

# Clinicopathological factors of pelvic lymph nodes involvement in advanced serous ovarian cancer

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## ABSTRACT

**Objectives:** Retroperitoneal lymph nodes metastases occur frequently in patients with ovarian cancer. Lymphadenectomy increases risk of perioperative complications. In clinical practice to reduce rate of complications aortocaval lymphadenectomy is omitted and solely resection of pelvic lymph nodes is performed. To establish factors affecting metastases to pelvic lymph nodes in advanced ovarian cancer.

**Material and methods:** A retrospective study among patients with serous advanced ovarian cancer (FIGO IIIB–IVB) was conducted at the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw and Department of Gynecologic Oncology, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw. All patients underwent surgical treatment including pelvic lymphadenectomy between 2014 and 2017. Data including age, body mass index (BMI), pretreatment CA125 serum level, tumor volume, grading, one-/both-sided tumor, menopausal status, ascites were analysed as possible factors influencing the pelvic lymph nodes involvement. The statistical analysis was performed with Python software.

**Results:** 87 consecutive patients were eligible for the study. Metastases to pelvic lymph nodes were found in 29 (33.33%) patients. Pretreatment serum CA-125 concentration (652 U/mL vs 360.9 U/mL,  $p < 0.05$ ) and high grade histology corresponded with pelvic nodal involvement.

**Conclusions:** The knowledge of factors influencing metastases to pelvic lymph nodes may help clinicians in proper counselling and tailoring of therapy.

**Key words:** ovarian cancer; metastasis to pelvic lymph node, clinicopathological factors

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## INTRODUCTION

Ovarian cancer is the fifth leading cause of death due to malignancies among women in Northern America and the European Union [1, 2]. According to FIGO 2014 Staging System resection of retroperitoneal lymph nodes remains an integral part of surgical treatment [3]. Retroperitoneal lymph nodes involvement occurs in 40–44% of all patients with ovarian cancer [4, 5]. In patients without peritoneal dissemination lymphadenectomy is used to determine stage. According to LION study systematic lymphadenectomy in advanced ovarian cancer does not improve overall survival and results in extended duration of the operation, higher median blood loss, higher

transfusion rate and more frequent serious postoperative complications (re-laparotomies, re-admittance, deaths within 60 days after surgery) [6]. However Panici et al. [7] found that systematic lymphadenectomy could prolong progression free survival, which in turn improved quality of life.

In clinical practice aortocaval lymphadenectomy is omitted up to 44% of patients to reduce the rate of complications, while resection of pelvic lymph nodes is performed in almost every patient [5, 8, 9]. Factors affecting retroperitoneal lymph nodes involvement were identified in previous studies [5, 8, 9]. However, they were established for both aortocaval and pelvic regions. The aim of this study is to

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**Table 1. Patients' characteristics**

Variable (median/number)		Total number of patients (n = 87)	MUW (n = 39)	MSCNRIO (n = 48)
Age [years]		62 (26–84)	63 (26–84)	61 (36–79)
Staging	IIIB	12	6	6
	IIIC	69	32	37
	IVA	0	0	0
	IVB	6	1	5
Tumor volume [cm <sup>3</sup> ]		179.59 (1.5–8704.9)	52.88 (1.5–2340)	179.59 (38–8704.9)
Number of resected lymph nodes		8 (1–28)	7 (1–14)	10.5 (2–28)
One/both sided tumor(s)		55 (63.22%) / 32 (36.78%)	28 (71.79%) / 11 (28.21%)	28 (58.33%) / 20 (41.67%)
Ascites		48 (55.17%)	23 (58.97%)	25 (52.08%)
Grading	Low	10 (11.5%)	6 (15.38%)	4 (8.3%)
	High	77 (88.5%)	33 (84.62%)	44 (91.66%)
Postmenopausal status		73 (83.91%)	37 (94.87%)	36 (75%)
Pretreatment CA-125 concentration [IU/mL]		451.9 (8.18–9418)	457.6 (53.11–7316)	446.2 (8.18–9418)
BMI		27.98 (14.91–49.25)	25.22 (16.85–49.25)	28.3 (14.91–37.35)

determine factors affecting metastases to pelvic lymph nodes in advanced ovarian cancer.

## MATERIAL AND METHODS

A retrospective study was conducted at the 1<sup>st</sup> Department of Obstetrics and Gynecology, Medical University of Warsaw (MUW) and Department of Gynecologic Oncology, Maria Skłodowska Curie National Research Institute of Oncology (MSCNRIO), Warsaw between January 2013 and March 2017 among patients with serous ovarian cancer in advanced stage (FIGO IIIB–IVB). Intraperitoneal dissemination was confirmed in all patients during primary cytoreductive surgery. In each case, bilateral pelvic lymphadenectomy was conducted. Patients were divided into two groups: A — with metastases in pelvic lymph nodes, B — without pelvic lymph nodes involvement.

