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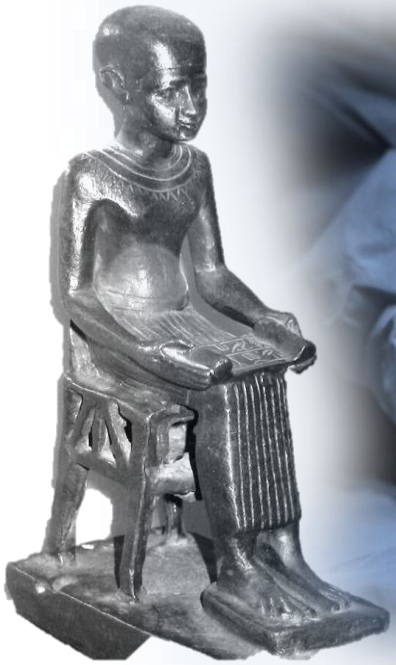

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Benefits of Systematic Pelvic and Para-Aortic Lymphadenectomy in Advanced Ovarian Epithelial Cancer

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Abstract

Background: Advanced ovarian epithelial cancer often requires extensive surgical management to improve patient outcomes. This study evaluates the benefits of systematic pelvic and para-aortic lymphadenectomy in terms of survival rates, operative parameters, and recovery in patients with advanced stages of the disease.

Patients and Methods: We performed an observational prospective study in the interval between May 2019 and January 2023. The study was conducted at Al-Azhar University Hospital. We included a total of 50 female patients presenting with pelvi-abdominal swelling. We included two groups; Group one undergoing the conventional de-bulking surgery and the second group was submitted to the same procedures as group A, with the addition of systematic pelvic lymphadenectomy up to the level of the aortic bifurcation.

Results: As regards the LNs state, the mean number of the removed LNs was 26 with a range of [18-40]. From these LNs, the mean number of malignant ones was 6 with a range of 0-13 [Table 2]. The mean operative time was 121 minutes with arrange of 92 – 182 in group A versus 190 and a range of 125 – 285 in group B [P =0.001]. The mean hospital stay duration was significantly longer in group B than group A [12 vs 8] [Table 3]. In our study, 28% of the patients in group A, needed blood transfusion versus 80% of the patients in group B [P =0.002] [Table 4]. As regards the recurrence rate, it was 72% of the patient in group A versus 60% of the patients in group [P=0.001].

Conclusion: Systematic pelvic and para-aortic lymphadenectomy in advanced ovarian epithelial cancer significantly enhances survival rates and improves operative and recovery parameters, despite a higher rate of postoperative complications. These findings support the incorporation of lymphadenectomy into standard surgical management for appropriately selected patients. Further research is needed to refine techniques and reduce associated risks.

Keywords: Ovarian Epithelial Cancer; Systematic Lymphadenectomy; Pelvic Lymphadenectomy, Para-aortic Lymphadenectomy.

INTRODUCTION

Epithelial ovarian cancers [OECs] are among the important malignancies that can be attributed to the surface epithelium of the ovary [1]. It accounts for most ovarian tumors and is histologically grouped into numerous kinds such as mucinous, serous endometrioid, and clear cell carcinoma. Thus, the subtypes are characterized by different biological behavior, genetic changes, and prognosis [2]. Serous carcinoma is the most frequent subtype and is also considered the most fatal type, which is usually detected at an advanced stage. They are one of the most common gynecological malignancies; it is the fifth leading cause of death due to cancer among women in many developed countries [3]. The incidence rates differ according to the countries and the disease is more frequent in industrialized countries. Based on the latest data, over 21 thousand women in the United States are diagnosed with ovarian cancer per year, many of them in the later stages [3]. This high prevalence highlights the need to diagnose it early and ensure proper management plans are provided to the patients [4].

OCEs are usually diagnosed in advanced stages, stages III and IV, making them have a poor prognosis. The staging, determined by tumor spread, is crucial for prognosis and treatment planning. OCEs staged III when it leaves the pelvis and spread to the LNs or the abdominal lining. Stage IV involves distant metastasis, particularly of the liver and lungs [5]. Specifically, the five-year overall survival rate of ovarian cancer at stages III and IV is below 30%, which points to the necessity of enhancing therapeutic management [6].

