

Lymph node involvement and the role of lymphadenectomy in patients with advanced ovarian cancer

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RESEARCH

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ABSTRACT

Background

Ovarian carcinoma (OC) is one of the most common types of cancer diagnosed in women and its clinical significance is reflected in the leading place it holds in the morbidity and mortality rates among women diagnosed with cancer. The evaluation of lymph node involvement by the oncosurgeons is a pivotal step towards proper disease staging and adjuvant therapeutic choices, towards optimal treatment outcomes.

Aims

The aim of this study was to investigate the lymph node metastases and patient characteristics in women with advanced OC (FIGO II-IV).

Methods

The study includes 58 patients with advanced OC (FIGO II-IV) operate in our clinic for the period 2004-2012. The patients were analysed with respect to age, FIGO stage, histological type and tumour grading, type of surgical verification of lymph nodes (biopsy, pelvic and/or para-aortic lymphadenectomy), results from histopathological reports describing the extent of lymphatic involvement, localization of lymph node metastases, and presence of ascites.

Results

Lymph node metastases were found in 56.7 per cent of the patients. 24.1 per cent of the patients had micrometastases in lymph nodes that were not initially detected on both pre-operative diagnostic imaging and intraoperative inspection.

Conclusion

The only reliable method for initial/early detection of lymphatic metastases in patients with OC is the surgical, through lymphadenectomy, with subsequent histological evaluation.

Key Words

Ovarian cancer, lymph node metastasis, surgery

What this study adds:

1. What is known about this subject?

The only reliable method for early initial detection of lymphatic metastases is surgical with subsequent histological examination.

2. What new information is offered in this study?

In big number of patients without clinical suspicion for nodal involvement, after lymph node dissection micrometastases will be found.

3. What are the implications for research, policy, or practice?

The evaluation of lymph node involvement in ovarian carcinoma is essential for the correct disease staging, prognosis determination, and optimal adjuvant therapy selection.

Introduction

In Europe, ovarian carcinoma (OC) is the fifth most common malignancy in women, preceded by breast, colon, lung, and uterine cancer. OC takes up 3.7 per cent of the total number of cases of women diagnosed with cancer, with 65,538 new cases diagnosed each year. In 2012, the incidence of ovarian carcinoma per 100,000 was 13.1, with 42,704 deaths. It is ranked fifth among the causes of death from malignant disease in women in Europe.¹

Lymphatic spread and lymph node involvement are common and typical in OC. In most cases, the lymph nodes are not enlarged, but exhibit malignant cells on microscopy. The incidence of lymph node metastasis in epithelial ovarian carcinoma reported in the literature varies widely and depends on the clinical stage of the disease and the lymphadenectomy extent.²⁻⁶ Nodal involvement is associated with a worse prognosis and stratifies the patient in advanced stage.⁷ Para-aortic lymphadenectomy, up to the level of renal vessels, may detect hidden micrometastases and help with optimal adjuvant therapy choices and proper prognosis evaluation.⁸

Diagnostic lymphadenectomy is an important component of the staging procedure in women with EOC confined to the ovaries. Approximately 30 per cent of early stage EOC patients get re-staged following a comprehensive surgical staging procedure.⁹ Although the role of complete lymphadenectomy in disease staging is well established, its therapeutic value remains controversial. In recent years, the percentage of OC patients having undergone lymphadenectomy has increased from 24 per cent in 2005 to 55 per cent in 2011.¹⁰

Methodology

We investigated lymph node involvement and patient characteristics in surgically treated women with advanced stage ovarian carcinoma (FIGO II-IV). We analysed

retrospectively collected data for the period 2004-2012 that included 58 patients that had undergone lymphadenectomy at various extents followed by a histological examination. The patients were analysed with respect to age, FIGO stage, histological type and tumour grading, type of surgical verification of lymph nodes (biopsy, pelvic and/or para-aortic lymphadenectomy), results from histopathological reports describing the extent of lymphatic involvement, localization of lymph node metastases, and presence of ascites. Disease grading was done according to the FIGO 1998 classification. All procedures were made by open surgery and include simple hysterectomy, total omentectomy and when systematic para-aortic lymphadenectomy was performed the dissection was to the point of renal artery.

Statistical analysis

The statistical analysis of the results was carried out with statistical software packages, namely, SPSS - 19.0, 19.0 A - form for expert science; STATISTIKA 8.0., AMOS-7, Lizrel - 8.1. A descriptive analysis was applied to determine distributions, mean values, standard deviations, as well as for trend comparison for the different study parameters and performing Student T-test to detect differences in the mean values between the variables in the different investigations. Statistical significance level defined was $p < 0.05$.

