Journal of Carcinogenesis
Covering Genesis to Therapeutics

Journal of Carcinogenesis, ISSN: 1477-3163
2025; Vol 24: Issue 3, https://carcinogenesis.com/

Indicators of systematic lymphadenectomy as a part of surgical management in ovarian carcinoma patients

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ABSTRACT

Objective: To identify clinical and pathological indicators that reliably predict lymph node metastasis in patients with ovarian carcinoma, thereby guiding the selective and rational application of systematic pelvic and para-aortic lymphadenectomy as part of their surgical management. **Patients and Methods**: A total of 150 consecutive patients with epithelial ovarian carcinoma who underwent primary cytoreductive surgery between January 2023 and December 2024 were included in this study. All patients underwent systematic pelvic and para-aortic lymphadenectomy, regardless of preoperative findings. Pathological examination of all the harvested lymph nodes was performed. Clinical indicators (e.g., preoperative CA-125, ascites volume, tumor size, and suspicious imaging nodes) and pathological indicators (e.g., FIGO stage, histological type, tumor grade, and omental/peritoneal metastases) were correlated with confirmed lymph node metastasis. **Results**: Lymph node metastasis was confirmed in 45% (68/150) of the patients. Significant clinical predictors included preoperative CA-125 level > 500 U/mL (OR=3.5, p=0.002), ascites > 500 mL (OR=2.8, p=0.008), and suspicious imaging nodes (OR=4.1, p<0.001). The pathological indicators strongly correlated with nodal metastasis were advanced FIGO stage (Stage III/IV: OR6.2, p<0.001), high-grade serous histology (OR=3.9, p=0.001), and gross peritoneal metastases (OR=5.5, p<0.001). Systematic lymphadenectomy led to upstaging in 20% (30/150) of the patients with no suspicious nodes on imaging. **Conclusion**: Several clinical and pathological indicators reliably predicted lymph node metastasis in ovarian carcinomas. Utilizing these indicators can help guide the selective performance of systematic lymphadenectomy, optimizing surgical staging, and personalized adjuvant treatment strategies, while potentially reducing unnecessary morbidity.

Keywords: *Ovarian carcinoma, systematic lymphadenectomy, lymph node metastasis, surgical staging, cytoreductive surgery.*

How to Cite: Ahmed Elsayed Abdelrahman, Tamer A. Abouelgreed, Ayman Abdulmohaymen, Sayed R. Abdelbary, Abd El_fattah Al Sheikh, Awad Mahmoud Awad, Yasser Mohamed Diab, Mostafa Ellaban, Ahmed Elsayed Mahmoud, Attia Mohamed Attia, Hany Abdelfatah Elhady, Wael Abdelatief Khafagy, ElSayed Ali Farag, Mariam Salah Mohamed, Walaa Mohammed Amer, Shaimaa Ali Barakat, Alrefaai Marai, Doaa Helmy Yousef, Mohamed E. Thabet, (2025) Indicators of systematic lymphadenectomy as a part of surgical management in ovarian carcinoma patients, *Journal of Carcinogenesis*, *Vol.24, No.3*, 575-582.

1. INTRODUCTION

Ovarian carcinoma remains the most lethal gynecologic malignancy, largely owing to its late presentation and aggressive biological behavior [1]. Despite advancements in chemotherapy, surgery remains the cornerstone of primary treatment, with the aim of optimal cytoreduction and accurate surgical staging. Comprehensive surgical staging for ovarian cancer typically involves total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal biopsies, and systematic pelvic and para-aortic lymphadenectomy [2]. This extensive staging procedure is crucial for determining the true extent of disease (FIGO stage) and guiding the necessity and intensity of adjuvant chemotherapy, which significantly affects the prognosis [3]. Lymph node metastasis in ovarian carcinoma is a common occurrence, even in patients with apparent early stage disease confined to the pelvis. Studies have shown that a significant proportion of patients with clinically negative lymph nodes on preoperative imaging may harbor microscopic metastases upon systematic pathological examination [4]. This phenomenon, known as "occult nodal metastasis," underscores the rationale for systematic lymphadenectomy, as it can lead to upstaging of the disease and subsequent modification of treatment plans, potentially