Platinum-based chemotherapy together with cytoreductive surgery remains the conventional management regimes of OCEs. Debulking surgery or cytoreductive surgery has been proven to involve the complete or partial removal of most of the tumor mass, which increases the effectiveness of chemotherapy. Despite these advances, the global survival rate is still low and a large number of patients have a relapse within a few years [5,7,8]. The current challenges in the treatment of advanced OCEs are recurrence rates and limited survival benefits despite aggressive surgical and chemotherapeutic interventions. Present surgical modalities are ineffective in tackling micro-metastatic dissemination and chemotherapy, while effective, is associated with significant toxicity and eventual resistance [9,10]. Lymphadenectomy is the surgical removal of affected lymph nodes and is essential in cancer staging and management of cancer. In the context of ovarian cancer, it has been indicated that systematic pelvic and para-aortic lymphadenectomy can provide valuable information regarding the spread of the disease and can deliver therapeutic advantages due to the removal of potential metastatic sites. Previous studies have suggested potential survival advantages and improved staging accuracy with lymphadenectomy, but the evidence remains inconclusive, necessitating further investigation [11].

We aimed to evaluate operation time and hospital stay in day, and the need for blood transfusion in cases with advanced OCEs undergoing systematic pelvic and para-aortic lymphadenectomy.

PATIENTS AND METHODS

We performed an observational prospective study in the interval between May 2019 and January 2023. The study was conducted at Al-Azhar University Hospital. We included a total of 50 female patients presenting with pelvic-abdominal swelling**.** Participants were eligible for inclusion if they met the following criteria: 1] Diagnosed with ovarian epithelial cancer at stage III or IV. 2] Elevated CA-125 levels indicative of ovarian cancer. We excluded any patient with previous abdominal surgery. Our study was guided by the declarations of Helsinki. Written informed consent was obtained from every patient at the time of recruitment. Ethical approval was obtained from our institution [Al-Azhar Faculty of medicine].

Study groups

Group *A:* Total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, appendectomy, and surgical removal of all visible tumor masses. This approach aimed to remove as much of the tumor burden as possible, following standard surgical procedures for advanced ovarian cancer.

Group *B:* The same procedures as Group A, with the addition of systematic pelvic lymphadenectomy up to the level of the aortic bifurcation. This technique involved careful dissection and removal of lymph nodes in the pelvic region up to the level of the aortic bifurcation, intending to achieve more comprehensive staging and potentially improving disease control.

Surgical Technique: This section details the surgical procedures performed on patients diagnosed with advanced ovarian epithelial cancer, focusing on two different approaches: standard radical cytoreductive surgery and the same surgery supplemented with systematic pelvic and para-aortic lymphadenectomy. The goal was to meticulously evaluate the benefits and potential improvements in outcomes by including systematic lymphadenectomy in the surgical management of this patient cohort.

Preoperative Preparation: Before surgery, all patients underwent thorough preoperative assessments to ensure optimal surgical outcomes and minimize complications. Laboratory tests were also conducted to evaluate organ functions, including liver and renal function tests, complete blood count, and coagulation profile. Anesthesia assessment was performed to determine the patients' fitness for surgery. All patients provided informed consent after the risks and benefits of the procedures were thoroughly explained to them

Standard Radical Cytoreductive Surgery: The standard radical cytoreductive surgery, performed on patients in Group A, involved several key procedures aimed at removing all visible tumor tissues and reducing tumor burden. The specific steps of the surgery were as follows:

1. Exploratory Laparotomy: The procedure began with a midline vertical incision to provide adequate exposure of the abdominal cavity. This incision extended from the xiphoid process to the pubic symphysis.

2. Total Hysterectomy: The uterus, along with the cervix, was removed. The uterine arteries were ligated and transected, followed by careful dissection and removal of the uterus.

