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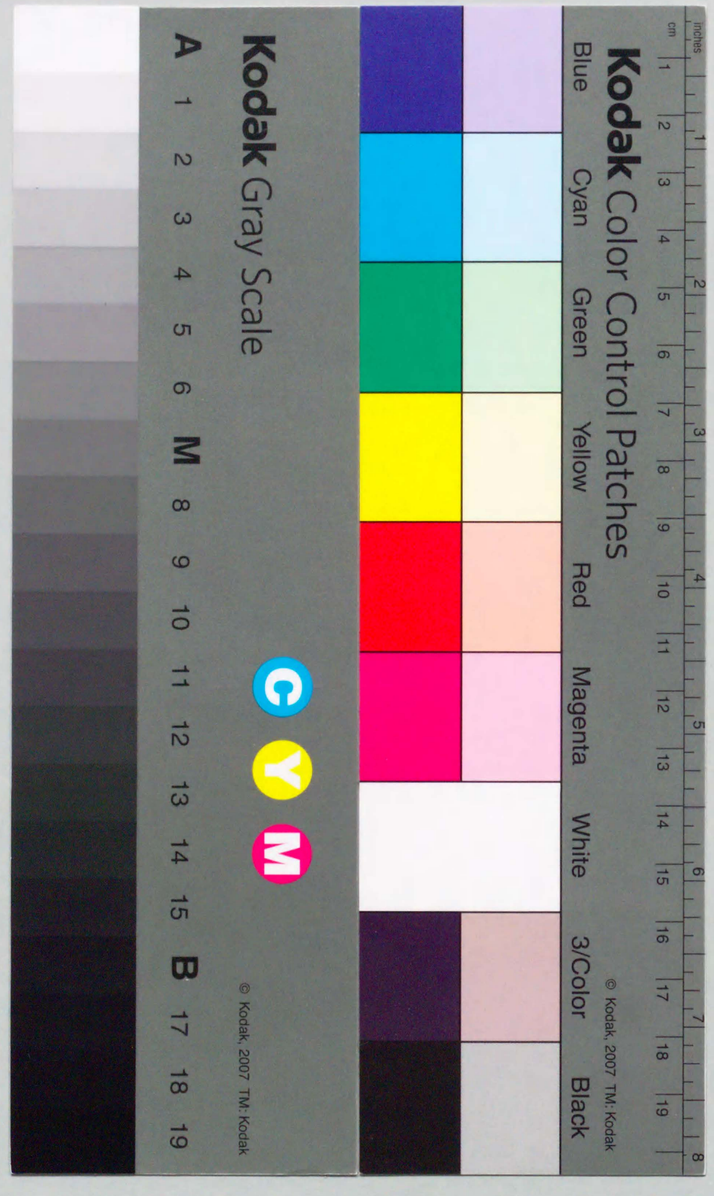

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Relationship between Pelvic Lymph Node Involvement and Other Disease Sites in Patients with Ovarian Cancer

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In 109 patients with epithelial ovarian cancer, 25 (23%) had pelvic lymph node (PLN) metastasis. Positive rates of PLN metastasis according to the clinical stage based on disease distribution except retroperitoneal lymph node were 2% for stage I, 6% for stage II, 44% for stage III, and 64% for stage IV. The nine disease sites, such as subdiaphragmatic surface, liver and spleen capsule, intestine and mesentery, omentum, pelvic peritoneum, sigmoid colon and rectum, uterus and tubes, peritoneal cytology, and paraaortic lymph node (PAN), were found to have a statistically significant relationship with PLN metastasis by univariate analysis. Multivariate analysis using a logistic regression model selected the omentum and PAN as independent factors with a statistical significance. The incidence of PLN metastasis in epithelial ovarian cancer with the above two parameters can be assumed to be greater than that without the two parameters by 42.6 times. The present data suggested that for the disease with PAN and/or omental metastasis, removal of the PLN may be mandatory from the standpoint of cytoreduction.

INTRODUCTION

It is recognized that the spread of ovarian cancer is manifested by extensive intraperitoneal implantation and local invasion [1]. During the past 10 years, however, attention has been paid increasingly to lymph node involvement. In this context, FIGO introduced lymph node involvement into the definition of stage III in 1985.