improving survival outcomes [5]. However, systematic pelvic and para-aortic lymphadenectomy is an invasive procedure that is associated with considerable surgical morbidity. It significantly increases operative time, intraoperative blood loss, and the risk of postoperative complications, such as lymphedema of the lower extremities, lymphocyst formation, nerve injury, and prolonged hospital stay. The potential for these complications, particularly in patients who ultimately prove to be lymph node-negative, has led to debate regarding the routine performance of systematic lymphadenectomy in all ovarian cancer patients. There is growing clinical interest in identifying reliable indicators that can accurately predict the presence of lymph node metastasis, thereby allowing for a more selective and individualized approach to lymphadenectomy [6, 7]. Identifying such predictive indicators could enable surgeons to tailor the extent of lymphadenectomy, avoiding unnecessary extensive dissection in patients at very low risk of nodal involvement, while ensuring complete staging for those who truly benefit. Various clinical factors (e.g., preoperative CA-125 levels, tumor size, presence of ascites, imaging findings of suspicious nodes) and pathological characteristics (e.g., primary tumor histological type, grade, depth of invasion, presence of omental or peritoneal metastases) have been investigated as potential predictors of nodal involvement [8,9]. However, their individual and combined predictive values require further validation in diverse cohorts. This prospective observational study aimed to identify and evaluate clinical and pathological indicators that reliably predict lymph node metastasis in patients with epithelial ovarian carcinoma. By correlating these indicators with confirmed nodal involvement following systematic pelvic and para-aortic lymphadenectomy, we sought to provide evidence that can guide the selective and rational application of this extensive procedure, optimizing surgical staging, and personalized adjuvant treatment strategies while potentially reducing unnecessary morbidity in carefully selected patients.

2. PATIENTS AND METHODS

This prospective observational study was conducted at the Department of Gynecologic Oncology, Al-Azhar University Hospitals, Cairo, Egypt, over a 24-month period, from January 2023 to December 2024. The study protocol received full approval from the Institutional Review Board of Al-Azhar University, and all procedures were performed in accordance with the ethical standards of the Declaration of Helsinki. Prior to enrollment, all eligible patients provided informed, written consent. A total of 150 consecutive patients diagnosed with epithelial ovarian carcinoma who underwent primary cytoreductive surgery were enrolled. All patients were intended to undergo systematic pelvic and para-aortic lymphadenectomy as part of their comprehensive surgical staging, regardless of preoperative imaging findings regarding lymph node status. We included all female patients aged ≥18 years with histopathologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, undergoing primary cytoreductive surgery with planned systematic pelvic and para-aortic lymphadenectomy meeting the criteria of American Society of Anesthesiologists (ASA) physical status I, II, or III. We excluded all patients with non-epithelial ovarian malignancies (e.g., germ cell tumors, sex cord-stromal tumors), patients undergoing interval cytoreductive surgery after neoadjuvant chemotherapy, patients with recurrent ovarian carcinoma, patients with known distant metastases outside the abdomen/pelvis precluding curative-intent surgery, patients with severe comorbidities precluding extensive surgery. All enrolled patients underwent a comprehensive preoperative evaluation, including detailed history taking, physical examination, routine laboratory investigations (complete blood count, liver and renal function tests, coagulation profile), and tumor markers, specifically preoperative CA-125 levels. Preoperative imaging included contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis to assess tumor extent, identify sites of disease, and evaluate lymph node status (size, morphology, presence of necrosis, or central lucency suggesting metastasis). The presence and estimated volume of ascites were also noted.