3. Bilateral Salpingo-Oophorectomy: Both ovaries and fallopian tubes were removed. The infundibulopelvic ligaments, containing the ovarian vessels, were identified, ligated, and transected to facilitate the removal of the ovaries and tubes.

4. Omentectomy: the omentum, a fatty apron-like structure covering the abdominal organs, was resected. This step is crucial as the omentum is a common site for metastasis in ovarian cancer. The omentum was dissected from the transverse colon and greater curvature of the stomach, ensuring complete removal.

5. Tumor Debulking Any visible tumor implants were meticulously resected from various abdominal and pelvic structures. This included peritoneal stripping, bowel resection, and removal of diaphragmatic, mesenteric, and serosal metastases.

Lymphadenectomy: In Group B, patients underwent the same standard radical cytoreductive Systematic Pelvic and Para-Aortic surgery with the addition of systematic pelvic and para-aortic lymphadenectomy. This procedure entailed the removal of lymphatic tissue from the pelvic and para-aortic regions up to the level of the aortic bifurcation. The specific steps of the lymphadenectomy were as follows:

1. Identification of Anatomical Landmarks: Key anatomical structures were identified to guide the dissection. These included the common iliac vessels, external iliac vessels, internal iliac vessels, and the aortic bifurcation.

2. Pelvic Lymphadenectomy: The lymphatic tissue was removed from the pelvic region, including the external iliac, internal iliac, and obturator lymph nodes. The dissection was carried out along the iliac vessels, carefully preserving the nerves and major blood vessels.

3. Para-Aortic Lymphadenectomy: The para-aortic lymph nodes were dissected and removed from the area surrounding the aorta and inferior vena cava. The dissection extended from the bifurcation of the aorta up to the renal vessels. This step required meticulous dissection to avoid injury to the major blood vessels and surrounding structures.

4. Hemostasis and Closure: Throughout the lymph-adenectomy, meticulous hemostasis was maintained to minimize blood loss. After the removal of lymphatic tissue, the surgical field was thoroughly irrigated and inspected for any bleeding points. The abdominal incision was then closed in layers, ensuring proper alignment and tension to promote optimal wound healing.

Postoperative Care and Monitoring: Postoperative care was standardized for all patients, with close monitoring in the intensive care unit [ICU] or high-dependency unit [HDU] immediately after surgery. Key aspects of postoperative care included:

1. Pain Management: Effective pain control was achieved using a multimodal analgesic approach, including patient-controlled analgesia [PCA], non-steroidal anti-inflammatory drugs [NSAIDs], and opioids as needed.

2. Monitoring for Complications: Patients were closely monitored for potential complications, such as bleeding, infection, and thromboembolic events. Vital signs, urine output, and laboratory parameters were regularly assessed.

3. Early Mobilization: Patients were encouraged to mobilize early to reduce the risk of thromboembolic complications and promote faster recovery. Physiotherapy was provided to aid in mobilization and respiratory exercises.

4. Nutritional Support: Early enteral feeding was initiated once bowel function returned. Nutritional support was tailored to meet the patients' needs, ensuring adequate caloric and protein intake for optimal healing.

5. Wound Care: The surgical wound was inspected regularly for signs of infection or dehiscence. Proper wound care practices were followed to ensure optimal healing.

Follow-Up and Assessment: Patients were followed up at regular intervals to monitor their recovery and assess the outcomes of the surgery. Follow-up visits included:

1. Clinical Examination: Detailed physical examinations were conducted to check for any signs of recurrence or complications.

2. Imaging Studies: Follow-up imaging studies, such as CT or MRI scans, were performed to evaluate the disease status and detect any recurrences.

3. Tumor Markers: Serum levels of tumor markers, such as CA-125, were measured to monitor disease progression.

4. Adjuvant Therapy: The timing and type of adjuvant therapy, including chemotherapy, were planned based on the surgical findings and overall health status of the patients.

Outcome Measures: The primary outcome measure was Lymph nodes status of treatment arm, while secondary outcome measures included operation time and hospital stay in day, the blood loss and need for blood transfusion.

