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Evaluation of Factors Affecting Lymph Node Metastasis in Clinical Stage I–II Epithelial Ovarian Cancer

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Keywords

Lymph node dissection · Lymph node metastases · Ovarian cancer

Summary

Background: Systematic lymphadenectomy is useful for accurate staging of early-stage ovarian cancer and has obvious prognostic value. Accurate staging may prevent unnecessary postoperative chemotherapy. The aim of this study was to evaluate the rate of lymph node involvement and factors affecting it in clinically early-stage epithelial ovarian cancer (EOC; stages I, II). **Patients and Methods:** The study included 163 patients who underwent surgery at our hospital between January 2004 and April 2017 and who were diagnosed with early-stage EOC based on preoperative and intraoperative examination. Patient data were retrospectively analyzed. The rate of lymph node involvement and factors affecting it were analyzed. **Results:** Of 163 patients, 21 (12.9%) had lymph node metastasis, whereas 16 (16.3%) of 98 patients who underwent comprehensive lymphadenectomy had lymph node metastasis. According to the univariate results for patients undergoing any type of lymphadenectomy, the rate of positive lymph nodes was significantly higher (37.1%) in those with bilateral ovarian involvement ($p < 0.001$). The rate was significantly higher in patients with positive intraabdominal fluid cytology (25.9%; $p < 0.001$), serous histology (20.5%; $p = 0.02$), and grade 3 disease (33.3%; $p < 0.001$). In multivariate logistic regression analysis, the rate was significantly higher in patients with bilateral adnexal involvement ($p = 0.012$). The risk of positive lymph nodes was significantly higher in patients with grade 3 disease ($p = 0.016$). **Conclusion:** Comprehensive lymphadenectomy increases the detection rate for metastatic lymph nodes in patients with clinically early-stage EOC. The rate of lymph node involvement is significantly higher in grade 3 tumors, serous cytology, bilateral adnexal involvement, and positive intraabdominal fluid cytology.

Introduction

Ovarian cancer is the second most common gynecologic cancer worldwide, and it is the leading cause of death associated with gynecologic malignancies in women. The life-long risk of developing epithelial ovarian cancer (EOC) is 1.3%, and about 70% of patients are already at an advanced disease stage at the time of initial diagnosis; only 30% of patients are diagnosed at an early stage (stages I, II) [1].

EOC spreads primarily through exfoliation of the tumor cells into the peritoneal cavity, but lymphatic and hematogenous spread can also occur [2]. According to the International Federation of Gynecology and Obstetrics (FIGO), the presence of lymph node involvement in the early stages of ovarian cancer raises the disease stage to 3A1 [3]. Systematic lymphadenectomy is useful for accurate stage assessment of early-stage ovarian cancer and has a proven prognostic value. Accurate staging in very early-stage disease may prevent unnecessary postoperative chemotherapy. However, there is still a debate on the therapeutic role of lymphadenectomy [4]. Lymphadenectomy is the major surgical procedure asso-

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ciated with other morbidities such as lymphedema, lymphocyst, ileus, blood loss, nerve or vascular injury, blood transfusion, prolonged length of hospital stay, and increased treatment costs [5–7].

In the present study, we aimed to evaluate the rate of lymph node involvement and factors affecting lymph node involvement in clinically early-stage (stages I, II) EOC.

Patients and Methods

This retrospective study was approved by the Kanuni Sultan Süleyman Training and Research Hospital Ethics Committee and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant.

