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Lymph node involvement in clinically apparent early ovarian cancer: a prospective study

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Summary

Purpose: The objective of this study was to identify the lymph node involvement in apparently early ovarian cancer (OC) *Materials and Methods:* Patients with clinically apparent early OC who underwent staging surgery between August 2012 and August 2015 were prospectively identified. Patients' characteristics and tumor histopathology were evaluated. *Results:* Twenty consecutive patients were operated for grossly apparent early ovarian carcinoma. All patients were surgically staged and underwent a systematic pelvic and para-aortic lymphadenectomy. There were eight patients (40%) with lymph node involvement. One of the eight lymph node metastasis was solely in para-aortic node, three patients had both positive-pelvic and aortic nodes, and the other metastasis was in ipsilateral pelvic lymph node. Positive lymph node involvement was significantly higher among patients with poorly differentiated tumor grade (62.5%) (p = 0.02). *Conclusion:* All patients diagnosed with early OC macroscopically confined to the ovaries should be considered for comprehensive staging surgery including pelvic and para-aortic lymphadenectomy.

Key words: Ovarian cancer; Pelvic and para-aortic lymphadenectomy.

Introduction

Ovarian cancer (OC) is the sixth most common cancer in women and the seventh most common cause of cancer death worldwide [1]. Its occurrence is associated with a positive family history [2]. Owing to the absence of effective measures for early detection, it is often diagnosed at an advanced stage, resulting in low long-term survival rates (30–40%) [3].

In recognition of the prognostic importance of lymphatic metastasis, the International Federation of Gynecology and Obstetrics (FIGO) staging classification was amended to include a sub-stage for node involvement [4] and systematic lymphadenectomy was included in the guidelines.

Lymphadenectomy is an integral part of surgical staging and treatment for OCs, and they have a potential role in both staging and retroperitoneal debulking. Lymphatic node metastasis results in a change from Stage I to Stage IIIC. Five-year survival decreases from more than 90% to 20% to 60% if lymphatic node metastasis is present and adjuvant therapy is needed [5-7]. However, there is debate on the extent of lymphadenectomy, particularly in early staged tumors [8, 9].

Despite a detailed history of lymphadenectomies in scientific literature, there are only a limited number of reports analyzing this topic [8-10]. Furthermore, most of them are of a retrospective nature. The staging procedures of these studies and the extent of lymphadenectomies performed are also debatable. In this study, the authors aim to analyze the role and the extent of systematic lymphadenectomies and the lymphatic metastatic pattern of grossly apparent early OCs in a prospective pattern.

Materials and Methods

Between August 2012 and August 2015, 20 patients with clinically apparent early-stage OC, referred to the Department of Obstetrics and Gynecology, Menoufia University Hospital, were enrolled in this prospective study. The study was approved by the hospital ethics committee and a written consent was obtained from each patient.

The surgical procedure consisted of total abdominal hysterectomy, bilateral salpingo-oophorectomy, and/or omentectomy, in addition to systematic pelvic and para-aortic lymphadenectomy. The pre-treatment evaluation consisted of a complete history, physical, and gynecologic examinations, laboratory work-up, tumor markers, ECG, chest X-ray, intravenous pyelogram, abdominal and pelvic ultrasonography, and CT scan. All the patients were assumed to have tumors in clinical Stage I after preoperative and intraoperative evaluations.

Lymphadenectomy eligibility requirements included a maximum age of 70 years, FIGO Stages I – III [4], adequate renal, cardiac, and hepatic function, and informed consent. Exclusion criteria included morbid obesity, high-risk chronic pulmonary and cardiovascular disease, locally advanced tumors, distant metastasis, and the presence of other malignancies. Patients were staged according to the surgical-pathological FIGO criteria [4]. Histological grading was based on the degree of differentiation in accordance with the FIGO guidelines [4].