Results

Patient characteristics are presented in Table 1. Patient age was 60.84 ± 11.67 years. The FIGO stage distribution showed the highest proportion of Stage IIIC at 60.34 per cent. The predominant histological type was the serous, with moderate and low differentiation. Systemic lymphadenectomy of pelvic and the para-aortic lymph nodes was carried out in 11 of the cases, while elective lymphadenectomy of either pelvic or para-aortic lymph nodes or biopsy was performed on the remainder of patients. Histopathological reports described lymphatic metastases in 33 of 58 patients (56.9 per cent). As a result, 3 of the patients received a restaging from FIGO stage II to stage III. In the presence of ascites, there is a tendency for cases to be node positive (approximately 62 per cent of patients with ascites were node-positive - 24 out of 39), without the result being statistically significant (p value?). With respect to the primary tumour localization, bilateral ovarian involvement was associated with a higher rate of lymphatic metastases compared to unilateral ovarian carcinoma (54.5 per cent vs. 45.4 per cent).

Of all 58 patients undergoing lymphadenectomy in 22 there was pre-operatively and/or intraoperatively suspected

nodal involvement, which was histologically confirmed in 86.4 per cent of the cases (in 19 of 22 patients) (Table 2). In the patients (n=36) with no prior clinical data for nodal involvement, the percentage of histologically confirmed lymphatic metastases (micrometastases) was considerable at 38.9 per cent (14 out of 36 patients). The total proportion of patients with lymphatic micrometastases was 24.1 per cent (n=14 out of 58 patients).

The percentage of patients with lymph node metastasis was significantly higher at 90.9 per cent in the systemic lymphadenectomy group ($p=0.001$) compared to 48.9 per cent in the non-systemic lymphadenectomy group (Table 3).

Discussion

The lymphatic drainage of the ovary is carried out via three pathways.⁹ The main pathway runs upwards along the ovarian vessels and reaches the para-aortic lymph nodes between the aortic bifurcation and the renal arteries. The second pathway runs through the broad ligament and ends in the internal, external and common iliac lymph nodes (Figure 1). A third group of efferent lymph vessels is drained through the round ligament in the external iliac and inguinal lymph nodes.⁹ In patients with advanced stage disease, retrograde dissemination may occur in the common iliac and femoral lymph nodes.¹¹ Identification of sentinel lymph nodes is done to reduce the extent of lymphadenectomy also in ovarian carcinoma.¹²

Metastasis via the lymphatic route is characteristic for advanced ovarian carcinoma. The most common pattern is the simultaneous spread to the pelvic and para-aortic lymph nodes, which occurs in 53 per cent to 73 per cent of all patients with lymph node involvement.^{2,5} Onda et al. report para-aortic lymph node metastases between the inferior mesenteric artery and the renal artery in 79 per cent of the patients with positive lymph nodes.⁵ Negishi et al. demonstrated, with sentinel technique, that lymph vessels in the course of the ovarian bundle and the para-aortic lymph nodes were the first to drain the lymph in all patients of their study group.²⁰

The histopathological reports in our study showed nodal involvement in 56.9 per cent of the patients who have undergone a certain extent of lymphadenectomy. Similar results have been reported by other authors, showing that lymph node metastases are found in over 50 per cent of the patients in advanced stage disease.^{6,13-16} Lymph node metastases cannot reliably diagnosed, neither by imaging methods nor by intraoperative palpation.^{6,15,17}

Intraoperative palpation is insufficient for the diagnosis of lymph node metastases.^{16,18}

In our study, 38.9 per cent of patients, without clinical suspicion for nodal involvement, having undergone pelvic and/or para-aortic lymphadenectomy were found to have lymph node metastases and 21.4 per cent of them were micrometastases. On the other hand, nodal involvement is not histologically confirmed in nearly 14 per cent of the patients with prior clinical suspicion for nodal involvement. This may be due to the low sensitivity and specificity of the lymph node size as an indicator for metastasis.^{18,19}

The frequency of lymph node metastases detection depends on the extent of the lymphadenectomy performed. A prospective randomized study performed in the UK, evaluating the role of lymphadenectomy, has reported a significant variation in the frequency of histological diagnosis of lymph node metastases with respect to the extent of lymphadenectomy - 70 per cent for systemic lymphadenectomy and 42 per cent for non-systemic lymphadenectomy.⁶ The latter is also confirmed by the results of our study, which revealed higher frequency of histologically confirmed nodal involvement in patients with systemic (pelvic and para-aortic) lymphadenectomy - 90.9 per cent compared to that in the group with non-systemic lymphadenectomy/biopsy, which showed lymph node metastases in less than 60 per cent of the cases. Noteworthy is the fact that in the para-aortic lymph nodes only group (excluding the pelvic lymph nodes) 100 per cent (6 of 6) had lymph node metastases confirmed histologically, which result can be attributed to the lymphadenectomy being performed upon clinical suspicion (83.3 per cent of cases) and due to para-aortic lymph nodes being the main pathway through which metastasis occurs in epithelial ovarian cancer.² This is confirmed by our observation that, in systemic lymphadenectomy, lymph node metastases in the para-aortic region are found in 72.7 per cent of the patients in our study. Metastases in the pelvic lymph nodes are also common.^{5,20,21} In some reports, isolated metastases have been reported in the inguinal lymph nodes.^{4,22-24}

Significant risk factors for lymph node involvement, according to some authors who have studied patients with early stage epithelial ovarian carcinoma, are: serous histological type, presence of ascites, positive peritoneal cytology, grade 3, bilateral primary tumour.^{8,25} The highest percentage of lymph node involvement is found to occur with poorly differentiated (G3) carcinomas and/or serous histological subtypes.

