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Incidence and Pattern of Spread of Lymph Node Metastasis in Patients With Low-grade Serous Ovarian Cancer

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Abstract. *Background/Aim: Involvement of lymph nodes (LNs) and their surgical resection in low-grade ovarian cancer remains a field of discussion. The aim of this study was to determine the incidence and pattern of distribution of lymph node metastases in patients with low-grade serous ovarian cancer. Patients and Methods: A retrospective analysis was carried out in patients with primary low-grade serous ovarian cancer who underwent primary surgery including systematic lymphadenectomy. Analysis of the affected LNs along with pattern of lymphatic spread was performed. Results: Thirty-seven patients who underwent systematic pelvic and para-aortal LN dissection were identified. The median age was 48 years (range=26-76 years). The majority of patients had International Federation of Gynecology and Obstetrics stage III (89.2%). A median of 41 (range=10-97) LNs were resected. LN metastases were found in 27 (72.9%) patients. In 15 (55.5%) patients, both pelvic and para-aortic LNs were affected concomitantly, in isolated para-aortal and pelvic lymph nodes in three (11.1%) and eight (29.6%) patients, respectively. The most frequently affected region was the right obturator fossa, found in 14 (51.8%) patients, followed by the left obturator fossa in 11 (40.7%) patients. Conclusion: Low-grade serous ovarian cancer exhibits a high percentage of lymphatic spread, with more confinement to the pelvic compared to the para-aortic region.*

Epithelial ovarian cancer is the leading cause of death among all gynecological malignancies, and the majority of patients are diagnosed with an advanced stage of disease (1). The two-tier grading system based on histology, low-grade and high-grade, was introduced in 2004 (2-4). Low-grade serous ovarian cancer represents approximately 6-8% of all ovarian cancer cases (5). This rarity of low-grade ovarian cancer makes it challenging to study the disease (5, 6). Both low- and high-grade ovarian cancer are considered two separate entities with different molecular and clinical characteristics (5, 7). The patient outcome depends on the initial spread of the disease and on the quality of surgical treatment. Current primary surgery standards do not differentiate between low- and high-grade histology (6).

Pelvic and para-aortic lymphadenectomy is a part of comprehensive surgical staging in patients with early International Federation of Gynecology and Obstetrics (FIGO) I-II epithelial ovarian cancer (8, 9) and currently in certain cases of advanced FIGO III-IV as a surgical therapeutic procedure. The role of lymphadenectomy as an essential part of staging and its outcome relevance has been a subject of continuing debate. A comprehensive review of 13 studies showed that the incidence of lymph node metastasis in patients with FIGO I-II low-grade ovarian cancer to be 2.9% (10). The fact that the incidence of lymph node metastasis in low-grade serous ovarian cancer varies widely in the few studies that concentrated on this issue makes the topic more controversial (11-16). Furthermore, the majority of these studies did not thoroughly define the systematic lymph node dissection approach, leaving the possibility of lymph node sampling as a potential bias. Therefore, the aim of our study was to evaluate the frequency and pattern of spread of lymph node metastasis in this group of patients.

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Key Words: Low-grade ovarian cancer, lymph-node, metastasis, lymphatic spread.

Patients and Methods

A retrospective analysis of the Department of Gynecology, Virchow Campus Clinic, Charité Medical University Berlin, database was performed. All consecutive patients with ovarian cancer who were treated at our Institute were documented (prospective since 2009) in a clinical tumor registry (Ovarian Cancer Network Tumor Bank Database). All patient records are updated annually.

All patients with primary low-grade serous ovarian cancer treated between 2000 and 2017 who underwent systematic pelvic and para-aortic lymphadenectomy during primary surgery were considered for enrollment. Systematic lymphadenectomy involved resection of lymph nodes from the following regions: Pelvic (bilateral along the *arteria communis, a. externa, a. interna* and obturatic fossa), para-aortal until the height of bilateral renal arteries (para-aortal below and above inferior mesenteric artery, inter aorto-caval, para-caval).

