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Lymph Node Metastasis in a Gynecologic Malignancy

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A radical hysterectomy was performed on patients with stage IA2 to IIB cervical cancer. For these patients, many histopathological parameters have been reported to be prognostic factors of cervical cancer, such as a pelvic lymph node (PLN) metastasis, the histological subtype, the tumor diameter, the depth of the stromal invasion, a lymph-vascular space invasion (LVSI), a parametrial invasion, a corpus invasion and a vaginal invasion. Ovarian cancer is normally treated with cytoreductive surgery followed by chemotherapy. Although physicians have paid a great deal of attention to intraperitoneal disease, a substantial number of ovarian cancers have reported to involve the retroperitoneal lymph nodes. Therefore, a lymph node metastasis has been introduced into FIGO staging. However, the prognostic significance of a lymph node metastasis is controversial. In order to determine the possibility of individualizing a pelvic lymph node (PLN) dissection in patients with endometrial cancer, the relationship between PLN metastasis and the various prognostic factors was investigated. In this paper, various prognostic variables including a lymph node metastasis were analyzed in cervical cancer, enodometrial cancer, and ovarian cancer.

Key Words: Metastasis, gynecologic malignancy

INTRODUCTION

Gynecologic cancer tends to metastasize to the distant organs via the lymph channels. Therefore, a dissection of the regional lymph nodes is conducted as a part of the standard surgery for gynecologic cancer. In this paper, the various prognostic variables including a lymph node metastasis were analyzed in cervical cancer, enodometrial cancer, and ovarian cancer.[1-3]

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Cervical cancer

A radical hysterectomy was performed on the patients with stage IA2 to IIB cervical cancer. For these patients, many histopathological parameters have been reported to be prognostic factors of cervical cancer, such as a pelvic lymph node (PLN) metastasis, the histological subtype, the tumor diameter, the depth of the stromal invasion, a lymph-vascular space invasion (LVSI), a parametrial invasion, a corpus invasion, and a vaginal invasion.[4-12]

In our institute, pelvic lymph node metastasis was revealed in 12% of the IA2 and IB stage cases, 17% of the IIA stage cases, and 34% of IIB stage cases. The tumor diameter and the extent of the stromal invasion, increased as the disease progressed. The other parameters also increased with increasing stage (Table 1). Concerning the prognostic significance, all the parameters except a corpus and vaginal invasion were significantly correlated with survival (Table 2). Therefore, the Cox regression analysis model was employed in order to produce a formula to estimate the survival rate. As a result, A PLN metastasis, histological subtype and the tumor diameter were found to be the most statistically significant parameters (Table 3). Based on this analysis, the hazard function of this model was given by the following formula; $\lambda(t)= \lambda 0(t) \times \exp\{0.7872(PLNi - 0.3019)+ 1.0562(Hxi-0.1525)+0.4973(SIZEi-0.8622)\}$. In this formula, $\lambda 0(t)$ is a constant and means the underlying hazard at time t. Therefore, the variables of the subject affect the patient's hazard ($\lambda(t)$) by the term in the large bracket. This term is called the

Table 1. Clinical Stage and Prognostic Factors[1]

	IA2-IB	IIA	IIB
PLN metastasis			
No	185 (88)	40 (83)	56 (66)
Yes	26 (12)	8 (17)	30 (34)
Histologic subtype			
SCC	169 (80)	46 (96)	74 (86)
Adeno	40 (19)	1 (2)	11 (13)
Undiff	2 (1)	1 (2)	1 (1)
Tumor diameter			
<20 mm	116 (55)	12 (25)	18 (21)
20 - 40	84 (40)	32 (67)	45 (52)
>40	11 (5)	4 (8)	23 (27)
Stromal invasion			
<3 mm	56 (27)	10 (21)	4 (5)
3 - 5	36 (17)	6 (13)	7 (8)
5 - 10	51 (24)	15 (31)	16 (19)
>10	68 (32)	17 (35)	59 (68)
Degree of stromal invasion			
<1/3	99 (45)	15 (31)	11 (13)
1/3 - 2/3	46 (22)	6 (13)	12 (14)
>2/3	66 (33)	27 (56)	63 (73)
LVSI			
No	133 (63)	29 (60)	38 (44)
Yes	78 (37)	19 (40)	48 (56)
Parametrial invasion			
No	189 (90)	38 (79)	47 (55)
Yes	22 (10)	10 (21)	39 (45)
Corpus invasion			
No	200 (95)	43 (90)	62 (72)
Yes	11 (5)	5 (10)	24 (28)
Vaginal invasion			
No	186 (88)	48 (100)	43 (50)
Yes	25 (12)	0 (0)	43 (50)