Burghardt *et al.* [6] have emphasized lymph node metastasis as an important prognostic factor of ovarian cancer, and the close relationship between intraabdominal tumor spread and lymph node involvement. In our previous report [11], the disease with omental involvement and/or uterine and tubal involvement is correlated to paraaortic lymph node (PAN) metastasis. In order to understand the relationship between metastasis to the total lymph node system and other disease sites, we investigated the relationship between intraperitoneal spread of the disease and pelvic lymph node (PLN) involvement.

MATERIALS AND METHODS

From 1980 to 1993, 109 patients with epithelial ovarian cancer underwent surgery followed by cisplatin-based chemotherapy at Kyushu University Hospital. Initial surgery consisted of the inspection and palpation of intraperitoneal organs, peritoneal cytology, sampling of PAN, PLN dissection, bilateral salpingo-oophorectomy, total hysterectomy, omentectomy, and appendectomy. When large tumors were present, maximal effort for cytoreduction was made. Since 1986, dissection of the pelvic lymph nodes has also been performed as a routine procedure during initial surgery. Following surgery, combination chemotherapy consisting of cisplatin, Adriamycin, and cyclophosphamide was given.

Pelvic lymph nodes were removed from in front of, behind, and between the iliac vessels up to the bifurcation of the aorta and down to the obturator fossa and the pelvic floor. The PAN sampling was performed from the aortic bifurcation of the aorta and extended cephalad for 8 to 10 cm. The mesentery of the small bowel was retracted and the aorta and the vena cava were visualized. In the event a swollen lymph node was observed, sampling was performed. In the absence of a swollen lymph node, however, the fatty tissue containing the lymph nodes anterior and lateral to the vena cava was carefully removed after the right ureter and the ovarian blood vessels were identified and retracted laterally. The same procedure was performed on the left-sided anterior and lateral to the aorta.

The clinical staging in this study was assessed according to intraabdominal findings during laparotomy without considering the pathologic findings of the retroperitoneal lymph nodes.

For our purposes, disease sites were divided into eight parts: the subdiaphragmatic surface, liver and spleen capsule, intestines and mesentery, omentum, pelvic peritoneum, sigmoid colon and rectum, uterus and tubes, and paraaortic lymph node. In statistical analysis, the absence or presence of a tumor on these parts, as well as in the pelvic lymph

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TABLE 1
FIGO Stage

Stage	No. of patients (%)
I	45 (41)
II	15 (14)
III	35 (32)
IV	14 (13)
Total	109

node, was expressed as 0 or 1, respectively. Cytologically negative pleural effusion was expressed as 0. Cytologically negative ascites was assigned to negative washing cytology and expressed as 0.

Statistical analysis was done using the statistical packages BMDP 1L, 4F, and LR on an International Business Machines (IBM) System 4381 computer (Armonk, New York, NY). Survival curves were estimated by the Kaplan–Meier method. The relationships between PLN metastasis and each of the above-mentioned variables were tested with a univariable analysis using the contingency table method. In order to select the variables which were independently correlated with PLN metastasis, logistic regression analysis was used. All variables which were significant at the 5% level in univariate analysis were included in the multivariate analysis.

RESULTS

The mean age of all 109 patients was 50 years old (range 18 to 72). Forty-five percent of the patients had advanced disease such as FIGO stage III or IV (Table 1). Positive rates of PLN metastasis according to the clinical stage, based on disease distribution except retroperitoneal lymph node, were 2% for stage I, 6% for stage II, 44% for stage III, and 64% for stage IV (Table 2). The cell types of ovarian cancer involved in this study consisted of 45 cases of serous adenocarcinoma, 17 mucinous, 14 endometrioid, 25 clear cell, and 8 undifferentiated carcinoma. The number of tumors for each grade were 50 for G1 adenocarcinoma, 35 for G2, and 24 for G3 (Table 3).

TABLE 2
Correlation between Retroperitoneal Lymph Node Metastasis and Clinical Stage

Clinical stage	No. of patients	No. with positive PLN (%)	No. with positive PAN (%)
I	46	1 (2)	1 (2)
II	17	1 (6)	1 (6)
III	32	14 (44)	17 (53)
IV	14	9 (64)	12 (86)
Total	109	25 (23)	31 (28)

Note. PLN, pelvic lymph node; PAN, paraaoritc lymph node.