In order to be eligible, patients had to meet the following criteria: (i) Primary diagnosis of low-grade serous ovarian cancer; (ii) primary surgery with systematic lymph node dissection. Patients were excluded if they have not undergone systematic lymphadenectomy, presented initially with recurrent disease, had high-grade or non-epithelial ovarian neoplasm, or had borderline tumors. Documentation of surgical procedures in standardized form was performed in the operating theater immediately after surgery and histological reports as well as postoperative morbidity data were included.

End points included the evaluation of lymph node dissection, its completeness, detection of sites of metastasis, and overall (OS) as well as progression-free survival (PFS), defined from the date of diagnosis until death and progression, respectively.

All statistical analyses were performed using IBM SPSS Statistics 24 (IBM, Armonk, NY, USA). The Kaplan–Meier method including a log-rank test was used to determine survival differences. All *p*-values were two-sided.

Results

Among patients with ovarian cancer listed in the database between 2000 and 2017, a total of 80 patients with low-grade serous ovarian cancer were identified. All histopathological results were re-assessed at the Institute for Pathology, Charité Medical University Berlin, regarding the two-tier grading criteria. Within this group, 48 patients had primary low-grade serous ovarian cancer. Among those, 37 underwent systematic lymphadenectomy, two new lymph node sampling and three had the lymph nodes found within the tissue resected from other regions with the same histopathological pattern resembling that of the primary tumor (Table I). In six patients, the status of lymph nodes was not assessed. Reasons for lymph node sampling, and even the inability to assess the lymph nodes status were the spread of intra-abdominal disease and performance status.

The median age of the 37 patients with primary low-grade serous ovarian cancer who underwent systematic lymphadenectomy was 48 years (range=26-76 years). Among those, 27 (72.9%) patients had lymph nodes with metastatic spread. The majority of patients with positive lymph nodes had pT3 status (24, 88.9%) as shown in Table II.

Table I. *Patient characteristics.*

Characteristic	Value
Age, years	
Median (range)	48 (26-76)
FIGO stage, n (%)	
I	2 (5.4%)
IA	1
IB	0
IC	1
II	2 (5.4%)
IIA	1
IIB	1
III	33 (89.2%)
IIIA1	3
IIIA2	3
IIIB	10
IIIC	17
Nodal involvement, n (%)	
N0	10 (27%)
N1	27 (73%)

Table II. *Correlation between TNM classification (8) of tumor size (T) staging and lymph node (N) status.*

TNM classification	Total patients, n	N0, n	N1, n
T1a	1	1	0
T1b	0	0	0
T1c	2	1	1
T2a	1	1	0
T2b	3	1	2
T3a	2		2
T3b	11	3	8
T3c	17	3	14

Table III. *Localization of lymph node metastases.*

Localization of positive lymph nodes	All patients (%)	Patients with pN1 (%)
Para-aortic (including upper & lower)	13.5	18.5
Inter-aorto cava	27	37
Para-cava	24.3	33.3
Pelvis		
Right external iliac	24.3	33.3
Left external iliac	18.9	25.9
Right common iliac	18.9	25.9
Left common iliac	18.9	25.9
Right internal iliac	8.1	11.1
Left internal iliac	8.1	11.1
Right obturator fossa	37.8	51.9
Left obturator fossa	29.7	40.7