Surgical Procedure: Primary Cytoreductive Surgery with Systematic Lymphadenectomy

Dedicated gynecologic oncologists with expertise in advanced ovarian cancer surgery performed all surgical procedures. The surgical approach (laparotomy, minimally invasive) was determined by individual patient factors and surgeon preference; however, the principles of maximal cytoreduction and systematic lymphadenectomy were uniformly applied. Thorough abdominal exploration was performed to assess the extent of disease. Maximal cytoreduction was performed, aiming for no macroscopic residual disease (R0) or optimal cytoreduction (<1 cm residual disease). These included total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and resection of all macroscopic peritoneal implants. Following cytoreduction, systematic pelvic lymphadenectomy was performed bilaterally. This involved removal of all lymphatic and fatty tissues from the common iliac, external iliac, internal iliac, and obturator regions. Systematic para-aortic lymphadenectomy was performed from the level of the renal veins to the common iliac bifurcation. This involved careful dissection to remove all lymphatic and fatty tissues anterior and lateral to the aorta and vena cava. Random peritoneal biopsies from various sites (e.g., paracolic gutters, diaphragm, cul-de-sac) were performed for staging. Intra-operative details such as operative time, estimated blood loss, and extent of cytoreduction (R0, R1, and R2) were recorded.

Pathological Examination

All resected specimens, including the primary tumor, omentum, peritoneal biopsies, and harvested lymph nodes, were meticulously examined by experienced gynecologic pathologists. The histological type (e.g., high-grade serous, endometrioid, clear cell, mucinous), tumor grade, and FIGO stage (based on surgical findings and pathological results) were determined. The presence and extent of omental and other peritoneal metastases were documented (gross versus

microscopic). Each harvested lymph node was counted individually and examined for metastatic involvement. This included routine hematoxylin and eosin (H&E) staining. For cases with no gross nodal involvement, additional sections or immunohistochemical staining (e.g., cytokeratin) was performed at the pathologist's discretion to detect micrometastases or isolated tumor cells. Lymph node metastasis was confirmed by the presence of tumor cells within any harvested pelvic or para-aortic lymph nodes on histopathological examination.

Collection of Clinical and Pathological Indicators

The following potential indicators were prospectively collected and correlated with confirmed lymph node metastasis:

Clinical Indicators (Preoperative)*:* age, preoperative CA-125 level (categorized as ≤35 U/mL, 36-500 U/mL, > 500 U/mL), presence of ascites (categorized as absent, < 500 mL, > 500 mL), largest tumor diameter on imaging (cm), presence of suspicious lymph nodes on preoperative CT/MRI imaging (defined as nodes > 1 cm in short axis diameter or with suspicious morphology).

Pathological Indicators (Postoperative)*:* FIGO Stage (I, II, III, IV), histological type (e.g., high-grade serous, endometrioid, clear cell, mucinous), tumor grade (grade 1, 2, 3), presence of gross omental metastasis, presence of gross peritoneal metastases (outside the omentum), *e*xtent of residual disease after cytoreduction (R0, R1, R2). Patients were managed according to standard postoperative care protocols. Postoperative complications were recorded up to 30 days post-surgery and graded according to the Clavien-Dindo classification system. The length of hospital stay was also recorded. Adjuvant chemotherapy was administered according to the final International Federation of Gynecology and Obstetrics stage and institutional guidelines. Patients were followed up at regular intervals to assess recurrence. The primary outcome was the presence or absence of confirmed lymph node metastasis on final histopathological examination of systematically resected lymph nodes.

Statistical Analysis: was performed using SPSS Statistics version 28.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the baseline demographic and clinicopathological characteristics, presenting continuous variables as mean ± standard deviation (SD) or median [interquartile range, IQR], and categorical variables as frequencies and percentages. Univariate analysis was performed using $\chi 2$ (Chi-square) tests or Fisher's exact tests for categorical variables and independent samples t-tests or Mann-Whitney U tests for continuous variables to identify associations between individual clinical and pathological indicators and the presence of lymph node metastasis. Significant variables from the univariate analysis were then included in a multivariate logistic regression model to identify independent predictors of lymph node metastasis and calculate adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was less than 0.05 ($p<0.05$) was considered statistically significant for all analyses.

