LYMPHADENECTOMY IN EPITHELIAL OVARIAN CANCER: CLINICO-PATHOLOGICAL PREDICTIVE FACTORS FOR NODAL INVOLVEMENT

Thesis
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The International Federation of Obstetrics and Gynecology (FIGO) had indicated that pelvic and para-aortic lymph node sampling is an integral part of the staging system of ovarian cancer. The FIGO staging classification was amended to include a sub-stage for node involvement to reflect the prognostic significance of metastatic spread to pelvic and para-aortic lymph nodes [1].

Lymphadenectomy is an integral part in the management of ovarian cancer, and it has a potential role in both staging and retroperitoneal debulking [2].

In disease confined to one or both ovaries, positive nodes resulted in upstaging from stage I to stage IIIC [3]. Retroperitoneal lymph node involvement occurred in approximately 20-23% of early epithelial ovarian cancer and 50% to 80% of advanced epithelial ovarian cancer [4], [5].

Approaches for management of lymph nodes ranged from biopsy of only grossly enlarged nodes to systematic dissection in the form of bilateral pelvic and para-aortic lymph node dissection [6].
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### List of Abbreviations

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<tr>
<td>FIGO</td>
<td>International Federation of Gynecology and Obstetrics</td>
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<td>EOC</td>
<td>Epithelial ovarian cancer</td>
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<td>NCCN</td>
<td>National Cancer Comprehensive Network</td>
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<td>SEER</td>
<td>Surveillance, Epidemiology, and End Results</td>
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<td>CDC-NPCR</td>
<td>Centers for Disease Control and Prevention's National Program of Cancer Registries</td>
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<td>GCDFP-15</td>
<td>Gross cystic disease fluid protein-15</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
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<td>DCE</td>
<td>Dynamic contrast-enhanced</td>
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<td>DWI</td>
<td>Diffusion-weighted imaging</td>
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<tr>
<td>ADC</td>
<td>Apparent diffusion coefficient</td>
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<tr>
<td>USPIO</td>
<td>Ultra small Particles of Iron Oxide</td>
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<td>PET</td>
<td>Positron emission tomography</td>
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<td>FDG</td>
<td>Fluorodeoxyglucose</td>
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<td>FES</td>
<td>Fluoroestradiol</td>
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<td>TAH</td>
<td>Total abdominal hysterectomy</td>
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<td>BSO</td>
<td>Bilateral salpingio-ophorectomy</td>
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<td>EORTC-ACTION</td>
<td>European Organization for Research and Treatment of Cancer-Adjuvant Chemotherapy in Ovarian Neoplasm</td>
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<td>PFS</td>
<td>Progression-free survival</td>
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<td>OS</td>
<td>Overall survival</td>
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<td>IMA</td>
<td>Inferior mesenteric artery</td>
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<td>SPOL</td>
<td>Symptomatic postoperative lymphocyst</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>SPSS</td>
<td>Statistical Package for Social Sciences</td>
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<td>CT</td>
<td>Computed tomography</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>IVC</td>
<td>Inferior vena cava</td>
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<td>LN</td>
<td>Lymph node</td>
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According to NCCN (National Cancer Comprehensive Network) guidelines 2011, bilateral pelvic and para-aortic lymph node dissection is part of the standard management of stage I,II and non bulky stage III and IV epithelial ovarian cancer [7].

Aortic lymph node dissection should be performed by stripping the nodal tissue from the vena cava and aorta bilaterally to at least the level of the inferior mesenteric artery and preferably to the level of the renal vessels [7].

Pelvic lymphadenectomy should be done by removal of lymph nodes overlying and medial to the external iliac and hypogastric vessels, from the obturator fossa anterior to the obturator nerve, and overlying and anterolateral to the common iliac artery [7].

