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Short Term Outcome of Para-Aortic Lymphadenectomy in Cases of Ovarian Cancer

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ABSTRACT

Background: This study Assess the frequency and nature of intraoperative and postoperative complications as well as short term outcomes in ovarian cancer patients treated with open surgery including para-aortic lymph node dissection (PALND). Methods: This descriptive cross-sectional study enrolled 36 patients underwent PALND up to the renal vessels as a part of open surgery for suspected early and advanced stages of ovarian cancer in Obstetrics and Gynecology Department, Zagazig University Hospitals, Egypt, during the period from August 2015 to November 2017. Results: In this study, the duration of PALND itself is more or less than one hour (mean 66.1±13.7 and range 45- 80 m) and the median volume of blood loss was (105 ml). 8 patients (22.2%) received intra and postoperative blood transfusion, the range of hospital stay for all patients was (7-14) days. the rate of postoperative ICU admission was (16.6%). There were no postsurgical treatment-related deaths. The most frequent postoperative complications were ileus (8.3%), LL lymphatic edema (8.3%) and major wound healing complications (11.1%). Conclusion: ovarian cancer patients may safely undergo comprehensive staging involving PALND in open surgeries without significant perioperative morbidity, if provided by trained Gynae-oncologists.

Keywords: Lymphadenectomy; ovarian cancer; treatment complications.

INTRODUCTION

Ovarian cancer (OC) is the seventh cause of cancer death worldwide, and the sixth most common cancer in women[1]. Metastasis to the Para-aortic lymph nodes (PALN) is the primary route of lymphatic dissemination in ovarian cancer, and the high PALN above the inferior mesenteric artery (IMA) is a frequently involved site[2] . Nodal positivity cannot be diagnosed reliably either with imaging or by intraoperative palpation[3], and thus, the best method available for the detection of nodal involvement is lymph node dissection (LND) with histopathological examination[4] . It has also been suggested that nodal metastases may be less sensitive to systemic chemotherapy, and thus lymphadenectomy in patients with nodal metastasis is therapeutic[5] . Pelvic and para-aortic LND is an integral part of ovarian cancer staging [6] . The primary purpose of LND in early-stage disease is for staging and to guide subsequent treatment. However, the primary purpose in late-stage disease is to achieve optimal debulking[7]. Also, it has been shown that lymphadenectomy in ovarian cancer patients has been associated with greater overall 5-year survival in both early and advanced stage disease [8] . In general, LND is a feasible and well-tolerated surgical

technique[9].However; systematic lymphadenectomy is technically difficult and may be associated with significant morbidity. Morbidity is particularly related to complications that may occur during or after surgery and may induce a longer hospitalization and delay treatment [10]. Due to the risk of complications related to this procedure, the routine performance of lymphadenectomy in ovarian cancer patients is still the subject of controversy [11]. The aim of this study was to evaluate the performance of the procedure of Para-aortic LND through laparotomy in management of patients with ovarian carcinoma.

MATERIALS AND METHODS

This is a descriptive cross-sectional study included 36 patients underwent PALND as a part of surgery for early and advanced stages of ovarian cancer during the period from August 2015 to November 2017 at the Obstetrics and Gynecology Department, faculty of medicine, Zagazig University Hospitals. Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Inclusion criteria included: 1. Patients undergoing staging surgery for suspected apparent early-stage ovarian cancer, 2. Patients undergoing Primary or interval debulking surgery for suspected advanced stage ovarian cancer, 3. Patients were candidate for major surgery, 4. Eastern Cooperative Oncology Group (ECOG) performance status (0-2). Exclusion criteria included: 1. Patients with associated malignancies, 2. History of previous surgically and radiologically treated abdomino-pelvic malignancy, 3.BMI >35, 4. Histological diagnosis other than invasive epithelial ovarian cancer (EOC). As the research is technically difficult and carry risks to the patients and to ensure the quality and the standard of the surgical procedures provided to our patients, surgeries were performed by one of the surgeons in the specialized gyne- oncology team. Cases diagnosed as unresectable advanced disease after exploration and Cases with advanced ovarian cancer and had residual tumor after cytoreduction, were withdrawn from the study. All patients underwent exploratory laparotomy with a midline vertical incision extending from the symphysis pubis to just above the umbilicus or the xiphisternum.