In our sample, the presence of ascites is associated with a higher frequency of lymph node involvement. Nearly 70 per cent of the patients with confirmed lymph node metastases had ascites, and in 75 per cent (18/24) the ascetic fluid was positive for malignant cells. Patients with positive ascetic fluid cytology have a higher percentage of lymphatic involvement - 60 per cent (18/30). In patients with histologically confirmed lymph node metastases, the serous histological type prevails (90.9 per cent). The predictive significance of tumour cell differentiation is confirmed in our study. 59.1 per cent of the Grade 3 OC cases had lymphatic metastasis detected. 62 per cent (18/29) of the patients with bilateral primary tumour had histologically proven lymph node metastasis, while in the unilateral primary tumour cases, the proportion of lymph node involvement was lower - 52 per cent (15 out of 29).

Conclusion

The evaluation of lymph node involvement in ovarian carcinoma is essential for the correct disease staging, prognosis determination, and optimal adjuvant therapy selection. The only reliable method for early initial detection of lymphatic metastases is surgical with subsequent histological examination. In almost 1/4 of the patients in our study, lymph node metastases were occult (micrometastases).

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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Figure 1: Lymphatic vessel lumen with dispersed and cohesive polymorphic tumour cells containing hyperechoic nuclei

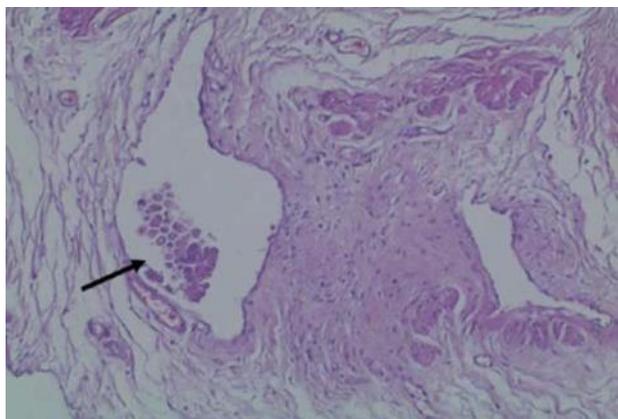


Table 1: Patient characteristics

Average age 60.84±11.67	N (%)	Positive LN N (%)
Total number	58	33
FIGO stage		
II	7 (12.06%)	3/33 (9.1%)
IIIA	2 (3.44%)	1/33 (3.0%)
IIIB	7 (12.06%)	2/33 (6%)
IIIC	35 (60.34%)	23/33
IV	7 (12.06%)	4/33
Histological type of tumor		
Serous	47 (81%)	30/33
Mucinous	3(5.2%)	1/33 (3.0%)
Endometrioid	1 (1.7%)	0
Poorly differentiated	1 (1.7%)	0
Undifferentiated	6 (10.3%)	2/33 (6.1%)
Tumor grading (differentiation)		
G1	2 (3.5%)	1/2 (50%)
G2	34 (58.6%)	19/34
G3	22 (37.9%)	13/22
Ascites		
Without ascites	19 (32.8%)	9/33
With ascites	39 (67.2%)	24/33
Ascites with positive cytology	30/39 (76.9%)	18/24 (75%)
Ascites with negative cytology	9/39 (23.1%)	6/24 (25%)
Localisation of primary tumour		
Right Ovary	19 (32.8%)	10/33
Left Ovary	10 (17.2%)	5/33
Unilater involvement	--	15/33
Bilateral involvement	29 (50%)	18/33
Extent of lymphadenectomy		
Biopsy	8 (13.8%)	
Selective pelvic or	39 (67.2%)	
Systemic pelvic and para-	11 (19%)	
Localization of lymphatic metastases		
Pelvic only	19 (32.8%)	
Para-aortic+pelvic	8 (13.8%)	
Para-aortic only	6 (10.3%)	

Table 2: Clinical suspicion in patients with lymphadenectomy

Patients with ha lymphnodectomy N=58	Patients with clinical suspicion for lymphatic metastases N=22	Patients without clinical suspicion for lymphatic metastases N=36
Histologically confirm positive lymph nodes, N=33 (56.9%)	N=19/22 (86.4%)	N=14/36 (38.9%)

Table 3: Distribution of positive lymph nodes with respect to the extent of lymphadenectomy

Patients with examined LN N=58	Non-systemic lymphadenectomy/ biopsy (either pelvic or para-aortic LV) N=47	Systemic lymphadenectomy/ biopsy (pelvic and para-aortic LV) N=11	p-value
Histologically confirmed positive LN N=33	Positive LN in non-systemic lymphadenectomy N=23/47 (48.9%)	Positive LN in systemic lymphadenectomy N=10/11 (90.9%)	0.001