The study included a total of 163 patients who underwent surgery in the Gynecologic Oncology Clinic of the Kanuni Sultan Süleyman Training and Research Hospital between January 2004 and April 2017 and were diagnosed with early-stage EOC based on preoperative and intraoperative findings. Patient data in the database of the Gynecologic Oncology Clinic were analyzed retrospectively. According to the standard procedures at the time of surgery, the patients underwent intraperitoneal fluid or intraabdominal lavage fluid sampling, total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy, careful exploration of the pelvic and upper abdominal cavity, random peritoneal biopsy from suspected or seemingly benign areas, and pelvic paraaortic lymphadenectomy for the purpose of disease staging. Demographic characteristics of the patients, CA-125 marker levels, surgical procedure, presence of ascites, results of cytological examination of the intraabdominal lavage fluid, tumor diameter, laterality, tumor grade, histological type, performance of lymphadenectomy, number and sites of lymph nodes, involvement of lymph nodes, and final surgical stage of the patients were recorded. Patients receiving neoadjuvant chemotherapy, those with a concomitant primary malignancy, those who had extrapelvic spread at the initial surgical exploration, and those with non-EOC were excluded from the study.

As described by Ayhan et al. [7], systematic bilateral pelvic and paraaortic lymphadenectomy removing 25 or more pelvic lymph nodes and 15 or more paraaortic lymph nodes was considered comprehensive lymphadenectomy. Cases that did not meet these conditions were considered sampling lymphadenectomies. Systematic lymphadenectomy involved the removal of external iliac, internal iliac, obturator, and presacral lymph nodes, as well as those related to the aorta and vena cava up to the level of the renal vein. The rate of patients with positive lymph nodes was identified, and possible factors affecting lymph node positivity were evaluated.

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed as mean, standard deviation, median, frequency, and percentage. In the univariate analysis, the Pearson's chi-square and Fisher's exact tests were used to evaluate the factors associated with lymph node positivity. Significant risk factors included in the univariate analysis underwent further multivariate analysis using logistic regression, and variables were selected with the enter method. The odds ratio was calculated by taking the first categories as reference. A p value of < 0.05 was considered statistically significant with a 95% confidence interval.

Results

The overall characteristics of the 163 patients included in the analysis are shown in table 1. The median age was 49 years (range 19–86 years). Of these patients, 79 (48.5%) were postmenopausal.

Table 1. Patient and tumor characteristics

Median age (range), years	49 (19–86)
Median parity (range), n	2 (0–13)
Menopausal status, n (%)	
Postmenopausal	79 (48.5)
Premenopausal	84 (51.5)
CA-125, median (range), U/ml	269 (5–5,500)
Tumor diameter, median (range), cm	14 (4–45)
Ascites present, n (%)	32 (19.6)
Final assigned stage, n (%)	
1B	55 (33.7)
1B	2 (1.2)
1C1	6 (3.7)
1C2	29 (17.8)
1C3	17 (10.4)
2A	8 (4.9)
2B	11 (6.7)
3A1	18 (11)
3A2	17 (10.4)
Histology, n (%)	
Serous	73 (44.8)
Mucinous	47 (28.8)
Endometrioid	25 (15.3)
Clear cell	9 (5.5)
Mixed	4 (2.4)
Undifferentiated	3 (1.8)
Squamous	2 (1.2)
Grade, n (%)	
1	42 (25.8)
2	67 (41.1)
3	54 (33.1)
Lymph node count, mean ± standard deviation, n	
Pelvic	23.7 ± 11.8
Paraaortic	9.7 ± 9.6

Table 2. Surgical procedures

Procedure	n (%)
Cytology collected	163 (100)
Omentectomy	163 (100)
Random peritoneal biopsies	154 (94.5)
Apendectomy	70 (42)
Comprehensive bilateral pelvic and paraaortic lymphadenectomy	98 (60.1)
Pelvic lymph node assessment	162 (99)
Paraaortic lymph node assessment	124 (76)

The applied surgical procedures are summarized in table 2. Over the period studied, 154 patients underwent hysterectomy and 157 underwent salpingo-oophorectomy; 9 patients had previously undergone hysterectomy and 6 had previously undergone salpingo-oophorectomy. Of the study patients, 98 (60.1%) underwent comprehensive bilateral pelvic and paraaortic lymphadenectomy and 65 (39.9%) underwent sampling lymphadenectomy during the period studied, while 162 (99%) patients underwent pelvic lymphadenectomy and 124 (76%) underwent paraaortic lymphadenectomy.