Lymphadenectomy was done after cytology, completion of total abdominal hysterectomy, bilateral salpingoopherectomy and omentectomy. The PALND included; dissection of the lymphatics from the common iliac vessels up to the level of left renal vein crossing the aorta to drain into the inferior vena cava (IVC) and laterally to the psoas muscle and the ureters. LND was performed after exposure of the retroperitoneal space starting caudally from the iliac vessels then heading cranially removing all the fibro- fatty tissue with the lymph nodes till skeletonization of the vessels. We used either cold scissors or electrocautery during LND. All specimens removed were marked and sent for histopathological examination for confirmation of diagnosis, grading, and lymph node affection. Evaluation of perioperative parameters were identified as total operative time, PALND time, the total operative blood loss, blood loss related to PALND, intra and postoperative blood transfusion, ICU admission, Period of postoperative ileus and postoperative hospital stay. LND-related perioperative morbidities were identified as bowel/ bladder injury, ureteric injury, vascular injury, hemorrhage, relaparotomy, deep venous thrombosis (DVT), pulmonary embolism, lower limbs lymphedema, symptomatic lymphocele, fistula and wound healing problems.

statistical analysis:

The statistical software SPSS version 23 (SPSS Inc., Chicago, IL, USA) was used. Data was represented in tables and graphs as mean + standard deviation, median and range for quantitative variables and as number and percentage for qualitative variables.

RESULTS

Initially, 42 Patients underwent surgery for suspected early and advanced stages of ovarian cancer were included in this study. 36 patients underwent PALND as a part of surgery and 6 cases were withdrawn from the results (PALND was omitted). 11 patients (30.6%) of the studied group were premenopausal, 25 patients (69.4%) were postmenopausal. The most frequent presenting symptoms were gastro-intestinal symptoms and abdominal distention (77.8% of cases). Basic patients' characteristics are demonstrated in Table (1). After surgical evaluation, serous adenocarcinoma was the most common histopathological type of epithelial ovarian carcinoma. Most of the patients (58.3%) in the present study had moderately differentiated tumor (G2). The range of retrieved RT & LT pelvic lymph nodes was (9-17) with median (11) nodes, the range of retrieved PA lymph nodes was (5-11) with median (8) nodes. One patient (12.5%) of 8 patients with apparent early stage ovarian cancer was upstaged to advanced stage after surgical staging which revealed pelvic and PA nodal metastasis. Nine patients (32.1%) of 28 patients with advanced stage ovarian cancer had pelvic and PA nodal metastasis, 4 patients (14.3%) with only positive pelvic nodes, 2 patients (7.1%) with only positive PA nodes and three patients (10.7%) had both pelvic and PA nodal metastasis. tumor characteristics are demonstrated in Table (2). In the present study, pelvic LND and PALND were performed to all patients (100% of cases), in the present study as shown in Table (3), 6 Patients were subjected to formal surgical staging. 2 patients were enrolled for fertility sparing surgery. 5 Patients were subjected to primary debulking surgery (PDS) followed by adjuvant chemotherapy. 23 Patients were subjected to neoadjuvant chemotherapy then interval debulking surgery (IDS) followed by adjuvant chemotherapy. The whole operation time from skin incision to skin closure was within a range (120-230 minutes) and the range of whole blood loss was 180-600 ml. The mean time of PALND was approximately 65 min, and the median volume of blood loss associated with PALND was approximately 105 ml. Table (3) shows that 8 patients (22.2%) of cases received intra and post-operative blood transfusion, the range of hospital stay for all patients was (7-14 days). Only 6 patients (16.6%) were admitted to ICU. there were no treatment-related deaths. Neither bowel, bladder injury nor hemorrhage had occurred during surgery. One patient (2.7% of cases) had ureteric injury and three patients (8.3%) had vascular injury during surgery. Three patients (8.3%) had lower limb lymphatic edema, three patients (8.3%) had paralytic ileus and 4 patients (11.1%) had postoperative wound infection. No patient had deep venous thrombosis (DVT), pulmonary embolism, fistula or symptomatic lymphocele

Table (1): Descriptive analysis of the patients enrolled in the study.

No. of Patients (36)			
Age (y), Mean ±SD		**48.9±11.9**	
	Menopausal state, No. (%)		
	Premenopausal	11	(30.6%)
Postmeopausal		25	(69.4%)
	Parity, No. (%)		
	nulli –para	2	(5.6%)
multi-para		34	(94.4%)
	ECOG performance status No. (%)		
	0	4	(11.1%)
1		23	(63.8%)
2		9	(25%)
Presenting symptoms No. (%)			
Asymptomatic (accidentally discovered)		8	(22.2%)
Pain (abdominal- pelvic-back)		18	(50%)
Abdominal mass		23	(63.9%)
GIT symptoms (distention –bloating)		28	(77.8%)
Urinary		4	(11.1%)
Weight loss		8	(22.2%)
Fatigue		8	(22.2%)
Preoperative CT findings No. (%)			
Complex pelvi-abd. Mass		28	(77.8%)
Ascites		28	(77.8%)
Omental involvement		25	(69.4%)
Mesenteric involvement		9	(25%)
Peritoneal carcinomatsis		11	(30.6%)
Liver involvement		3	(8.3%)
Bowel involvement		2	(5.5%)
Lymphadenopathy		7	(19.4%)
Pleural effusion		5	(13.8%)