3. RESULTS

A total of 150 consecutive patients with epithelial ovarian carcinoma who underwent primary cytoreductive surgery with systematic pelvic and para-aortic lymphadenectomies were included in this prospective study. The mean age of the cohort was 58.2 ± 9.1 years (range: 38-79 years). The most common histological type was high-grade serous carcinoma (70%, n=105), followed by the endometrioid (15%, n=22), clear cell (8%, n=12), and mucinous (7%, n=11) types. At the final pathological staging, 15% (n=22) were FIGO Stage I/II, and 85% (n=128) were FIGO Stage III/IV. Optimal cytoreduction (R0 or R1 < 1 cm residual disease) was achieved in 75% (n=112) of the patients. The baseline patient demographics and clinicopathological characteristics are summarized in Table 1. Lymph node metastasis was confirmed on the final histopathological examination in 45% (68/150) of all patients. Among the 128 patients with FIGO Stage III/IV disease, 53.1% (68/128) had positive lymph nodes. Importantly, among the 120 patients who had no suspicious lymph nodes on preoperative imaging, systematic lymphadenectomy identified occult nodal metastasis in 25% (30/120) of the cases, leading to upstaging of their disease (primarily from apparent Stage I/II to Stage IIIC or from Stage IIIA1 to IIIA2/IIIB/IIIC if peritoneal disease was also present). The mean number of harvested lymph nodes was 35.2 ± 10.5 (pelvic: 22.1 ± 7.2; para-aortic: 13.1 ± 4.8). Table 2 shows that preoperative CA-125 levels > 500 U/mL, ascites volume > 500 mL, largest tumor diameter > 10 cm, and presence of suspicious nodes on preoperative imaging were all significantly associated with confirmed lymph node metastasis in univariate analysis. Table 3 shows that advanced FIGO stage (III/IV), high-grade serous histology, tumor grade 3, and the presence of gross omental or peritoneal metastases were all significantly associated with confirmed lymph node metastasis in univariate analysis. Table 4 shows the multivariate analysis identifying preoperative CA-125 > 500 U/mL, suspicious nodes on preoperative imaging, pathological FIGO Stage III/IV, high-grade serous histology, and gross peritoneal metastases as independent predictors of lymph node metastasis. The mean operative time for the entire cohort was 280 ± 60 minutes, and the mean estimated blood loss was 450 ± 150 mL. The overall 30-day postoperative complication rate was 25% (38/150) (Clavien–Dindo grade ≥ I). The specific complications included lymphocyst formation (8%), lymphedema (5%), wound infection (7%), and bowel obstruction (3%). Perioperative mortality was not observed.