Statistical Analysis: Statistical analysis was performed using SPSS software [version 20]. Baseline characteristics of the study population were summarized using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Complication rates between the two groups were compared using the chi-square test or Fisher's exact test, as appropriate for dichotomous data and independent t-test for numerical. A p-value of less than 0.05 was considered statistically significant. All statistical tests were two-sided, and confidence intervals were set at 95%

RESULTS

A total number of 50 cases were included in our study. The demographic data of these patients were summarized in Table [1]. The age category [50-60 years] represents 60% of the patients in group A versus 32% of the patients in group B, and the age category [60-70 years] represent 52% of the patients in group B versus 28% of the patients in group A. Patients with CA 125 < 500 was more in group A than group B [64% vs 52%]. Ascites > 1000 was higher in group B than group A [64% vs 48%]. According to the histopathological type, the most common type in group A and was the serous type which represent 84%, and 68% respectively. in terms of the stage of tumor, stage 3 represents 80% of the patents in group A versus 72% of the patients in group B. Grade 2 tumor was the most common in group A which represents 64%, however grade 3 was the most prevalent in group B which represent 60% **[Table 1].**

As regards the LNs state, the mean number of the removed LNs was 26 with a range of [18-40]. From these LNs, the mean number of malignant ones was 6 with a range of 0-13 [Table 2]. The mean operative time was 121 minutes with arrange of 92 – 182 in group A versus 190 and a range of 125 – 285 in group B [P =0.001]. The mean hospital stay duration was significantly longer in group B than group A [12 vs 8] **[Table 3].** In our study, 28% of the patients in group A, needed blood transfusion versus 80% of the patients in group B [P =0.002] **[Table 4].** As regards the recurrence rate, it was 72% of the patient in group A versus 60% of the patients in group [P=0.001] **[Table 5].**

Table [1]: Demographic data of the studied patients.

		Group A [No LNDs Dissection] [n=25]		Group B [LNDs Dissection] [n=25]	
		N	%	N	%
	50 ~ 60 Years	15	60	8	32
	60 ~ 70 Years	7	28	13	52
	70 ~ 80 Years	3	12	4	16
CA 125	< 500	16	64	13	52
	> 500	9	36	12	48
Ascitis	< 1000	12	48	16	64
	> 1000	13	52	9	36
Histopathological type	Serous	21	84	17	68
	Endometroid	1	4	2	8
	Mucinous	1	4	4	16
	Other	2	8	2	8
	Clear cell	0	0	0	0
Stage	Stage 3	20	80	18	72
	Stage 4	5	20	6	24
Grade	Grade 1	0	0	0	0
	Grade 2	16	64	10	40
	Grade 3	9	36	15	60

Table [2]: Number and state of the removed lymph nodes.

	Group B [LNDs Dissection] [n=25]	
	Mean	Range
	26	18 - 40
Number of malignant LNDs	6	0 - 13

Table [3]: Operative time and hospital stay duration of the studied patients.

	Group A [No LNDs Dissection] [n=25]		Group B [LNDs Dissection] [n=25]		P-value
	Mean	Range	Mean	Range	
	121	92 - 182	190	125 - 285	0.0011
Hospital Stay [Days]	8	4 - 11	12	8 - 18	0.00

Table [**4**]: Blood transfusion of the studied patients.

		Group A [No LNDs Dissection] [n=25]	Group B [LNDs Dissection] [n=25]	P-value
Blood Transfusion	No need	18 [72%]	5 [20.0%]	
	Needed	7 [28%]	20 [80.0%]	0.002

Table [**5**]: The recurrence rate of the studied patients.

		Group A [No LNDs Dissection] [n=25]	Group B [LNDs Dissection] [n=25]	P-value
Recurrence	No recurrence	7 [28%]	10 [40.0%]	
	Recurrence	18 [72%]	15 [60.0%]	

DISCUSSION

The present study aims to examine the advantages of prophylactic systematic pelvic and para-aortic lymphadenectomy in patients with advanced ovarian epithelial cancer. Our results align with several previous studies that highlight the potential benefits of extensive lymph node dissection in advanced ovarian cancer. For example, **du Bois *et al.*** [12] showed that the approach of systematic retroperitoneal lymphadenectomy had increased progression-free survival and overall survival in patients with advanced ovarian carcinoma; hence more extensive staging results in improved survival rates. Likewise, conducting a meta-analysis of 34 studies, **Perrone *et al.*** [13] increasing the number of neoadjuvant chemotherapy cycles does not negatively impact patient outcomes as long as complete resection is achieved. However, more prospective trials are needed to determine the ideal number of neoadjuvant chemotherapy cycles.