Table 3. Risk factors for lymph node metastasis among patients with any lymph node assessment (univariate)

		Total, n (%)	LN-negative, n (%)	LN-positive, n (%)	p value
Number of patients		163	142 (87.1)	21 (12.9)	
Laterality of adnexal involvement	unilateral	128 (78.5)	118 (92.2)	10 (7.8)	< 0.001[a]
	bilateral	35 (21.5)	22 (62.9)	13 (37.1)	
Cytology	negative	105 (64.4)	99 (94.3)	6 (5.7)	< 0.001[b]
	positive	58 (35.6)	43 (74.1)	15 (25.9)	
Ascites	absent	131 (80.4)	114 (87)	17 (13)	0.604[a]
	present	32 (19.6)	28 (87.5)	4 (12.5)	
Histology	serous	73 (44.8)	58 (79.5)	15 (20.5)	0.02[b]
	mucinous	47 (28.8)	45 (95.7)	2 (4.3)	
	other	43 (26.4)	39 (90.7)	4 (9.3)	
FIGO grade	1	42 (25.8)	40 (95.2)	2 (4.8)	< 0.001[b]
	2	67 (41.1)	66 (98.5)	1 (1.5)	
	3	54 (33.1)	36 (66.7)	18 (33.3)	
CA-125	≤ 35 U/ml	33 (20.2)	31 (93.9)	2 (6.1)	0.153[a]
	> 35 U/ml	130 (79.8)	111 (85.4)	19 (14.6)	

[a]Fisher's exact test.
[b]Pearson's chi-squared test.
LN = Lymph node.

Table 4. Risk factors for lymph node metastasis (univariate) in 98 patients with comprehensive lymph node assessment

		Total, n (%)	LN-negative, n (%)	LN-positive, n (%)	p value
Number of patients		98	82 (83.7)	16 (16.3)	
Laterality of adnexal involvement	unilateral	75 (76.5)	69 (92)	6 (8)	< 0.001[a]
	bilateral	23 (23.5)	13 (56.5)	10 (43.5)	
Cytology	negative	58 (58.9)	39 (90.7)	4 (9.3)	0.014[a]
	positive	40 (41.1)	22 (73.3)	8 (26.7)	
Ascites	absent	75 (76.5)	63 (84)	12 (16)	0.549[a]
	present	23 (23.5)	19 (82.6)	4 (17.4)	
Histology	serous	53 (54.1)	40 (75.5)	13 (24.5)	0.05[b]
	mucinous	19 (19.4)	18 (94.7)	1 (5.3)	
	other	26 (26.5)	24 (92.3)	2 (7.7)	
FIGO grade	1	20 (20.4)	18 (90)	2 (10)	0.001[b]
	2	38 (38.8)	37 (97.4)	1 (2.6)	
	3	40 (40.8)	27 (67.5)	13 (32.5)	
CA-125	≤ 35 U/ml	15 (15.3)	14 (93.3)	1 (6.7)	0.247[a]
	> 35 U/ml	83 (84.7)	68 (81.9)	15 (18.1)	

[a]Fisher's exact test.
[b]Pearson's chi-squared test.
LN = Lymph node.

The mean number of removed pelvic lymph nodes was 23.72 ± 11.85, and the mean number of removed paraaortic lymph nodes was 9.718 ± 9.603. Of the patients, 55 (33.7%) had stage 1A disease, 29 (17.8%) had stage 1C2 disease, and 18 (11%) had stage 3A1 disease. Pathological examination showed that 73 (44.8%) patients had serous, 47 (28.8%) mucinous, 25 (15.3%) endometrioid, and 9 (5.5%) clear cell tumors, while 9 (5.5%) patients had other types of tumors (mixed, undifferentiated, squamous) (table 1).