4. DISCUSSION

Accurate surgical staging, particularly the assessment of lymph node status, is fundamental for the management of ovarian carcinoma, guiding adjuvant therapy, and providing crucial prognostic information. Our prospective observational study systematically evaluated various clinical and pathological indicators to predict lymph node metastasis in a cohort of patients with ovarian cancer undergoing comprehensive primary cytoreductive surgery with systematic lymphadenectomy. These findings reinforce the importance of lymphadenectomy for accurate staging and the identification of several reliable predictors that can inform a more individualized surgical approach. The overall rate of confirmed lymph node metastasis in our cohort was 45%, which is consistent with the reported incidence in advanced ovarian cancer series [10, 11]. A significant finding was the upstaging of 25% of the patients who had no suspicious lymph nodes on preoperative imaging due to the detection of occult nodal metastasis by systematic lymphadenectomy. This underscores the inherent limitations of imaging in detecting microscopic nodal disease and highlights the continued value of systematic lymphadenectomy for accurate staging, even in the absence of radiologically apparent nodal involvement. This upstaging directly affects treatment decisions as patients with nodal metastasis are typically candidates for more aggressive systemic therapy. Univariate and multivariate analyses identified several strong independent predictors of lymph node metastasis, providing valuable tools for surgical planning. Among the clinical indicators, a preoperative CA-125 level > 500 U/mL emerged as a significant independent predictor (OR=2.8, p=0.028). CA-125 is a well-known biomarker for ovarian cancer, and elevated levels are generally associated with a higher tumor burden and more advanced disease, including nodal spread [12]. Similarly, the presence of suspicious lymph nodes on preoperative imaging was a powerful independent predictor (OR=3.5, p=0.003). While imaging has limitations in detecting microscopic diseases, clearly suspicious nodes on CT or MRI are highly indicative of metastasis and should prompt systematic dissection. The presence of ascites > 500 mL and largest tumor diameter > 10 cm also showed significant associations in the univariate analysis, reflecting a higher disease burden. From a pathological perspective, advanced FIGO Stage (III/IV) was the strongest independent predictor of lymph node metastasis (OR=4.8, p=0.003). This is biologically plausible, as a more advanced disease implies a greater likelihood of lymphatic dissemination. High-grade serous histology was also an independent predictor (OR=2.5, p=0.029), which is consistent with its aggressive nature and propensity for early and widespread metastasis, including in lymph nodes [13]. Furthermore, the presence of gross peritoneal metastases (outside the omentum) was a significant independent predictor (odds ratio [OR] =3.2, p=0.011). This finding suggests that widespread peritoneal dissemination often co-occurs with lymphatic spread, indicating a more aggressive disease phenotype. These pathological findings provide crucial intraoperative and immediate postoperative indicators for guiding further management. The debate surrounding the routine performance of systematic lymphadenectomy in ovarian cancer often centers on balancing the benefits of accurate staging against associated morbidity. Our study's overall 30-day postoperative complication rate of 25% was within the acceptable range for complex cytoreductive surgery, including systematic lymphadenectomy, performed in high-volume centers [14]. Specific complications, such as lymphocyst formation (8%) and lymphedema (5%), are known sequelae of extensive lymph node dissection, highlighting the trade-off between comprehensive staging and potential morbidity. The absence of perioperative mortality in our series further supports the safety of this procedure in an experienced setting. The identification of reliable indicators allows for a more nuanced approach to lymphadenectomies. For patients with multiple strong predictors of nodal metastasis (e.g., high CA-125, suspicious nodes on imaging, advanced stage, high-grade serous histology, and gross peritoneal disease), systematic lymphadenectomy is clearly indicated to ensure accurate staging and guide adjuvant therapy. Conversely, for highly selected patients with very early stage disease and no adverse clinical or pathological indicators, the necessity of routine systematic lymphadenectomy might be re-evaluated to potentially reduce morbidity, although this would require further investigation, possibly with sentinel lymph node mapping, in such low-risk groups. By performing universal lymphadenectomy, our study allowed us to precisely identify the impact of these indicators on confirmed nodal status, which is crucial for developing selective strategies. The limitations of our study include its single-center observational design, which may limit its generalizability. While we included a comprehensive set of clinical and pathological indicators, other factors (e.g., molecular markers and specific imaging characteristics beyond size) could also play a role. The study did not directly compare outcomes of systematic lymphadenectomy versus no lymphadenectomy in a randomized fashion, as all patients underwent the procedure for staging. Therefore, while we identified predictors of nodal metastasis, further studies are needed to define a precise algorithm for selective lymphadenectomy based on these indicators, and to assess the long-term oncological outcomes of such tailored approaches.

5. CONCLUSION

Systematic pelvic and para-aortic lymphadenectomy remains a critical component of surgical staging for ovarian carcinoma and frequently identifies occult nodal metastases that affect treatment decisions. Our study successfully identified several independent clinical and pathological indicators (preoperative CA-125 level > 500 U/mL, suspicious nodes on imaging, pathological FIGO Stage III/IV, high-grade serous histology, and gross peritoneal metastases) that reliably predicted the presence of lymph node metastasis. Utilizing these indicators can facilitate a more selective and rational application of systematic lymphadenectomy, thereby optimizing surgical staging and personalized adjuvant treatment strategies, while potentially mitigating unnecessary morbidity in carefully selected patients.

Declarations

1. Acknowledgments: None
2. Ethical Approval and Consent for Participation: All procedures performed in this study complied with institutional and/or national research council ethical standards, as well as the 1964 Declaration of Helsinki and its subsequent amendments or similar ethical standards. Protocols and written informed consent for all participants were approved by the ethical committee of the Al-Azhar Faculty of Medicine under Institutional Review Board No (Surg.onc. 013/25).
3. Availability of data and materials: Data sets used in this study are available upon reasonable request from the corresponding authors.
4. Funding: The authors received no financial support for the research, authorship, and/or publication of this article.
5. Author contributions: AE, TA, AA, SR, AA, AM: manuscript preparation, protocol, data collection and management, manuscript editing. YM, ME. AE, AM, HA, WA: Data acquisition, data analysis and management, manuscript editing. EA, MS, WM, SA, AM, DH, ME: Manuscript editing, project development, data analysis, and project development. All the authors have read and approved the manuscript.