The exclusion criteria for primary cytoreductive surgery included: inoperable tumor *i.e.* dissemination in the porta hepatis or mesentery of the intestines, neoplastic infiltration into the aorta/inferior vena cava/pelvic main vessels estimated by computed tomography or magnetic resonance.

Potential factors affecting pelvic lymph nodes involvement were analysed. Data including age, body mass index (BMI), CA125 blood concentration, tumor volume, grading, one-/both-sided tumor, menarche, menopause, ascites were collected.

Statistical analysis was performed with Python Software. Patients' characteristics were presented as numbers of cases and percentages for categorical data, and as means with standard deviations (SD) for continuous data or — for non-continuous — medians and quartiles. The groups were compared by Chi-squared test for categorical vari-

ables. Statistical analysis was performed with t-Student test and Mann-Whitney U-test for continuous variables. The level of statistical significance was set at  $p < 0.05$ .

All the procedures were conducted according to the Declaration of Helsinki for Medical Research involving Human Subjects. Institutional ethics committee approval was not required — the research is an ex-post analysis of clinical experience. The clinical decisions concerning the treatment were not influenced by the purpose of this paper.

## RESULTS

A total of 87 patients (39-MUW, 48-MSCNRIO) with serous ovarian cancer in advanced stage were included to the study. Pelvic lymph nodes involvement was confirmed in 29 (33.33%) patients — Group A, while in 58 women (66.67%) metastases in pelvic lymph nodes were not observed — group B. Data regarding patients' characteristics are presented in Table 1. 82 (94.25%) patients underwent primary debulking surgery. 5 patients (5.75%) received neoadjuvant chemotherapy followed by interval cytoreduction.

In group A (n = 29) number of metastatic lymph nodes were: 1 in 13 patients, 2 in 6 patients, 3 in 3 patients, 4 in 3 patients, 5 in 1 patient, 9 in 3 patients.

Patients' mean age at surgery was 61 years (26–84). 72 of 87 (82.76%) patients were after menopause. The majority of patients 72 of 87 (82.76%) were postmenopausal women. The most common histology was high-grade serous carcinoma — 77/87 (88.51%). Optimal cytoreduction (< 1 cm) was achieved in every patient. 10 (11.49%) patients underwent also aortocaval lymphadenectomy.

Pretreatment CA-125 serum concentration and grading were related to pelvic lymph nodes involvement. Patients

Variable (median/number)		Group A (n = 29; 33.33%)	Group B (n = 58; 66.67%)	Statistics
Age [years]		62 (36–84)	63 (26–80)	p = 0.822
Tumor volume [cm <sup>3</sup> ]		179.59 (4.18–767.15)	69.27 (1.5–8704.9)	p = 0.067
One-sided tumor		17 (58.62%)	38 (65.52%)	p = 0.12
Ascites		18 (62.07%)	28 (48.28%)	p = 0.508
Grading	Low	0	10 (15.38%)	p = 0.007
	High	29 (100%)	48 (82.76%)	
Postmenopausal status		21 (72.41%)	50 (86.21%)	p = 0.973
Pretreatment CA-125 concentration [IU/mL]		652 (54.8–5216)	360.9 (8.18–9418)	p = 0.039
BMI		24.74 (14.91–36.4)	27.98 (18.59–49.25)	p = 0.11

with pelvic lymph nodes metastases had higher pretreatment median concentration of CA-125 in serum (652 IU/mL vs 360.9 IU/mL,  $p < 0.05$ ). All patients with pelvic nodal involvement were diagnosed with high-grade tumors (Tab. 2).

For other analysed variables, there was no statistically significant relation with pelvic lymph nodes involvement. However, patients in group A with present lymph node metastases tend to had higher median tumor volume compared to patients in group B (179.59 cm<sup>3</sup> vs 52.88 cm<sup>3</sup>,  $p = 0.067$ ).

## DISCUSSION

Retroperitoneal dissemination to pelvic and aortocaval lymph nodes is commonly found in ovarian cancer. It results from lymphatic drainage pathways of the ovaries [10]. Some authors reported that lymph nodes invasion occurred more often in para-aortic than pelvic region [4, 11]. However, Bachmann et al. [12] found simultaneous metastases to both region as the most common. Other study showed that pelvic lymph nodes were more often affected by metastases than in aortocaval region [13].

Our results showed pelvic nodal involvement in 33.33% cases. Morice et al. [4] established that overall lymph nodes involvement in ovarian cancer was 44% and frequency increased with stage. Fournier et al. [14] presented similar observations, but the ratio of metastases in primary surgery was 50%. In other studies, metastases to retroperitoneal lymph nodes in early ovarian cancer were found in 13–25% [4, 15], while in advanced stage were observed in 45–75% cases [4, 7, 16, 17]. Elective pelvic and aortocaval lymphadenectomy in patients with clinical stage I and II results in final diagnosis of stage III in 20% [4]. Compared to previous studies, our outcome, showing that 1/3 of patients with advanced OC had lymph nodes involvement, is lower. This discrepancy may be caused by limitation of analysis to pelvic lymph nodes in our study. Another reason may be different number of resected lymph nodes between studies.