PLN, pelvic lymph node; SCC, squamous cell carcinoma; Adeno, adenocarcinoma; LVSI, lymph-vascular space invasion.

prognostic index (PI). The PI for a given subject defines the patient's place in the prognostic spectrum. The higher the PI value, the higher the hazard and the shorter the expected survival time. The PI value increases with increasing number of PLN metastases (PLNi), the presence of an adenocarcinoma (Hxi), and an increasing tumor diameter (SIZEi). Table 4 shows the PI values calculated for every combination of PLN metastases, histological subtype, and tumor diameter by increasing order of PI value. Based on the PI value, all the patients were divided tentatively into three prognostic groups with cutoff points in the PI value between -0.3302 and -0.0430 and another cutoff point between 0.7260 and 0.7469. The definitions of these three groups are described in Table 5. In order to evaluate the life expectancy by our definition, the survival curves according to the prognostic subgroups were compared with those of the FIGO stages (Fig. 1). A significant difference was observed among the three prognostic groups ($p < 0.0001$), when compared with the survival curves of the FIGO stages. For cervical cancer patients undergoing a radical hysterectomy, a surgical staging system based on a multivariate analysis of the histopathological variables could

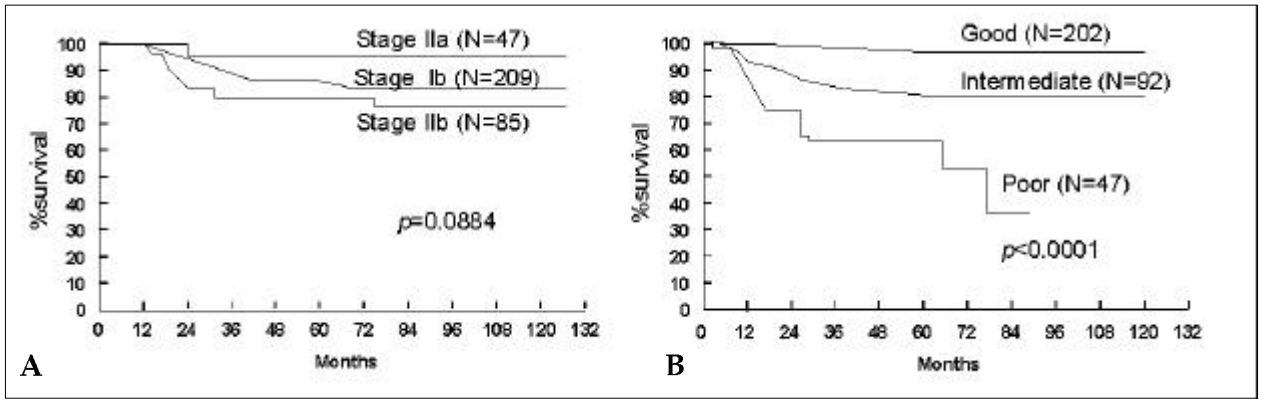

Fig. 1. Survival according to the clinical FIGO stages (A). Survival according to the prognostic groups (B).

Table 2. Survival Analysis for the Prognostic Factors[1]

Variables	No of pts	Estimated 5y survival rate(%)	*p* value
PLN metastasis			
None	278	90.8	
1 group	33	96.7	
2	17	44.5	
>3	13	36.0	<0.0001
Histologic subtype			
SCC	289	91.1	
Adeno	52	70.1	<0.0001
Tumor diameter			
<20 mm	142	97.6	
20 - 40	161	85.6	
>40	38	80.1	0.0058
Stromal invasion			
<3 mm	69	95.7	
3 - 5	49	91.7	
5 - 10	82	83.0	
>10	141	81.8	0.0119
Degree of stromal invasion			
<1/3	123	94.8	
1/3 - 2/3	63	88.1	
>2/3	155	79.9	0.0007
LVSI			
No	198	91.5	
Yes	143	82.4	0.0042
Parametrial invasion			
No	272	90.3	
Yes	69	77.3	0.0017
Corpus invasion			
No	301	87.2	
Yes	40	91.7	0.8586
Vaginal invasion			
No	223	88.6	
Yes	118	84.7	0.2767

PLN, pelvic lymph node; SCC, squamous cell carcinoma; Adeno, adenocarcinoma; LVSI, lymph-vascular space invasion.

