high risk for that model. The strength of risk groups to predict PA-region lymph node status was analyzed using sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV).

Results

The mean age of the patients was 57.5 years (range: 35–83) and mean tumor size was 39.3 mm (range: 0–110 mm). Tumor stage ranged between IA and IVB and 91 (59.9%) patients had stage I tumor. Pathologic diagnosis was endometrioid-type tumor in 128 (84.2%) patients. Surgical and pathological data are shown in detail in Table 2.

Table 1. Risk groups.

Risk group	Cell type	Grade	DMI	LVSI	CI	Serosal invasion	Ovarian metastasis	Tubal metastasis	Positive peritoneal cytology	Pelvic LN metastasis	Tumor size
1	+	+	+			+					
2	+	+	+			+					+
3	+	+	+			+	+	+			
4	+	+	+		+	+					
5	+	+	+	+		+					
6	+	+	+	+		+				+	
7	+		+	+	+	+	+	+	+		
8	+		+	+	+	+	+	+	+	+	
9	+	+	+	+		+	+	+	+	+	
10	+			+		+	+	+		+	
11	+			+		+	+	+			
12	+			+		+	+	+			+
13	+	+	+	+		+	+	+			
14	+	+	+	+	+	+					+

Cell type: endometrioid vs. nonendometrioid; Grade: 2 and 3; DMI: depth of myometrial invasion ≥ 1/2; LVSI: lymphovascular space invasion; CI: cervical invasion; LN: lymph node; Tumor size: ≥40 mm.

The average number of lymph nodes removed was 61.1 (range: 27–122). The average number of pelvic and PA lymph nodes removed was 42.1 (range: 16–81) and 19.2 (range: 10–46), respectively. There was lymph node metastasis in 32 (21.1%) patients. Of these patients, 18 had lymph node metastasis in the PA region. There were 5 (3.3%) patients who had PA lymph node metastasis and no pelvic lymph node metastasis, and this group of patients was categorized as having isolated PA lymph node metastasis.

Except for 2 risk groups (group 10 and 7), more than 80% of patients carried at least 1 of the risk factors in the groups (Table 2). In group 10, 52% of patients carried a risk factor, while in group 7, 69.7% of patients carried a risk factor.

Univariate analysis revealed that depth of myometrial invasion, tumor size (cut-off value of <40 mm), presence of LVSI, cervical invasion, peritoneal spread, and pelvic lymph node metastasis were determining factors for PA lymph node metastasis (Table 3). However, it was seen in binary logistic regression analysis that LVSI and pelvic lymph node metastasis were independent prognostic factors for PA lymph node involvement (OR: 6.4, 95% CI: 1.6–25.8 and OR: 17.5, 95% CI: 5.1–59.5, respectively).

Pelvic lymph node metastasis was an important factor for predicting PA lymph node status in the risk modeling system. In groups where pelvic lymph node metastasis was included in the modeling system (groups 6, 8, 9, and 10), univariate analysis showed that for patients carrying at least one risk factor, PA lymph node involvement was increased significantly or the increase was at a borderline level of insignificance (Table 4). In 3 of these groups (groups 6, 8, and 9), sensitivity and NPV were 100%, while in group 10 these rates were 94% and 98.6%, respectively. However, specificity was 53.7% in group 10, 32.8% in group 8, and less than 15% in the other 2 groups. Hence, group 10 had the highest PPV (21.5%). The reason for this was the number of factors used to create the group. As the number of factors increase in the modeling system, sensitivity and NPV are increased while specificity and PPV are decreased.

By removing the pelvic lymph node metastasis risk factor from group 10, the remaining factors (cell type, LVSI, serosal spread, ovarian metastasis, and tubal involvement) formed group 11. In group 11, PA lymph node metastasis rate was similar between patients carrying at least one risk factor and

Table 2. Characteristics, surgical and pathological factors, and risk groups.