Table (2): Tumor characteristics**.**

	No. of Patients (36)		
FIGO stage, No. (%)			
Stage I-II		7	(19.4%)
Stage III-IV		29	(80.6%)
Histo-pathological type, No. (%)			
Serous		23	(63.9%)
Mucinous		6	(16.7%)
Clear		3	(8.3%)
Endometrial		1	(2.7%)
Others (undifferentiated anaplastic)		3	(8.3%)
	Histological grade, No. (%)		
	G3	14	(38.9%)
G2		21	(58.3%)
G1		1	(2.8%)
Prevalence of pelvic and para-aortic nodal metastasis. No. (%)			
	No metastasis	26	(72.2%)
	With metastasis	10	(27.7%)
	Pelvic	4	(11.1%)
	Para-Aortic (PA)	2	(5.5%)
	Pelvic & PA	4	(11.1%)
	No. of iliac LN harvested, median (IQR)	11	(9-17)
	No. of para-aortic LN harvested, median (IQR)	8	(5-11)

Table (3): Treatment surgical regimen**.**

	No. of patients (36)		
	Classes of surgery, No. (%)		
	Fertility preservation surgery	2	(5.5%)
	Formal Surgical staging	6	(16.7%)
	PDS	5	(13.9%)
	IDS	23	(63.9%)
	Surgical procedures, No. (%)		
	TAH	34	(94.4%)
	BSO	34	(94.4%)
	Infarcolic omentectomy	32	(.88.9%)
	Total omentectomy	4	(11.1%)
	Unilateral adnexectomy	2	(5.6%)
	Appendectomy	10	(27.8%)
	Bowel resection	3	(8.3%)
	Partial Peritoneal resection	5	(13.8%)
	Pelvic LND	36	(100%)
	Para-aortic LND	36	(100%)

	peri-operative parameters		
	total Operative time in minutes, Mean ±SD, range	183.7±40.7	(120-230)
	PALND operative time in minutes, Mean ±SD, range	66.1±13.7	(45-80)
	Total operative blood loss (ml), median (IQR)	434	(180-600)
	PALND associated blood loss (ml), median(IQR)	105	(80-190)
	Blood transfusion, No. (%)	8	(22.2%)
	ICUadmission, No.(%)	6	(16.6%)
	Hospital stay (d), Mean +_SD, range	7.8±4.	(4-14)
	Peri-operative morbidities and mortality, No. (%)		
	Treatment related deaths	0	(0%)
	Bowel injury	0	(0%)
	Bladder injury	0	(0%)
	Ureteric injury	1	(2.7%)
	Vascular injury	3	(8.3%)
	DVT	0	(0%)
	Pulmonary embolism	0	(0%)
	Fistula	0	(0%)
	Ileus	3	(8.3%)
	Symptomatic Lymphocele	0	(0%)
	Wound infection	4	(11.1%)
	LL lymphedema	3	(8.3%)
	Intraoperative Hge.	0	(0%)

DISCUSSION

Assessment of the regional lymph node status in early stage ovarian cancer patients is the mainstay of accurate clinical disease stage assessment and appropriate treatment decision-making as lymphatic spread of early stage ovarian cancer upstages the patient to FIGO stage III, making them appropriate candidates for adjuvant chemotherapy after surgery. Also, when the initial surgical staging is correct, patients with low-risk disease may be spared from undergoing cytotoxic chemotherapy[12] . The therapeutic role of lymphadenectomy in patients with advanced ovarian cancer is the subject of various clinical studies. Du Bois et al showed that in patients with no residual disease, lymphadenectomy increased median survival. For patients with small residual disease, lymphadenectomy made no significant difference[13] . More recently in 2016, a meta-analysis of 14 studies including 3488 patients confirmed improved overall survival rate in patients undergoing systematic lymphadenectomy even with residual tumors attaining 2 cm[14] . In the presen study and based on the above data, it was the policy of the surgical team to perform routin extensive LND in all advanced cases only when optimal cytoreductive surgery was achieved and to be omitted in patients with residual disease. After publication of the results of the LION study after completion of cases included in this study, we started to discuss practice shift to resection of bulky nodes after macroscopic complete

tumor resection in patients with advanced ovarian cancer. In the present study LND included both the pelvic and aortic lymph nodes up to level of renal vessels. In this study, one patient (12.5%) of 8 patients with apparent early stage ovarian cancer was upstaged to advanced stage after surgical staging which revealed pelvic and PA nodal metastasis. Nine patients (32.1%) of 28 patients with advanced stage ovarian cancer had pelvic and para-aortic nodal metastasis, 4 patients (14.3%) with only positive pelvic nodes, 2 patients (7.1%) with only positive paraaortic nodes and three patients (10.7%) had both pelvic and para-aortic nodal metastasis. Due to the risk of complications related to this procedure, the routine performance of lymphadenectomy in ovarian cancer patients is still the subject of controversy. Therefore, the present study aimed to evaluate the frequency and nature of intraoperative and postoperative complications in ovarian cancer patients treated with surgery inclding para-aortic LND.