Table 3. Significant Prognostic Factors Selected by the Cox Regression Analysis[1]

Variable	Coefficient	SE	*p* value
PLN metastasis	0.7872	0.1544	<0.001
0: None			
1: 1 group			
2: 2			
3: ≥3			
Histologic subtype	1.0562	0.3386	0.002
0: SCC			
1: Adeno			
Tumor diameter	0.4978	0.2533	0.048
0: <20 mm			
1: 20 - 40			
2: >40			

SE, standard error; PLN, pelvic lymph node; SCC, squamous cell carcinoma; Adeno, adenocarcinoma.

Table 4. Prognostic Factors and PI Value[1]

PLN Metastasis	Histologic subtype (PLNi)*	Tumor diameter (Hxi)†	PI value (SIZEi)‡	No of pts
0	0	0	-0.8274	90
0	0	1	-0.3302	112
1	0	0	-0.0430	4
0	0	2	0.1671	37
0	1	0	0.2287	11
1	0	1	0.4570	14
0	1	1	0.7260	26
2	0	0	0.7469	2
1	0	2	0.9543	8
1	1	0	1.0159	1
0	1	2	1.2233	2
2	0	1	1.2442	6
1	1	1	1.5132	4
3	0	0	1.5341	0
2	0	2	1.7415	6
2	1	0	1.8031	0
1	1	2	2.0105	2
3	0	1	2.0314	6
2	1	1	2.3004	1
3	0	2	2.5287	4
3	1	0	2.5903	1
2	1	2	2.7977	2
3	1	1	3.0876	1
3	1	2	3.5849	1

PI, prognostic index; PLN, pelvic lymph node; -----: tentative cutoff points.
*0: no PLN metastasis, 1: one positive node group, 2: two positive groups, 3: three or more positive groups.
†0: squamous cell carcinoma, 1: adenocarcinoma.
‡0: <20 mm, 1:20 - 40 mm, 2: ≥40 mm.

Table 5. Definition of the Prognostic Group[1]

Group	Definitions	No. of pts
• Good prognostic group	SCC/PLN(-)/ <20 mm	202
• Intermediate prognostic	Adeno/PLN(-)/ <40 mm	37
group	SCC/PLN(-)/ >40 mm	37
	SCC/PLN(1)	18
• Poor prognostic group	Adeno/PLN(+)	7
	SCC/PLN(+)/ >40 mm	8
	PLN(>1)	30

SCC, squamous cell carcinoma; Adeno, adenocarcinoma; PLN, pelvic lymph node.

Table 6. PAN Metastasis in Ovarian Cancer[2]

Clinical Stage	No. of pts	No. withpositive PAN
I	51	1 (2%)
II	22	2 (9)
III	37	16 (43)
IV	15	13 (87)

PAN, paraaortic lymph node.

be used to predict a more precise prognosis.

Ovarian cancer

Ovarian cancer is normally treated with cytoreductive surgery, which is followed up by chemotherapy. Although physicians have paid much attention to intraperitoneal disease, a substantial number of ovarian cancers have been reported to involve the retroperitoneal lymph nodes. Therefore, a lymph node metastasis has been introduced into the FIGO staging. However, the prognostic significance of a lymph node metastasis is controversial. In addition, a surgical evaluation of the lymph node is time consuming and can cause complications such as excessive bleeding, a lymph cyst, a lymph edema and a post-surgical ileus. In this context, the possibility of predicting the presence of a paraaortic lymph node (PAN) metastasis from the distribution of the intraperitoneal disease, histology and grade of the primary tumor was investigated. Sampling of the PAN was performed on 125 patients with epithelial ovarian cancer. The rate of PAN metastasis was found to be higher with increasing clinical stage (Table 6). The clinical staging in this study was defined as the intra-abdominal findings during a laparotomy without considering the retroperitoneal lymph nodes. The intraperitoneal surface was divided into seven parts: the subdiaphragmatic surface, the liver and spleen capsule, the intestines and mesentery, the omentum, pelvic peritoneum, the sigmoid colon and rectum, and the uterus and tubes. With regard to the histological variables, serious and undifferentiated carcinomas involved the PAN more frequently than the other subtypes (Table 7). As for the grade, a G3 tumor was found to have a higher PAN metastasis rate than G1 and G2. All the intraperitoneal variables significantly correlated with a PAN metastasis, respectively (Table 8). The provability of a patient suffering from an epithelial ovarian cancer with a PAN metastasis was assessed by the function of the above two histological variables and the 8 intraperitoneal disease site variables using multivariate logistic regression analysis. As a result, the omentum, the uterus and tubes, and the grade were retained as independent prognostic factors with a statistical significance (Table 9). Based on these results, the relative risk of having a PAN metastasis was calculated for a different combination of these

Table 7. PAN Metastasis in Ovarian Cancer[2]

Variables	No. of pts (%)	No. with positive PAN(%)
Histology		
Serous	53 (42)	22 (42)
Clear cell 28(22)	3 (11)	
Mucinous	20 (16)	0 (0)
Endometioid	16 (13)	3 (19)
Undifferentiated 8(7)	4 (50)	
Grade		
G1 and G2 96(77)	19 (20)	
G3	29 (23)	13 (43)

PAN, para-aortic lymph node.