Parameter		Mean (n)	Range (%)
Age		57.5	35–83
Tumor size (mm)		39.3	0–110
Number of removed total lymph nodes		61.1	27–122
Number of removed paraaortic lymph nodes		19.2	10–46
Number of removed pelvic lymph nodes		42.1	16–81
Stage	IA	9	6
	IB	43	28.1
	IC	39	25.5
	IIA	1	0.7
	IIB	12	7.8
	IIIA	11	7.2
	IIIB	1	0.7
	IIIC	33	21.6
	IVA	1	0.7
	IVB	1	0.7
Cell type	Endometrioid	128	84.2
	Clear cell	6	3.9
	Serous	8	5.3
	Mixed type	10	6.6
Grade	1	47	30.9
	2	63	41.4
	3	42	27.6
Depth of myometrial invasion	Only endometrium	11	7.2
	<1/2	58	38.2
	≥1/2	76	50
	Serosal infiltration	7	4.6
Peritoneal cytology	Negative	143	94.1
	Positive	9	5.9
Metastasis to ovary	Negative	314	88.2
	Positive	18	11.8
Metastasis to tuba uterina	Negative	142	93.4
	Positive	10	6.6
Cervical invasion	Negative	120	79.5
	Glandular	4	2.6
	Stromal	28	17.9
Lymphovascular space invasion	Negative	89	58.6
	Positive	63	41.4
Lymph node status	Pelvic and paraaortic lymph node metastasis	13	8.6
	Isolated pelvic lymph node metastasis	14	9.2
	Isolated paraaortic lymph node metastasis	5	3.3
Number of high-risk patients according to risk groups	Group 1	129	84.9
	Group 2	139	88.9
	Group 3	131	86.2
	Group 4	130	85.5
	Group 5	132	86.8
	Group 6	133	87.5
	Group 7	106	69.7
	Group 8	109	71.7
	Group 9	134	88.2
	Group 10	79	52
	Group 11	129	84.9
	Group 12	137	90.1
	Group 13	133	87.5
	Group 14	139	91.4

Table 3. Univariate analysis of surgical and pathological factors for paraaortic lymph node metastasis.

Parameter		Metastatic PALN (%)	P
Cell type	Endometrioid	12.5	0.562
	Nonendometrioid*	8.3	
Grade	1	14.9	0.436
	2 and 3	10.5	
Depth of myometrial invasion	No invasion and <1/2	4.3	0.009
	≥1/2 and serosal infiltration	18.1	
Age	≤57 years	7.5	0.081
	>57 years	16.7	
Tumor size	≤20 mm	9.1	0.580
	>20 mm	12.6	
	≤40 mm	5.7	0.006
	>40 mm	20.3	
Lymphovascular space invasion	Negative	3.4	<0.0001
	Positive	23.8	
Metastasis to ovary	Negative	11.2	0.500
	Positive	16.7	
Metastasis to tuba uterina	Negative	10.6	0.066
	Positive	30	
Cervical invasion	Negative	9.2	0.007
	Positive	19.4	
Peritoneal cytology	Negative	9.8	0.002
	Positive	44.4	
Metastasis to pelvic lymph nodes	Negative	4	<0.0001
	Positive	48.1	

PALN: Paraaortic lymph node; *: clear cell, serous tumor, mixed type.

patients carrying no risk factor (10.7% and 9.5%, respectively; P = 0.870) (Table 4). These rates were 21.5% and 1.4% in group 10. NPV also fell from 98.6% to 90%. This means that by using the risk model we missed the metastasis in the PA region in 1.4% of patients in group 10 and 10% of patients in group 11. When we added tumor size and/or tumor grade and/or depth of myometrial invasion and/or cervical invasion (groups 12, 13, and 14), predictive strength increased when compared with group 11, as expected. NPV was 100% in 2 of these groups and 94.4% in 1 group. However, in univariate analysis, there was no difference between patients who were in the risk group and who were not in terms of PA lymph node involvement. Additionally, even though they included more parameters, the strength of these 3 groups to predict PA region involvement was significantly lower when compared with group 10.

Although group 7 did not have the pelvic lymph node involvement risk factor, it was the group that most closely approached the groups having this risk factor in terms of predicting PA lymph node involvement, especially group 8 and group 10. Though statistically not significant, the PA lymph node metastasis rate increased from 4.3% to 15.1% in patients carrying at least 1 of the factors forming this group. Among all the groups, this group was second in terms of specificity (32.8%), although it included

Table 4. Risk model and paraaortic lymph node metastasis.