Intraoperative complications. Although we have started only in the recent years to practice this way of para-aortic nodal assessment in form of extensive sampling, only few intraoperative complications occurred in direct relation to the paraaortic lymphadenectomy. The results of the present study showed that the most frequent intraoperative complications were vascular injury in three patients and urinary system injury in 1 patient. The incidence of major organ and vessel injury related to lymphadenectomy is low [15] . in the present study and during the very first procedure performed, one patient had IVC small tear immediately repaired by 5/0 vicryl and two patients had inferior mesenteric vascular injury immediately clamped and ligated. In the present study one patient had ureteric injury happened during left para-aortic LND, diagnosed intraoperative and immediately repaired using 5/0 polyglactin sutures over a stent, then removed by a cystoscope 2 weeks postoperatively. All iatrogenic injuries were controlled by the surgical team with no assistance from other surgeons from other related disciplines except for one case of IVC injury when a vascular surgeon joined for consultation. In the present study the duration of para-aortic lymphadenectomy itself is more or less than one hour (mean 66.1±13.7 and range 45-80 m) and the median volume of blood loss was (105 ml). In a study published in 2016 Comparing the morbidity between patients in the Inframesenteric para aortic dissection (IMLND) and infrarenal paraaortic dissection (IR-LND) groups, the median volume of blood loss in IR-LND was 100 ml [16] . In present study, 8 patients (22.2%) received intra and postoperative blood transfusion, the range of hospital stay for all patients was (7-14) days, the rate of postoperative ICU admission was (16.6%).

Postoperative complications

There were no postsurgical treatment-related deaths. In the present study, the most frequent postoperative complications were ileus (8.3%), LL lymphatic edema (8.3%) and major wound healing complica-tions (11.1%). These complications resolved with appropriate manage-ment within 2 weeks. Most of our patients were able to restart their chemotherapy within 3 weeks of surgery and without a higher risk of hematologic or infectious complications. No patient had hemorrhage, relaparotomy, deep venous thrombosis (DVT), pulmonary embolism, fistula or symptomatic lymphocele. The incidence of postoperative ileus was 8.3%, but almost all the patients were cured within seven days without surgical treatment. Lymphedema is the most common complication of pelvic and paraaortic lymphadenectomy, reported in 1.5 to 28 percent of patients. This is likely lower than the actual incidence, since this complication is likely to be underreported in retrospective reports[17] . In the present study 3 patients (8.3%) had lower limb lymphedema and presentation was being quite variable. Some patients only notice some increased ankle swelling, others noticed edema extended from the feet to the abdominal wall.

Another potential complication related to nodal dissection is lymphocele. In a prospective study of 800 women who underwent solo pelvic and/ or paraaortic lymphadenectomy for gynecologic cancer, the rate of lymphocele was 20 percent, and the rate of symptomatic lymphocele was 6 percent[18] . In the present study no case presented with symptomatic lymphocele, asymptomatic lymphocele may pass unnoticed as routine imaging postoperative not done.

This study showed that ovarian cancer patients may safely undergo comprehensive staging involving extensive para-aortic lymph node dissection in open surgeries without significant perioperative morbidity, if provided by trained gynaeoncologists. Notwithstanding, systematic lymphadenectomy is associated with an increased operating time, blood loss, blood transfusions, hospital stay and a higher incidence of postoperative complications. Such data are in keeping with the results of the all randomised studies in early or advanced ovarian cancer. In addition, morbidity associated with systematic lymphadenectomy through laparotomy in ovarian cancer patients should not be considered the factor that pushes the surgeon to omit lymph node dissection or shift to lymph node sampling. Yet, the decision to proceed or not for a systematic lymphadenectomy should be solely based on oncological basis.

Finally, the main limitations of this study were the small sample size, absence of matched comparative group treated without lymphadenectomy, the short period of follow up which is not enough to comment on patient survival and the total lymph node count retrieved was relatively small. This may result in the underestimation of the incidence of nodal metastasis in our study or underestimation of perioperative outcome. Authors recommend the following 1- Surgical treatment of ovarian cancer, including para-aortic lymphadenectomy, should be performed only at specialized institutions. 2- Further large scaled comparative studies with longer follow up period are recommended to evaluate the morbidity associated with lymphadenectomy in management of ovarian cancer.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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