Table 8. Correlation of a PAN Metastasis and the Intraperitoneal Disease Sites[2]

Disease sites	No of pts(%)	No. with positive PAN(%)	*p* value
Subdiaphragmatic surface			
Absent	93 (74)	12 (13)	
Present	32 (26)	20 (63)	<0.001
Liver and spleen capsule			
Absent	112 (42)	23 (20)	
Present	13 (10)	9 (69)	<0.001
Intestines and mesentery			
Absent	90(72)	11 (12)	
Present	35(28)	21 (60)	<0.001
Omentum			
Absent	80 (64)	7 (9)	
Present	45 (36)	25 (56)	<0.001
Pelvic peritoneum			
Absent	73 (58)	7 (10)	
Present	52 (42)	25 (48)	<0.001
Sigmoid colon & rectum			
Absent	82 (66)	10 (12)	
Present	43 (34)	22 (51)	<0.001
Uterus and tubes			
Absent	74 (42)	7 (10)	
Present	51 (41)	25 (49)	<0.001
Peritoneal cytology			
Negative	49 (39)	4 (8)	
Positive	76 (61)	28 (37)	<0.001

PAN, paraaortic lymph node.

three variables (Table 10). The relative risk for a patient with an omental involvement, uterine and tube involvement, and a G3 tumor was 18.48 times greater than the risk for the reference category composed of patients with no omental, uterine, or tubal involvement, and grade 1 or 2 disease. From these analyses, it can be suggested that for a disease with at least one of the three parameters, a sampling of the PAN is mandatory for staging, even if the tumor appears to be confined to the pelvic cavity.

Table 9. Significant Variables Affecting a PAN Metastasis in Ovarian Cancer[2]

Variable	Coefficient	SE	*p* value
Omentum	1.9325	0.5613	0.0003
0: Absent			
1: Present			
Uterus & tubes	1.3521	0.5715	0.0171
0: Absent			
1: Present			
Grade	1.1701	0.5507	0.0320
0: Absent			
1: Present			

PAN, paraaortic lymph node; SE, standard error.

Table 10. Relative Risk of a PAN Metastasis in Ovarian Cancer[2]

Variable	Omental involvement	
	Absent	Present
Uterine and tube Absent		
G1 & G2	1.00	5.51
G3	2.94	11.63
Uterine and tube Present		
G1 & G2	3.44	12.68
G3	8.35	18.48

PAN, paraaortic lymph node.

Endometrial Cancer

In order to determine the possibility of individualizing a pelvic lymph node (PLN) dissection in patients with endometrial cancer, the relationship between a PLN metastasis and the various prognostic factors was investigated. The analyses were performed on 175 endometrial cancer patients treated with either a total or a radical hysterectomy combined with a PLN dissection. Univariate analysis revealed that variables most significantly correlated with a PLN metastasis were the clinical stage, the degree of myometrial invasion (DMI), the tumor diameter (TD), a cervical invasion, and an adnexal metastasis (Table 11). Among these prognostic factors, logistic regression analysis showed the TD and DMI to be independent variables with a statistical significance regarding the PLN status. The mean DMI and TD of a disease with a PLN metastasis were 77% and 89 mm, while in those without a metastasis was 34% and 45 mm, respectively (Fig. 2). The probability of a certain patient having a PLN metastasis, P(PLN)i, was calculated by the following formula: P(PLN)i=exp(h(PLN)i/(1+exp(h(PLN)i), where h(PLN)i=-4.759+(0.01998 × DMI(%))+(0.02821 × TD(mm)). All the numerals in this formula were constant and the coefficients

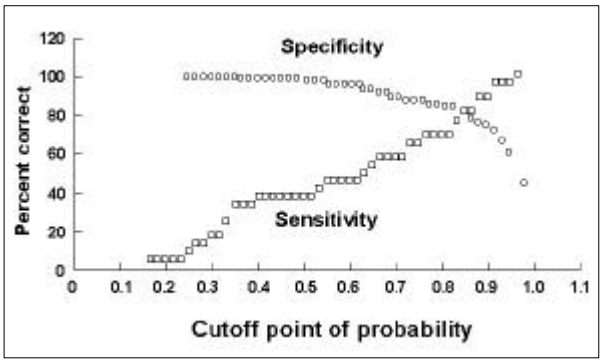

Fig. 2. Accuracy in estimating a pelvic lymph node(PLN) metastasis according to the tumor diameter and the extent of the myometrial invasion.