TABLE 3
Correlation of Pelvic Lymph Node Metastasis and Histological Characteristics

Variables	No. of patients (%)	No. with positive PLN (%)
Histology		
Serous	45 (41)	16 (36)
Mucinous	17 (16)	1 (6)
Endometrioid	14 (13)	4 (29)
Clear cell	25 (23)	1 (4)
Undifferentiated	8 (7)	3 (38)
Grade		
G1	50 (46)	5 (10)
G2	35 (21)	11 (31)
G3	24 (22)	9 (38)

The estimated 5-year survival rate for those patients with PLN metastasis was significantly worse than that for cases without PLN metastasis: 26% vs 74%, $P < 0.01$. The median survivals for positive and negative PLN metastasis were 39 and >135 months, respectively (Fig. 1). A significant difference in survival between patients with and without PLN metastasis was also seen among patients with advanced stage, clinical stage III and IV (Fig. 2).

The rate of PLN metastasis was found to be higher with increasing stage according to the clinical stage based on only the spread of intraperitoneal disease, as shown in Table 2.

The incidence of lymph node metastasis in different histologic types of tumors is shown in Table 3. Positive nodes were found in 3 of 8 cases with undifferentiated carcinoma (38%), in 16 of 45 cases with serous adenocarcinoma (36%), and in 4 of 14 cases with endometrioid adenocarcinoma (29%).

The relationship between histologic grading and node metastasis is shown in Table 3. The higher the grade of tumor,

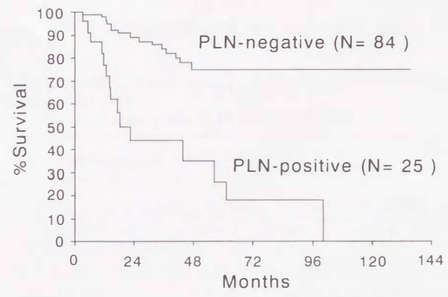

FIG. 1. PLN metastasis and survival in all patients (generalized Wilcoxon test, $P < 0.01$).

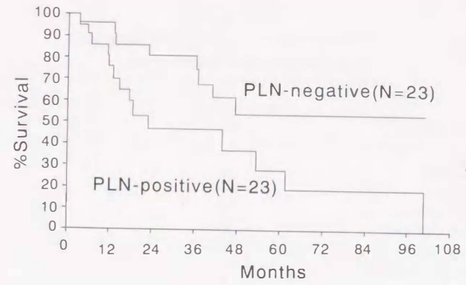

FIG. 2. PLN metastasis and survival in patients with clinical stages III–IV (generalized Wilcoxon test, $P < 0.05$).

the higher the incidence of PLN metastasis. External LN is the most common site of PLN metastasis, following common iliac LN and internal iliac LN (Table 4).

The relationship between tumor site and laterality of PLN metastasis is shown in Table 5. Of 8 patients with unilateral ovary involved, 5 had contralateral PLN metastasis. All 5 patients had both advanced disease (1 with stage III, 4 with stage IV) and PAN metastasis. Among the 10 disease sites, positive peritoneal cytology had the highest frequency (65%) (Table 6). With the exception of pleural effusion, all the disease sites examined were found to have a statistically significant relationship with PLN metastasis by univariate analysis. The probability of a patient with epithelial ovarian cancer having PLN metastasis was assessed using multivariate logistic regression analysis with 10 disease sites and 2 histological factors, grade, and histological type, as variables. All 12 parameters were given one of two values, that is 1 for the presence of disease at a particular site, serous or undifferentiated, and G3 adenocarcinoma, and 0 for the absence of disease at a particular site, remaining histologic subtype and G1 or G2. Among those parameters, multivariate analysis using a logistic regression model selected the omentum and PALN as independent factors with a statistical significance ($P < 0.05$) (Table 7).

The actual frequency for PLN metastasis in the patient with a disease on the omentum and PAN was 42.6 times higher than that in patients without these lesions (Table 8).

TABLE 4
Distribution of PLN Metastasis

Pelvic lymph node	Frequency (%)	
	Lt	Rt
Obturator	4	6
Internal iliac	8	6
Inguinal	4	7
External iliac	10	14
Common iliac	7	7

TABLE 5
The Relationship of Laterality between Primary Tumor Site and Metastatic Lymph Node in the Patients with Positive PLN

Primary tumor site	Pelvic lymph node		
	Lt	Rt	Bil
Left ovary	0	1	2
Right ovary	0	3	2
Bilateral ovary	4	4	9

DISCUSSION

In 1985, FIGO introduced lymph node involvement into the definition of stage III as an important prognostic factors [2]. However, the prognostic significance of lymphadenectomy in this disease is controversial. Chen [3] reported that nodal involvement is the critical prognostic factor, whereas the stage of disease, histology, grade, and residual disease were risk factors for nodal metastasis.