The surgical technique for lymphadenectomy has been previ-

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Table 1. — *Clinico-pathological features of the patients.*

Characteristics		Ovary (n = 20) No. (%)
Age (years), median (range)		45 (24 – 70)
BMI (kg/m^2), mean ± SD		36.26 ± 3.96
Menopausal status	Premenopausal	12 (60)
	Postmenopausal	8 (40)
Pathology	Serous	6 (30)
	Mucinous	6 (30)
	Endometroid	4 (20)
	Other*	4 (20)
Stage	I	9 (45)
	II	7 (35)
	III	4 (20)
Grade	Well	5 (25)
	Moderate	8 (40)
	Poor	7 (35)
Lymph node.	Positive	8 (40)
	Negative	12 (60)

*Three cases germ cell tumor and one clear cell adenocarcinoma.

Table 2. — *Relation between pelvic and para-aortic lymph node involvement.*

Para-aortic nodes	Pelvic nodes Positive (n =7) No. (%)	Pelvic nodes Negative (n = 13) No. (%)	Fisher's exact test	*p*-value
Positive	3 (42.9)	1 (7.6)	7.49	0.02(S)
Negative	4 (57.1)	12 (92.4)		

Table 3. — *Relationship between lymph node involvement and tumor characteristics.*

Characteristics	Lymph node involvement Positive (n =8) No. (%)	Lymph node involvement Negative (n = 12) No. (%)	Test	*p*-value
Age (years)			Fisher's	1
< 60	5 (62.5)	7 (58.3)	exact	
≥ 60	3 (37.5)	5 (41.7)	0.03	
Stage			Z	
I	0 (0.0)	7 (58.3)	2.12	0.03(S)
II	5 (62.5)	3 (25)	1.02	0.32
III	3 (37.5)	2 (16.7)	0.34	0.48
Grade			Z	
Well	1 (12.5)	6 (50)	1.65	0.073
Moderate	2 (25)	4 (33.3)	0.27	0.86
Poor	5 (62.5)	2 (16.7)	2.01	0.02 (S)

Table 4. — *Operative data.*

Operative data	Patients (n = 20) Median	Range
Operation time (minutes)	160	120-240
Estimated intra-operative blood loss (ml)	550	400-2000
Blood transfusion (units)	4	0-4
Duration of drainage (days)	7	5-10
Post-operative stay (days)	6	4-11

ously described elsewhere [6, 11, 12]. The upper margin of aortic lymphadenectomy was the origin of the renal vessels and the lower margins of pelvic lymphadenectomy were the femoral ring and the pelvic floor. All the lymphatic tissue located within these margins was excised [11]. For classification purposes, the pelvic lymph nodes were divided into four different node sites: internal iliac, external iliac, common iliac those lymph nodes lying next to the respectively named blood vessels, and obturator lymph nodes which were defined as those lying within the obturator fossa, medial, and inferior to the external iliac vessels, and surrounding the obturator vessels and nerves. Para-aortic lymph nodes were defined as all lymph nodes lying adjacent to the aorta or inferior vena cava up to the level of the renal vessels [8].

The resected lymphatic tissue was grouped and labeled according to the different sites and was subjected to histopathologic examination individually. In addition, lymph nodes were counted in each group, as well as number of lymph node metastasis was also examined.

Postoperative thromboembolic prophylaxis based on low molecular weight heparin was used over ten to 15 days. Morbidity and mortality rates of systematic pelvic and para-aortic lymphadenectomy were investigated.

Operating time was defined as the time from abdominal incision to completion of abdominal closure. Mortality was defined as postoperative death due to any cause within 30 days of the procedure. The anesthesiologist estimated blood loss based on observation of the suction catheter and sponges at the completion of the operation.

The collected data were tabulated and analyzed by a commercially available statistical package SPSS version 16. Quantitative data were expressed as median and range or mean ± standard deviation (SD). Qualitative data were expressed as number and percentage and analyzed by applying Z test or Fisher's exact test. The test is considered significant when p-value is < 0.05 and highly significant when $p < 0.001$ [13].