Risk group		PA lymph node metastasis (%)	P	Sensitivity	Specificity	PPV	NPV
Group 1	Negative	8.7	0.621	88.9%	15.7%	12.4%	91.3%
	Positive	12.4					
Group 2	Negative	8.3	0.795	92.9%	9.2%	10.7%	91.7%
	Positive	10.7					
Group 3	Negative	5	0.382	92.9%	16%	11.5%	95%
	Positive	11.5					
Group 4	Negative	9.1	0.666	88.9%	14.9%	12.3%	91.3%
	Positive	12.3					
Group 5	Negative	5	0.310	94.4%	14.2%	12.9%	95%
	Positive	12.9					
Group 6	Negative	0	0.068	100%	14.2%	13.5%	100%
	Positive	13.5					
Group 7	Negative	4.3	0.060	88.9%	32.8%	15.1%	95.7%
	Positive	15.1					
Group 8	Negative	0	0.005	100%	32.1%	16.5%	100%
	Positive	16.5					
Group 9	Negative	0	0.098	100%	13.4%	13.4%	100%
	Positive	13.4					
Group 10	Negative	1.4	<0.001	94.4%	53.7%	21.5%	98.6%
	Positive	21.5					
Group 11	Negative	9.5	0.870	85.7%	16%	10.7%	90%
	Positive	10.7					
Group 12	Negative	0	0.135	100%	11.2%	13.1%	100%
	Positive	13.1					
Group 13	Negative	5.3	0.343	94.4%	13.4%	12.8%	94.7%
	Positive	12.8					
Group 14	Negative	0	0.167	100%	9.7%	12.9%	100%
	Positive	12.9					

PA: paraaortic; PPV: positive predictive value; NPV: negative predictive value.

quite a lot of factors (8). However, with this group, 11.1% of patients with PA lymph node metastasis could not be diagnosed and NPV was 95.7% (Table 4).

The results of group 6 were similar to group 7. In the patients who did not carry factors in this risk model group, there was no metastasis to the PA region, and hence sensitivity and NPV were 100%. The difference between group 6 and group 7 was that group 6 did not include ovarian metastasis, tubal involvement, peritoneal spread, or cervical invasion and did include tumor grade and pelvic lymph node metastasis.

Group 1 was formed by using cell type, tumor grade, depth of myometrial invasion, and serosal involvement. However, results were poor in predicting metastasis to the PA region. Predictive strength was not improved even when tumor size (group 2), adnexal involvement (group 3), cervical invasion (group 4), or LVSI (group 5) were added. In

these groups that did not include pelvic lymph node metastasis as a risk factor, adequate statistical data to direct treatment could not be obtained.

Discussion

The need for PA lymphadenectomy in the treatment of endometrial cancer in terms of survival is controversial. Additionally, the incidence of finding metastatic lymph nodes in the PA region in patients undergoing systematic pelvic and PA lymphadenectomy is not very high. In the present study, there were tumors in the PA region in 11.9% of patients undergoing systematic lymphadenectomy up to the level of the renal vein. Hence, PA lymphadenectomy was an unnecessary procedure in nearly 90% of these patients. This high rate can be reduced by creating risk groups and thus morbidity associated with this procedure can be prevented.

Isolated PA lymph node metastasis varies in the literature by up to a rate of 8% (6,8,10–14). In the current study the rate of isolated PA lymph node metastasis was 3.3%. Furthermore, in almost half of the patients with pelvic lymph node metastasis there was paraaortic lymph node metastasis. Therefore, the existence of pelvic lymph node status as a risk factor in the groups created in this study was important in determining the strength of groups in terms of predicting PA lymph node metastasis. Group 10 especially was capable of directing treatment by determining the need for PA lymphadenectomy. In univariate analysis, whether the patient was in the risk group or not was an important factor in determining PA region involvement, and the metastasis rate to this region increased from 1.4% to 21.5% if the patient was in this group. By using this risk model, 94.4% of patients with PA lymph node metastasis and 53.7% of patients who did not have metastasis were diagnosed correctly. According to the group 10 model, among 'not high-risk' patients, only 1.4% had PA lymph node metastasis. Another difference in this group was that the number of patients considered as being high-risk was low (52% of all patients). In the other groups, the percentage of patients considered as being high-risk was greater than 80% of all patients studied. Hence, only group 10 was appropriate for the purpose of the study, with the ability to significantly reduce the number of unnecessary PA lymphadenectomy procedures. When the group 10 model was used, the number of patients who underwent unnecessary PA lymphadenectomy fell from 134 to 62, meaning that it was reduced by more than 50%.