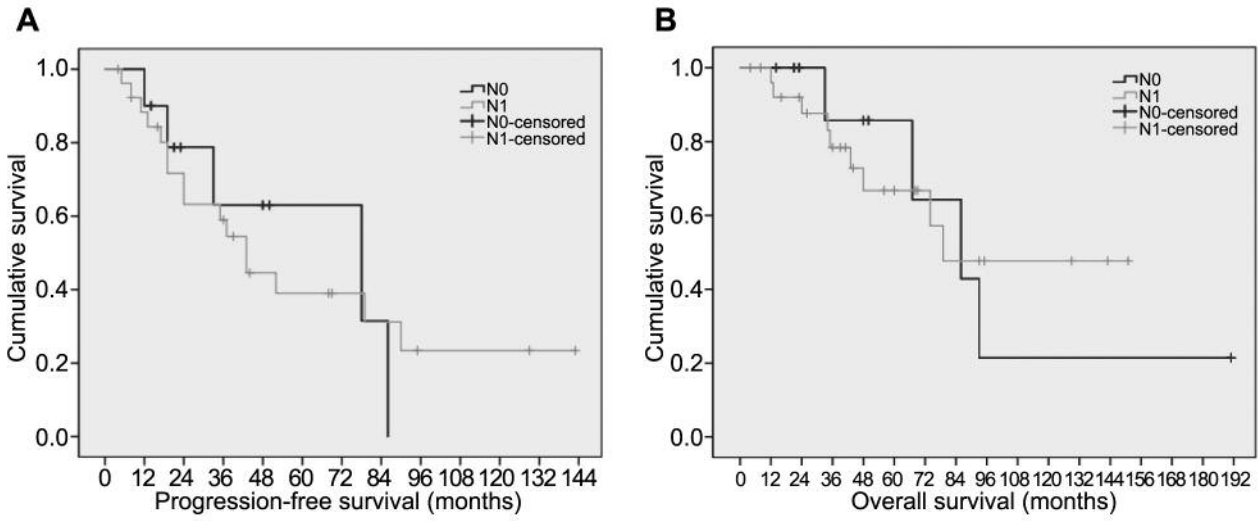

Figure 1. *Progression-free (A) and overall (B) survival in patients with primary epithelial ovarian cancer without (N0) and with (N1) lymph node metastases.*

A median of 41 (range=10-97) lymph nodes were removed, with a median of 21 pelvic nodes (range=1-47), and 18 para-aortic nodes (range=3-65). Regarding the pattern of lymph node involvement, we found eight (29.6%) patients with isolated pelvic lymph nodes involved, while in three (11.1%) patients, only the para-aortic lymph nodes were affected. Both pelvic and para-aortic lymph node involvement was found in 15 (55.5%) patients. The most common location of positive lymph nodes was in the right and the left obturator fossae in 37.8% and 29.7% of patients, respectively. The distribution of lymph node metastases is presented in Table III.

Patients who had no lymph nodes metastasis (N0) showed no significant difference regarding the progression-free survival in comparison to those who had affected lymph nodes (N1) ($p>0.05$) as shown in Figure 1A. No significant difference regarding overall survival between patients with N0 and N1 status ($p>0.05$) was found (Figure 1B).

Discussion

Systematic lymph nodes dissection in primary epithelial ovarian, tubal and peritoneal cancer has been described in several publications (10-16). The frequency and pattern metastatic spread in lymph nodes and its influence on the outcome were reported. However, the clinical data in regard to low-grade ovarian cancer cases are still very limited. Only few publications are devoted to low-grade serous ovarian cancer and surgical procedures are available. The aim of our study was to describe the pattern of lymph node metastasis and its' impact on prognosis in this group of patients.