Of 163 patients, 21 (12.9%) were found to have positive lymph nodes. The rate of pelvic lymph node metastasis was 7.4% (12/162). The rate of paraaortic lymph node metastasis was 9.6% (12/124). 3 patients had both pelvic and paraaortic lymph node metastasis. Of 98 patients who underwent comprehensive lymphadenectomy, 16 (16.3%) were found to have lymph node metastasis. The risk factors for lymph node metastasis were evaluated and the results are shown in tables 3 and 4.

Among the patients who underwent any type of lymphadenectomy, the rate of positive lymph nodes was significantly higher in those with bilateral ovarian involvement (37.1%; $p < 0.001$). The rate of lymph node positivity was significantly higher in the patients with positive intraabdominal fluid cytology (25.9%; $p < 0.001$). There was no significant difference in lymph node posi-

tivity between the patients with and without ascites (p = 0.604). The rate of lymph node involvement was significantly higher in patients with serous histology (20.5%; p = 0.02) and in those with grade 3 disease (33.3%; p < 0.001). There was no significant difference in lymph node positivity between patients with CA-125 values ≤ 35 and those with CA-125 values > 35 (p = 0.153).

Among patients who underwent comprehensive lymphadenectomy, the rate of lymph node positivity was significantly higher among patients with bilateral ovarian involvement (43.5%; p < 0.001). The rate was significantly higher in patients with positive intraabdominal fluid cytology (26.7%; p = 0.014). There was no significant difference in lymph node positivity between patients with and without ascites (p = 0.549). The rate of lymph node involvement was significantly higher in patients with serous histology (24.5%; p = 0.05) and in those with grade 3 disease (32.5%; p = 0.001). There was no significant difference in lymph node positivity between patients with CA-125 values ≤ 35 and those with CA-125 values > 35 (p = 0.247).

Table 5. Risk factors for lymph node metastasis (multivariate)

Variable	RR (95% CI)	p
Laterality of adnexal involvement		
Unilateral	1	
Bilateral	4.14 (1.37–12.5)	0.012
Cytology		
Negative	1	
Positive	2.07 (0.64–6.66)	0.219
Grade		
1	1	
2	0.44 (0.03–5.39)	0.527
3	7.02 (1.43–34.3)	0.016

RR = Risk ratio; CI = confidence interval.

Table 6. Risk factors for lymph node metastasis (multivariate) among those with comprehensive staging

Variable	RR (95% CI)	p
Laterality of adnexal involvement		
Unilateral	1	
Bilateral	4.71 (1.32–16.9)	0.017
Cytology		
Negative	1	
Positive	1.40 (0.36–5.49)	0.624
Grade		
1	1	
2	0.28 (0.02–3.57)	0.333
3	2.63 (0.46–14.9)	0.274

RR = Risk ratio; CI = confidence interval.

The variables that showed significant difference in univariate analysis in patients who underwent any type of lymphadenectomy were further evaluated via multivariate analysis (table 5). According to multivariate logistic regression analysis, the rate of lymph node positivity was significantly higher in patients with bilateral adnexal involvement (p = 0.012). The effect of positive intraabdominal fluid cytology on lymph node involvement was not statistically significant (p = 0.219). The risk of positive lymph nodes was significantly higher in patients with grade 3 disease (p = 0.016).

The variables that showed significant difference in univariate analysis in patients who underwent comprehensive lymph node assessment were further evaluated via multivariate analysis (table 6). Multivariate logistic regression analysis showed that the rate of lymph node positivity was significantly higher in patients with bilateral adnexal involvement (p = 0.017). The effects of grade and positive intraabdominal fluid cytology on lymph node involvement were not statistically significant (p > 0.05).