Nomura et al. showed in their study that, of the patients with no metastasis in the pelvic region, 96.4% also had no metastasis in the PA region, and they suggested that by considering pelvic lymph node status unnecessary PA lymphadenectomies could be prevented (10). However, in their study they found that 48% of patients with pelvic lymph node metastasis also had metastasis in the PA region. Thus, according to this study, using only pelvic lymph node status will lead to unnecessary PA lymphadenectomy in 52% of patients. It can be seen that even though the addition of independent prognostic factors could reduce unnecessary PA lymphadenectomy, it seems difficult to reach target levels without creating risk models.

Tanaka et al. questioned the need for PA lymphadenectomy by considering external iliac and common iliac lymph node status, taking into account the lymphatic spread pattern of the tumor (9). The sensitivity and specificity of this parameter was 90% and 96.7%, respectively. This meant that 10% of patients with PA lymph node metastasis could be missed; furthermore, the number of lymph nodes removed was not mentioned in the study. Mariani et al., in their study focusing on lymphatic spread of endometrial cancer, found that obturator lymph node status was more valuable than iliac region lymph node status in determining PA lymph node status (17). There was PA lymph node metastasis in 64% of patients with obturator lymph node metastasis and 23% of patients with iliac lymph node metastasis ($P = 0.01$).

Similarly, McMeekin et al. showed that common iliac region status and PA lymph node status were not associated (18). In their study, they observed that 57% of the patients with PA lymph node metastasis did not have tumors in the common iliac region. Unlike cervical cancer, lymphatic spread in endometrial carcinoma does not occur by regional order. The reason for this is the variability of the location of tumor and markedly frequent occurrence of adnexal metastasis in endometrial carcinoma. Hence, lymphatic chain order is not associated

with predictable lymphatic spread in endometrial carcinoma.

The low specificity and PPV obtained in the current study may seem to be disadvantages. However, the probability of a model that is composed of a few prognostic factors to detect nonexistence would be low since the aim is to detect the existence at a high rate, and so the PPV value will decrease. On the other hand, today we perform systematic bilateral pelvic and PA lymphadenectomy from the renal vein down to the circumflex iliac vein in cases with cell types other than endometrioid adenocarcinoma, tumor grade 2 or 3, ≥1/2 myometrial invasion, and tumor size greater than 2 cm, which are detected in frozen section analysis for the staging of endometrial carcinoma. PA lymph node metastasis is detected in 11.9% of these cases. This means that the PPV of our classical practice in detecting spread to the PA region was 11.9%. Therefore, although the rates that were obtained with the risk models seemed low, they were actually better than our classical practice. Especially in group 10, where it was almost twice (21.5%) the classical practice.

As a result, with the help of risk models, PA lymph node status can be more clearly identified and unnecessary dissection of the PA region and associated morbidity can be prevented. These models should also be utilizable. In our institution, accuracy of frozen section analysis for myometrial invasion and grade in endometrial carcinoma is quite high and similar to that in the literature (85% and 89%, respectively; unpublished data). In the present study, the factors constituting group 10 (cell type, LVSI, serosal invasion, adnexal metastasis, and pelvic lymph node metastasis) can be identified easily with frozen section pathology. By the help of this group, metastasis to the PA region can be predicted correctly in most cases and the number of PA lymphadenectomies can be significantly reduced. However, for defining risk groups more clearly and for standardization of treatment, there is still the need for further prospective studies with larger numbers of patients.

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