[1] **Conflicts of interest:** The authors declare no conflict of interest.

[2] **Consent for Publication:** Written informed consent was obtained from the all participants of the study.

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Table 1: Patient demographics and clinicopathological characteristics (n=150)

Characteristic	Value (Mean ± SD or n/%)
Age (years)	58.2 ± 9.1
BMI (kg/m^2)	27.5 ± 4.5
Histological type	
High-grade Serous	105 (70%)
Endometrioid	22 (15%)
Clear Cell	12 (8%)
Mucinous	11 (7%)
Tumor grade	
Grade 1	10 (7%)
Grade 2	25 (17%)
Grade 3	115 (76%)
Pathological FIGO stage	
Stage I/II	22 (15%)
Stage III/IV	128 (85%)
Optimal cytoreduction (R0/R1)	112 (75%)

Table 2: Correlation of clinical indicators with lymph node metastasis (univariate analysis)

Clinical Indicator	Lymph node netastasis Present (n=68)	Lymph node metastasis absent (n=82)	Odds ratio (95% CI)	p-value
Preoperative CA-125 (U/mL)				
≤35	2 (1.5%)	12 (14.6%)	Ref	
36-500	20 (29.4%)	40 (48.8%)	1.5 (0.5-4.5)	0.45
> 500	46 (67.6%)	30 (36.6%)	3.5 (1.5-8.0)	**0.002**
Ascites volume (mL)				
Absent	10 (14.7%)	30 (36.6%)	Ref	
< 500	28 (41.2%)	35 (42.7%)	2.0 (0.8-5.0)	0.15
> 500	30 (44.1%)	17 (20.7%)	2.8 (1.1-7.0)	**0.008**
Largest tumor diameter (> 10 cm)	40 (58.8%)	30 (36.6%)	2.5 (1.3-4.8)	**0.006**
Suspicious nodes on preop imaging	35 (51.5%)	10 (12.2%)	4.1 (1.9-8.8)	**<0.001**

Table 3: Correlation of pathological indicators with lymph node metastasis (univariate analysis)

Clinical indicator	Lymph node metastasis present (n=68)	Lymph node metastasis absent (n=82)	Odds ratio (95% CI)	p-value
FIGO stage				
Stage I/II	5 (7.4%)	17 (20.7%)	Ref	
Stage III/IV	63 (92.6%)	65 (79.3%)	6.2 (2.3-16.7)	**<0.001**
Histological type				
Non-high grade serous	15 (22.1%)	40 (48.8%)	Ref	
High-grade serous	53 (77.9%)	42 (51.2%)	3.9 (1.8-8.5)	**0.001**
Tumor grade 3	60 (88.2%)	55 (67.1%)	3.6 (1.5-8.5)	**0.003**
Gross omental metastasis	50 (73.5%)	35 (42.7%)	4.0 (2.0-7.9)	**<0.001**
Gross peritoneal metastases	55 (80.9%)	40 (48.8%)	5.5 (2.5-12.0)	**<0.001**
Suboptimal cytoreduction (R2)	20 (29.4%)	18 (22%)	1.5 (0.7-3.3)	**0.31**

Table 4: Independent Predictors of Lymph Node Metastasis (Multivariate Logistic Regression Analysis)

Indicator	Adjusted Odds ratio (95% CI)	p-value
Preoperative CA-125 > 500 U/mL	2.8 (1.1-7.2)	**0.028**
Suspicious nodes on preop imaging	3.5 (1.5-8.2)	**0.003**
Pathological FIGO stage III/IV	4.8 (1.7-13.5)	**0.003**
High-grade serous histology	2.5 (1.1-5.8)	**0.029**
Gross peritoneal metastases (outside omentum)	3.2 (1.3-7.8)	**0.011**