The involvement of lymph nodes in patients with ovarian cancer represents a frequent feature of metastasis (10-16). Maggioni *et al*. analyzed the surgical data of 138 patients with ovarian cancer macroscopically confined to the pelvis (T1-2) who underwent systemic lymph-node dissection. They found more frequent lymph node involvement in those with grade 3 tumors *versus* those with grade 1/2 tumors (31% *vs*. 11%, $p=0.004$). In regard to the pattern of spread, the majority (54%) had aortic lymph node metastasis, however, this calculation in regard to grade 1 cancer was not provided (14). In a review from 2016, Minig *et al*. analyzed data regarding lymph-node involvement in presumably stage I low-grade ovarian cancer. They reported 4.3% incidence of lymph node metastasis. The most frequent lymph node involvement was reported in the para-aortic region (85.7%). The limitations of this trial were the uni-centric nature of the study, the retrospective design, and inhomogeneous and not well-defined surgical standards in regard to systematic lymph node dissection (10). Harter *et al*. found that the incidence of lymph node metastasis in patients with early epithelial ovarian cancer (pT1-3a) was 53% and concluded that the most commonly affected region was the para-aortic region, with upper para-aortic area to be the most frequently affected (32% of patients). However, in 11 patients identified as having grade 1 disease, no lymph node metastases were reported (17). A further publication from 2017 showed an increased risk of para-aortal involvement to be associated with low-grade cancer (18). Our findings are comparable in regard to the frequency of lymph nodes involvement with the aforementioned data; however, the distribution of metastasis differs. Our results show more confinement to the pelvis in comparison to the para-aortic

region, especially in the right obturator fossa (37.8%), followed by the left obturator fossa (29.7%).

A recent prospective study on 650 enrolled patients with primary advanced ovarian (FIGO IIB-IV) cancer showed 55.7% lymph-node involvement. Regarding the primary aim, no difference in progression-free and overall survival between patients who underwent lymphadenectomy and those who did not undergo this procedure in the absence of bulky lymph nodes intraoperatively and advanced ovarian cancer was found (19). In this regard, our data in low-grade ovarian cancer correspond with this lack of difference in survival rates. An interesting aspect affecting survival in low-grade ovarian cancer was reported by Matsuo *et al*. (20), describing reduced progression-free survival in patients with lymphovascular space invasion. This factor needs further investigation, especially considering the lack of any relevant impact on survival of lymph nodes involvement itself.

To our knowledge, our study is the largest single-center analysis on the pattern of lymph node involvement in low-grade serous ovarian cancer. Moreover, it is the first study focusing exclusively on lymph node involvement and its influence on prognosis in low-grade ovarian cancer irrespectively of disease stage. Lymph node metastases are not rarely detected in low-grade serous ovarian cancer and are more likely to be found in the pelvic region. Nevertheless, further prospective trials on this patient group are needed in order to evaluate the necessity and impact of this procedure.

Conclusion

Low-grade serous ovarian cancer seems to be prone to metastatic spread, with more confinement to the pelvic region. In this study, we focused only on the serous subtype of low-grade serous ovarian cancer, and tried to unify the pattern of lymph node dissection as much as possible in order to be as precise as possible. Yet this topic still needs further multi-centric prospective studies.

Conflicts of Interest

The Authors declare no conflict of interests in regard to this study.

Authors' Contributions

Guarantor of the integrity of the study: Jacek P. Grabowski, J. Sehouli, M. Wafa; Study concepts: Jacek P. Grabowski, J. Sehouli, M. Wafa; Study design: J Jacek P. Grabowski, J. Sehouli, M. Wafa; Definition of intellectual content: Jacek P. Grabowski, J. Sehouli, M. E. Taube, Wafa; Literature research: J. P. Grabowski, P. Harter, A. du Bois; Clinical studies: Jacek P. Grabowski, J. Sehouli, M. Wafa, EI Braicu, MZ Muallem; Data acquisition: Jacek P. Grabowski, J. Sehouli, M. Wafa, E. Taube, MZ Muallem, EI Braicu, R. Richter; Data analysis: J. P. Grabowski, J. Sehouli, M. Wafa, R. Richter; Statistical analysis: J. P. Grabowski, J. Sehouli, M. Wafa, R. Richter; Article preparation: J. P. Grabowski, J. Sehouli, M. Wafa, R. Richter; Article editing: J. P. Grabowski, J. Sehouli, M. Wafa, R. Richter; Article review: J. P. Grabowski, J. Sehouli, M. Wafa, R. Richter.

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