Table 11. Prognostic Variables and PLN Metastasis in Endometrial Cancer[3]

Variables	No of pts	PLN positive rate(%)	*p* value
Clinical stage			
I	19	4	<0.0001
II	51	35	
III	3	0	
IV	2	50	
Age			
<50	45	13	0.9361
>50	130	14	
Grade			
1	96	9	0.0554
2	50	18	
3	29	32	
DMI			
0	42	0	<0.0001
<1/2	64	5	
>1/2	69	30	
TD(mm)			
<50	104	5	<0.0001
50-100	47	19	
>100	24	42	
Cervical invasion			
None	136	8	<0.0001
Glandular	13	0	
Stromal	26	50	
Adnexal metastasis			
No	162	11	0.0028
Yes	13	46	

PLN, pelvic lymph node; DMI, degree of myometrial invasion; TD, tumor diameter.

were obtained by logistic regression analysis, respectively. Fig. 2 shows the correct classification of the cases as a function of the probability cutoff point. These sensitivity and specificity curves can assist in determining the appropriate probability value as a cutoff point. If 0.892 were chosen as the probability cutoff, the correct sensitivity, specificity, and accuracy would be 83, 72, and 73%, respectively. The results of this investigation suggest that a PLN dissection can be individualized by predicting a metastasis using a combination of the tumor diameter and the extent of the myometrial invasion.

REFERENCES

1. Kamura T, Tsukamoto N, Tsuruchi N, Saito T, Matsuyama T, Akazawa K, et al. Multivariate analysis of the histopathologic prognostic factors of cervical cancer in patients undergoing radical hysterectomy. Cancer 1992;69:181-6.
2. Tsuruchi N, Kamura T, Tsukamoto N, Akazawa K, Saito T, Kaku T, et al. Relationship between paraaortic lymph node involvement and intraperitoneal spread in patients with ovarian cancer-a multivaliate analysis. Gynecol Oncol 1993;49:51-5.
3. Kamura T, Yahata H, Shigematsu T, Ogawa S, Amada S, Kaku T. Predicting pelvic lymph node metastasis in endometrial carcinoma. Gynecol Oncol 1999;72:387-91.
4. Mitani Ym, Fujii J, Miyamura M. Lymph node metastases of the uterin cervix. Am J Obstet Gynecol 1962; 84:515-22.
5. Matsuyama T, Inoue I, Tsukamoto N, Kashimura M, Kamura T, Saito T. Stage IB, IIA, and IIB cervix cancer, postsurgical staging, and prognosis. Cancer 1984;54: 3072-7.
6. Burghardt E, Pockel H. Local spread and lymph node involvement in cervical cancer. Obstet Gynecol 1978;

52:138-45.
7. Piver MS, Chung WS. Prognostic significance of cervical lesion size and pelvic node metastasis in cervical carcinoma. Obstet Gynecol 1973;46:507-10.
8. Boyce J, Frucheter RG, Nicastri AD, Ambiavagar PC, Reinis MS, Nelson JH. Prognostic factors in stage I carcinoma of the cervix. Gynecol Oncol 1981;12:154-65.
9. Barber BR, Sommers SC, Rotterdam H, Kwon T. Vascular invasion as a prognostic factor in stage IB cancer of the cervix. Obstet Gynecol 1978;52:343-8.
10. Grundsell H, Henriksson H, Johnsson JE, Trope C. Prognosis of adenocarcinoma of the uterine cervix. Gynecol Oncol 1979;8:204-8.
11. Inoue T, Okumura M. Prognostic significance of paremetrial extension in patients with cervical carcinoma stage IB, IIA, and IIB: A study of 628 cased treated by radical hysterectomy and lymphadenectomy with or without postoperative irradiation. Cancer 1984; 54:1714-9.
12. Perez CA, Camel HM, Askin F, Breaux S. Endometrial extension of carcinoma of the uterine cervix: A prognostic factor that may modify staging. Cancer 1981;48: 170-80.