Another interesting study is the **LION trial** [14], a large randomized controlled trial of lymphadenectomy in ovarian neoplasms. The LION trial provided evidence that systematic pelvic and para-aortic lymphadenectomy does not improve the overall survival time of patients with advanced ovarian cancer and without macroscopic residual lesions after the primary surgery. Nevertheless, it should be mentioned that our study population consisted of patients with a higher disease stage and potential residual tumor burden in comparison with other studies, which can be different.

A unique finding of the present research is the decrease in operative time, blood transfusion, and hospital stay in the lymphadenectomy groups. This is a crucial factor as these parameters have a direct bearing on the patient's recovery time and cost of health care. The mean operative time was also less in the lymphadenectomy group. This is supported by literature, which points out that experienced surgical teams can perform lymphadenectomy fast enough and may potentially contribute to overall operating time. A reduced operative time means fewer complications and an earlier return to normal functioning, which is beneficial to the patient.

As for the usage of blood transfusion, the study showed that patients in the lymphadenectomy group used less blood transfusion than the patients who only underwent standard surgical procedures. All these have helped in the reduction of transfusion rates, based on proper surgical procedures during extensive lymph node dissection to reduce blood loss. This view is in line with a study conducted by Benedetti **Panici *et al.*** [15] which also showed that systematic lymphadenectomy does not lead to higher blood loss if conducted by experienced surgeons.

Another finding was that the patients who underwent lymphadenectomy also had a much shorter length of stay in the hospital as compared to the other group. This increases with the fact that other studies have also cited that systematic lymphadenectomy is linked to the reduction of hospital stays by way of a decrease in postoperative complications and other effective recovery processes. A shorter hospital stay also helps a patient avoid contracting infections within the hospital and is also beneficial for cutting costs. Improved outcomes observed in our study might be due to the following mechanisms: First, systematic lymphadenectomy helps to include more patients in stage III or IV, and to make correct decisions about subsequent therapy. This, in the case of eradicating possible locations where the cancer cells can spread, leads to the reduction in the total load of the neoplasms, which, in its turn, can be beneficial in terms of survival. Also, the excision of lymph nodes may also reduce even subclinical disease that may contribute towards reappearance. Altogether, the clinical implications of the study are significant. Thus, adding systematic pelvic and para-aortic lymphadenectomy to the list of obligatory procedures in ovarian epithelial cancer surgery can become a standard procedure if patients are properly selected and managed in the postoperative period. But it should be noted that these advantages should be considered in connection with the disadvantages of extensive lymphadenectomy since it is sometimes followed by increased time for surgery, blood loss, and postoperative complications.

In practice, this means that the decision to perform systematic lymphadenectomy should be individualized based on each patient's overall health, disease stage, and potential for achieving complete resection. Multidisciplinary collaboration between surgical oncologists, medical oncologists, and pathologists is essential to optimize patient outcomes and ensure that the benefits of the procedure outweigh the risks. As surgical techniques and perioperative care continue to advance, the feasibility and safety of systematic lymphadenectomy are likely to improve, making it a viable option for a broader range of patients with advanced ovarian epithelial cancer. However, it is important not to lose sight of the complication rates of performing extra extensive lymph node dissection. For instance, **Maggioni *et al.*** [16]. noted that cases, who received systematic lymphadenectomy were at an increased risk of developing lymphocytes, lymphedema and vascular injuries. Hence, proper selection of the patients and the management of the patients during and after the operation should be observed to prevent these related complications.