TABLE 6
Correlation of Pelvic Lymph Node Metastasis and Disease Spread

Disease sites	No. of patients	Positive PLN (%)	*P* value
Pleural effusion			
+	11	45%	0.081
−	98	20	
Subdiaphragmatic surface			
+	30	53	<0.001
−	79	11	
Liver and spleen capsule			
+	11	55	0.016
−	98	19	
Intestine and mesentery			
+	29	45	0.002
−	80	15	
Omentum			
+	38	50	<0.001
−	71	8	
Pelvic peritoneum			
+	46	43	<0.001
−	63	8	
Sigmoid colon and rectum			
+	42	43	<0.001
−	67	10	
Uterus and tubes			
+	42	40	0.001
−	67	12	
Peritoneal cytology			
+	66	33	<0.001
−	43	7	
Paraaortic lymph node			
+	31	65	<0.001
−	78	6	

Wu *et al.* [4] and Burghardt *et al.* [5] reported that the incidence of positive pelvic nodes were 56.6 and 61.8%, for all stages, respectively. Especially in advanced disease (stage III and IV), the incidence of pelvic nodes was 50–100% [4–7]. At initial laparotomy, PLN metastasis was found in 23% of all patients in this study. The more advanced the disease, the higher the incidence of positive nodes (53% for stage III and 86% for stage IV). The incidence of pelvic lymph node metastasis in this study was less than that found in other reports; however, in the advanced stage, the figure were compatible.

With regard to histological type, serous adenocarcinoma, undifferentiated carcinoma, and endometrioid adenocarcinoma involved PLN more frequently than other types. The higher the grade of tumor, the higher the incidence of PLN metastasis. The same tendency was observed in other investigations [4, 5, 8].

In general, the lymphatics of the ovary take a course identical to the ovarian veins, in the infundibulopelvic ligament to the abdominal aorta and inferior vena cava along the psoas muscle. In addition to this classical lymphatic pathway, anatomic studies have shown the presence of a lymphatic trunk which arises from the hilus of the ovary, courses within the folds of the broad ligaments, and terminates in the external, obturator, and common iliac nodes [9]. In this study, external iliac LN were most commonly involved, which may be considered the primary site of pelvic lymphatic spread as mentioned above.

Of the 8 cases with unilateral ovarian involvement, 5 metastasized contralateral PLN, and these cases had both peritoneal dissemination and PALN metastasis.

In our previous report, omental involvement, uterine and tubal involvement, and histological grade were independently correlated with PAN metastasis. On the other hand, the present study revealed that disease on the omentum and disease in the PALN had significant and independent effects on the presence of PLN metastasis. From these studies, PAN and PLN metastasis were found to be closely related to disease on the omentum.

TABLE 7
Significant Variables Affecting Pelvic Lymph Node Metastasis

Variables	Coeff	SE	Coeff/SE	*P* value
Omentum 0, absent 1, present	1.419	0.640	2.22	0.028
PAN 0, absent 1, present	2.851	0.638	4.47	<0.001
Constant	−3.149	0.551	−5.71	<0.001

Note. Coeff, coefficient; SE, standard error.

TABLE 8
Actual Frequency of PLN Metastasis

PAN metastasis	Omental involvement	
	Absent	Present
Absent	1/63 (1.6)	4/16 (25.0)
Present	5/8 (62.5)	15/22 (68.2)

Note. Percentage is indicated in parentheses.

A possible explanation that connects PLN and omentum might be as follows: The omentum has many milky spots consisting of macrophages and lymphocytes, called omentum-associated lymphoid tissue. The milky spot was reported to be the first place to which disseminating ovarian cancer cells attached [10]. Therefore both metastatic cancer cells in PLN and omentum might express common properties necessary to make a colony among lymphocytes. Further studies will need to focus on the lymphatic pathway between the omentum and PLN.

The incidence of PLN metastasis in epithelial ovarian cancer with the above two parameters can be assumed to be greater than that without the two parameters, by 42.6 times. Burghardt *et al.* [5] reported that the 5-year survival rate for stage III disease was 53.0% after lymphadenectomy compared with 13.0% without. Even in case of positive nodes it was high (45.9%). The present data, therefore, suggested that for the disease with PALN and/or omental metastasis, removal of the pelvic lymph node may be mandatory from the standpoint of cytoreduction. However, further randomized studies involving a larger number of patients is thus required to confirm that such cases can in fact be treated with pelvic lymphadenectomy.

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