Discussion

In gynecologic malignancies, cancer spreads mostly through the lymphatic vessels, which has a prognostic value [8]. In EOC, the rate of lymph node metastasis is lower in early-stage tumors [9]. Powless et al. [10] reported that the rate of lymph node metastasis was 13.2% in patients with clinically early-stage EOC who under-

Table 7. Incidence of lymph node metastasis according to histological subtype

Study [ref.]	Serous, %	Mucinous, %	Endometrioid, %	Clear cell, %	Other, %
Desteli et al. [9]	14.2	0.0	0.0	0.0	11.1
Harter et al. [16]	15.4	0.0	7.1	0.0	0.0
Morice et al. [6]	30.8	0.0	0.0	–	64.3
Negeishi et al. [11]	14.3	4.1	20.0	17.4	20.0
Nomura et al. [15]	50.0	0.0	7.4	5.6	–
Onda et al. [17]	33.3	6.7	0.0	31.3	0.0
Suzuki et al. [18]	30.8	0.0	0.0	11.1	0.0
Tsumura et al. [12]	8.7	3.4	–	19.0	–

went any type of lymphadenectomy and 16.5% in patients who underwent comprehensive lymphadenectomy. Negishi et al. [11] reported a rate of 12.7% for lymph node involvement in patients who underwent systematic lymphadenectomy, whereas Tsumura et al. [12] reported a rate of 8.6% for lymph node involvement in 81 patients who underwent systematic lymphadenectomy. In a meta-analysis of 14 studies in the literature, Kleppe et al. [13] reported a rate of 14.2% for lymph node metastasis. The present study reports a rate of 12.9% for lymph node metastasis in patients with clinically early-stage (stages I, II) EOC who underwent any type of lymphadenectomy and a rate of 16.3% in patients who underwent extended lymphadenectomy.

The present study evaluated via univariate analysis the variables that were shown to affect early-stage EOC; among patients who underwent any type of lymphadenectomy, bilaterality, malignant intraabdominal fluid cytology, serous histological type, and the presence of FIGO grade 3 tumors were found to increase the risk of lymph node metastasis. In multivariate analysis, laterality and tumor grade were found to be independent risk factors for lymph node metastasis.

Among patients who underwent comprehensive lymphadenectomy, bilaterality, malignant intraabdominal fluid cytology, serous histological type, and presence of FIGO grade 3 tumors were found to increase the risk of lymph node metastasis. In multivariate analysis, bilateral adnexal involvement was found to be an independent risk factor for lymph node metastasis. The majority of patients who underwent comprehensive lymphadenectomy had grade 3 disease (40.8%); we therefore concluded that the effect of grade on lymph node metastasis did not show statistical significance in the multivariate analysis.

Powless et al. [10] reported that tumor grade, histological type, laterality of adnexal involvement, and presence of ascites were independent risk factors. Sakuragi et al. [14] reported an 11.1% lymph node involvement rate in grade 3 tumors, whereas Nomuro et al. [15] reported a rate of 33.3%. In a meta-analysis of 7 studies in the literature, Kleppe et al. [13] reported a rate of 20% for lymph node involvement in grade 3 tumors. The present study found a significantly higher rate of lymph node involvement in grade 3 tumors (33.3%). Table 7 shows the studies in the literature that examined lymph node involvement according to histological type. In the present study, the rate of lymph node involvement was higher in serous tumors when compared with mucinous tumors and tumors of other histological types.

Our study has some limitations, such as its retrospective design and the small number of affected lymph nodes. Because our clinic is a tertiary referral gynecologic oncology center, we are primarily referred patients with low performance status. In addition to bad performance status, morbid obesity is another major problem. Depending on these factors, the number of removed pelvic and paraaortic lymph nodes should be less than the minimum number of lymph nodes described in the literature.

In conclusion, based on our study results, comprehensive lymphadenectomy increases the detection rate of metastatic lymph nodes in patients with clinically early-stage EOC. In addition, the rate of lymph node involvement significantly increases in grade 3 tumors, in tumors with serous histology, in the presence of adnexal involvement, and in cases with positive intraabdominal fluid cytology.

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