In our study, we analysed only serous tumors regarding it was the histologic type associated with the most common pelvic and para-aortic lymph nodes involvement. Although Roger et al. [18] found similar frequency for lymph nodes involvement in different histological types of epithelial ovarian cancer, other studies presented higher rate of lymph nodes metastases in serous tumor [8, 9, 16, 19, 20]. Zhou et al. showed higher risk (OR 2.728, 95% CI 1.072–6.945,  $p = 0.035$ ) for nodal involvement in serous ovarian cancer [8]. Powless et al. [9] found metastases to retroperitoneal lymph nodes more frequent in serous tumor than in other types (23% vs 9%). Similar observations presented Takeshima et al., who demonstrated that the nodal involvement was the most common in serous tumors and occurs in 36.7% [21]. Nodal spread rarely occurs in mucinous tumor [4, 9].

Although in some studies tumor grading was not associated with lymph nodes involvement [5, 22], our results showed that metastases in pelvic lymph nodes were observed only in high-grade tumors. Zhou et al. [8] had similar observations to our results. They did not find metastases to retroperitoneal lymph nodes in low grade tumors, while in grade-2 and grade-3 malignancies nodal involvement was 54.8% and 45.2%, respectively. Other authors presented that the incidence of metastatic nodes was significantly higher in patients with poor-differentiated tumors [9, 20, 23]. Kleppe et al. [24] investigated patients with early stage ovarian cancer. They demonstrated that nodal involvement in low-, middle- and high-grade ovarian cancer was 4.0%, 16.5%, and 20.0%, respectively. The percentage of affected lymph nodes increases when considering an early and advanced malignancies together. Tsumura et al. [25] showed that incidence rates of lymph nodes metastases in grade I, II and III tumors were 7.1%, 31.4% and 58.3%, respectively.

In our study, we found that pretreatment CA-125 serum level was higher in patients with metastatic pelvic lymph nodes. We observed significant difference in median serum CA-125 among patients with and without nodal involvement

(652 IU/mL vs 360.9 IU/mL,  $p < 0.05$ ). Zhou et al. [8] demonstrated that patients with CA-125 level of  $> 740$  IU/mL at diagnosis had higher risk for lymph node metastasis compared to those with CA-125 level of  $\leq 740$  IU/mL (53.5% vs 22.4%,  $p < 0.001$ ). Kim et al. [5] showed that the preoperative serum CA-125 level ( $> 535$  IU/mL) was a significant predictor of lymph node metastasis. Although our results are in line with other studies, we have concerns about the importance of serum pretreatment CA-125 in predicting lymph nodes involvement, especially in patients with advanced ovarian cancers. In such cases elevated serum CA-125 level may be a result of tumor volume, peritoneal spread or distant metastasis. Nevertheless, Powless et al. [9] used the cut-off value of 35 U/mL and showed that patients with increased preoperative serum CA-125 had positive lymph nodes in 22.4%. When preoperative CA-125 level was  $\leq 35$  IU/mL, no metastases in lymph nodes was detected [9]. Sodolmus et al. found 72 and 123 IU/mL as a significant cut-off values for lymph nodes involvement, but the false positive ratio was 67.4% and 55%, respectively. Authors concluded that although these values may be helpful in guiding clinical management, the false positive ratios are too high to use as a screening tool for predicting lymph nodes metastases [26]. In opposition to the above studies, Ditto et al. [22] did not find any relation between lymph node metastasis and serum CA-125 level.

Although the patient's age is associated with an increased risk of ovarian cancer, it was not identified as risk factor for nodal involvement [5, 8]. Menopausal status had no effect on metastases to retroperitoneal lymph nodes as well [5, 8]. Our results were consistent with these observations. Powless et al. [9] found that ascites and bilateral adnexal masses were associated with an increased risk of retroperitoneal lymph nodes involvement. We did not observe these coincidence in our results. It may be a consequence of different characteristics of patients. Our study included patients only in advanced stage, while Powless et al. [9] analysed patients in early and advanced stage. Another explanation is a lack of aortocaval lymph nodes dissection in our study.

Our study had several limitations. First, it had a retrospective character and was not randomised, therefore, we cannot exclude bias. Patients in our study underwent predominantly pelvic lymphadenectomy without dissection of aortocaval lymph nodes. Furthermore, the median number of resected lymph nodes in our analysis was lower than in other studies so proportion of metastatic lymph nodes may be underestimated.

## CONCLUSIONS

Pretreatment serum level of CA-125 and tumor grading differed significantly among both analysed groups. LION trail showed similar OS among patients with and without

lymphadenectomy, but decisions about lymph node status was done by highly-skilled surgeons. In clinical practice, intraoperative lymph nodes assessment by less experienced gynecologist/surgeon may appear challenging, especially if preoperative imaging is inconclusive. In such cases high pre-treatment CA-125 serum level and serous high grade histology of tumor may be helpful in lymphadenectomy extension.

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