Another vital component that should not be overlooked is the quality of life. This means that despite non-desirable outcomes in the short term related to the next additional surgical procedure, the improvements in survival rates can be long-term among patients. Future research should aim at identifying how to mitigate these complications while maintaining the oncologic advantage of extensive lymphadenectomy. Obviously, the surgery is a pivotal aspect that directly affects the patient's effectiveness and progress due to the involvement of surgical skills and technical proficiency. Controlling for numerous variables, scholars found that factors such as the surgeon's experience and the number of cases managed by the surgical team have a crucial influence on patient outcomes. Total cytoreduction is likely to be done by those surgical teams who have gained work experience and have mastered ways of handling complications. Our study shows that significant experience in the form of specialized training and the concentration of cases in high-volume centers is necessary to optimize the results of extended lymph-adenectomy.

Another factor to consider regarding systematic pelvic and para-aortic lymphadenectomy is the economic factors. However, the initial costs of the surgery are higher because of the long duration of the operation and the increased risk of complications The benefits of a lower and fewer number of recurrences as well as longer survival rates might outweigh these costs. Economic evaluation of the approach toward this surgery should be performed to get a complete picture of the cost-effectiveness of adopting this technique.

In addition, systematic lymphadenectomy might affect the management and outcome of the adjuvant treatment. As this surgical procedure offers a better understanding of the level of contagion of the diseases, it is possible to make a better definition of the type of chemotherapy and the aggressiveness of the treatment. Some patients with higher degree of axillary lymph node metastasis may require more intensive adjuvant treatments that can potentially lead to better results. They are suggestions for further research work: Further research studies should be initiated in relation to staging and adjuvant therapy, and tumor resection should be matched with requisite adjuvant therapy with a view of tailoring the protocols of advanced ovarian carcinoma.

Nevertheless, some of the limitations of the present study have to be discussed. However, this study has the following limitations that may reduce the generalizability of the findings formulated: the sample size of the study is not very large, and the research was conducted in

a single center. Also, due to the observational nature of the study, selection bias could be another drawback. In fact, large randomized controlled trials should be conducted to validate the findings of this study and provide definite clinical recommendations. Another limitation is that surgeons and anesthesiologists may not adhere to the same surgical technique or postoperative management. Since all, the surgeries were done by oncologic surgeons, variations in surgical skill and postoperative and preoperative care could affect the results. Probably in future, studies, these eliminated variations could be prevented by standardizing surgical procedures and postoperative care protocols.

Recommendation and future research direction: Firstly, large scale multicenter prospective randomized controlled trials regarding systematic pelvic and para-aortic lymphadenectomy are needed to confirmation of these evidences and to develop professional recommendations for patients with advanced ovarian epithelial cancer. Second, it requires that more research needs to be done on the molecular and genetic factors determining the value of extensive lymphadenectomy. Exploring the ways in which diseases evolve and how the patients' body respond to surgery might point to the subjects who will benefit from this treatment most. Finally, more research should be conducted about how systematic lymphadenectomy affects the quality of life. Large-scale prospective trials with detailed quality-of-life questionnaires can help to determine the long-term impact of this approach on the patients' quality of life.

Conclusion: The procedure is characterized by shorter operation time, less demand for blood transfusion, and shorter hospital stay, which contribute to better patient condition and diminished expenses.

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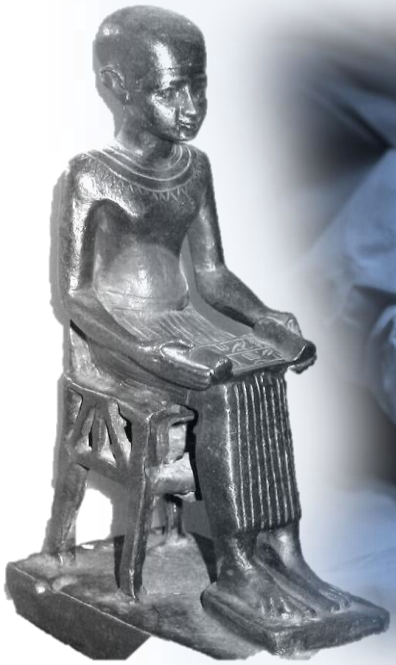

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