Results

Patients' clinic-pathological characteristics are listed in (Table 1). The median age was 45 (range: 24-70) years. BMI mean ± SD was 36.26 ± 3.96. Premenopausal patients were (60%). Tumor histology was serous in six patients (30%), mucinous in six patients (30%), endometrioid in four patients (20%), germ cell tumor in three patients (15%), and clear cell in one patients (5%). The majority of patients had Stage I, II disease (80%), and moderately differentiated cancer (40%). Eight patients (40%) had positive lymph nodes and 12 patients (60%) had negative lymph nodes. One of the eight lymph node metastasis was solely in para-aortic node, three patients had both positive-pelvic and aortic nodes, and the other metastasis was in ipsilateral pelvic lymph node.

The relationship between pelvic lymph node involvement and para-aortic lymph nodes is shown in (Table 2). This relation shows that para-aortic lymph nodes were significantly higher among patients with positive pelvic lymph node involvement (42.9%) than among patients with negative pelvic lymph node involvement (7.6%) ($p = 0.02$).

Table 3 shows the relationship between lymph node status and other variables of the disease. This table shows that FIGO Stage I was significantly higher among patients with negative lymph node involvement (58.3%) than among patients with positive lymph node involvement (0.0%) (p = 0.02). On the other hand, FIGO grade (poor) was significantly higher among patients with positive lymph node involvement (62.5%) than among patients with negative lymph node involvement (16.7%) (p = 0.03).

Operative data of systematic lymphadenectomy are shown in (Table 4). The median duration of postoperative hospitalization was six days (range 4-11 day) and the duration of drainage was seven days (range 5-10 day). Operative complications during lymphadenectomy included one case (5%) with intestinal injury and one patient (5%) had deep venous thrombosis resolved by drug therapy. There was one case (5%) of wound infection and one case with bowel obstruction (5%).

Discussion

Although the relationship between the retroperitoneal spread of lymph nodes and patient prognosis has been demonstrated in several studies [14, 15], lymphadenectomy, as a routine treatment procedure in gynecological oncology, remains controversial [16-18]. Despite the vast amount of data detailing the role and extent of lymphadenectomies in published literature, there are still many questions that need to be answered. These debates are particularly important for unilateral tumors apparently confined to the ovaries. Questions regarding lymphadenectomies include: the limits of lymphadenectomies for these tumors, the sufficiency of performing a unilateral pelvic lymphadenectomy, the need to perform a para-aortic lymphadenectomy for patients, and the role of surgical staging in these patients. These questions are particularly important if one also considers the morbidity of lymphadenectomy and staging laparotomy.

There are a limited number of published reports evaluating the role of lymphadenectomies in early-staged OCs [14, 19-26]. Most previous studies are of a retrospective nature. From these studies, lymphatic metastasis is thought to be present in about 4-27% of early-staged patients [14, 25-31]. In this study, there were eight patients (40%) with lymph node involvement. One of the eight lymph node metastasis was solely in para-aortic node, four lymph nodes metastasis was in ipsilateral pelvic lymph node, and three patients (15%) had both positive-pelvic and aortic nodes.

Para-aortic node metastasis was found in 32-78% of the patients with pelvic node involvement [30-31]. In this study, para-aortic lymph node involvement were significantly higher among patients with positive pelvic LN involvement (42.9%) than among patients with negative pelvic LN involvement (7.6%) (p = 0.02). Thus, lymph node assessment should include both the para-aortic and pelvic lymph nodes in agreement with previous published series [6, 7, 30, 32].

Tumor grades were not reported homogeneously in all reports. Among the reported cases, majority of the lymphatic metastasis was seen in poor grade (grade 3) tumors or in unfavorable tumor histology (transitional, clear cell etc.) [14]. In the present report, positive lymph node involvement was significantly higher among patients with poorly differentiated tumors grade (grade 3) (62.5%) (p = 0.02). However, one patient with lymphatic metastasis had well-differentiated (grade 1) tumor.

The present report prospectively shows that systematic lymphadenectomy including para-aortic lymph nodes could be carried out with an acceptable morbidity and no mortality, even in clinical Stage I and well differentiated OC.

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