Adding lymphadenectomy to hysterectomy and omentectomy is not without complications and increase in morbidity. Complications of lymphadenectomy include lymphedema, ileus, lymphocele, vascular and organ injury [8], [9], [10], [11].
The role of lymphadenectomy has been shown to impact survival. In a retrospective study of 6,686 patients with stage I ovarian cancer, Chan and colleagues found that lymphadenectomy improved survival from 85.9% to 93.3% [12]. Bergzoll and colleagues found that in patients with FIGO stage III ovarian cancer, the 5-year overall survival rate was 22% in women who had not undergone lymphadenectomy, and 52% in those in whom more than 9 nodes were resected [13]. There are several possible mechanisms that may explain the improvement in survival that was found to be associated with a more extensive lymphadenectomy in advanced cancers. A more complete lymphadenectomy is likely to remove occult microscopic disease, resulting in a more complete cytoreduction [8]. In a randomized trial reported by Benedetti Panici and colleagues, patients with stage IIIB-C and IV epithelial ovarian cancer randomized to undergo systematic pelvic and para-aortic lymphadenectomy were found to have a statistically significant increase in positive lymph nodes compared to those randomized to resection of bulky nodes only (70 vs 42%; P ≤ 0.001) [14].
A meta-analysis of the survival effect of maximum cytoreductive surgery in advanced ovarian carcinoma reported that each 10% increase in maximum cytoreduction was associated with a 5.5% increase in median survival time [15].

Furthermore, an extensive lymph node resection may lead to an improvement in survival by removing micro metastatic disease within the lymph nodes that may be resistant to chemotherapy [16].

Prior studies on patients who underwent chemotherapy followed by second-look surgery showed that 33.3-65.3% of patients with advanced-stage disease had residual disease in the retroperitoneal lymph nodes [17]. These studies suggested that chemotherapy appeared to have minimal effect on tumor deposit in the nodes; thus, retroperitoneal lymphadenectomy should be an integral component of ovarian cancer cytoreductive surgery [16], [17].
The aim of this study is:

(1) To study the pattern of lymph node involvement in epithelial ovarian cancer (distribution and laterality).

(2) To evaluate possible predictive factors for nodal affection in epithelial ovarian cancer.

(3) To study the impact of lymph node involvement in the upstaging of early ovarian cancer.
BASIC SCIENCE BACKGROUND:

[1] Anatomy:

Anatomy of lymphatics and lymph nodes 
draining the ovaries and the retroperitoneum

The lymphatic drainage of the pelvis has been divided into 
the following groups: Common iliac, external iliac, internal
iliac, obturator and para-aortic lymph nodes.

1-External iliac Lymph nodes:
Lie in proximity to the external iliac artery and vein, and 
are found caudal to the bifurcation of the common iliac
vessels and cranial to the inguinal ligament [18] . The 
relationship of the nodes to the vessels determines the
subgroups of the external iliac nodes (fig.1): The lateral
subgroup lies lateral to the external iliac artery, the middle
subgroup is located medial to the external iliac artery and
lateral to the accompanying vein, while in the medial
subgroup the nodes are medial to both external iliac
vessels.
In some cases the medial external iliac lymph node group contained a node group posteromedial to the external iliac vessels. In that case, these nodes were found in proximity to the obturator internus muscle and were, therefore, called by some the obturator nodes.

Although the subject of some debate, obturator nodes were generally considered to be a part of the medial external iliac node group [18].

Figure (1): Volume-rendered reformation of contrast-enhanced CT image show location of named subgroups of external iliac lymph nodes: 1 = lateral, 2 = middle, 3 = medial (including obturator). [19]
2-Internal iliac Lymph nodes:
Lie within the adipose tissue around the branches of the internal iliac vessels and are more posterior in the pelvis than are the external iliac nodes. There are many subdivisions named according to the adjacent vessel (fig.2). The lateral sacral nodes are near the paired lateral sacral arteries. The presacral nodes lie immediately anterior to the sacrum and posterior to the mesorectal fascia. The anterior internal iliac nodes were the most anterior of the internal iliac nodes and were located anteriorly at the origin of the proximal branches of the anterior division of the internal iliac arteries [20].

The term hypogastric nodes has been used in a variable way, with some authors using it to describe the most cephalic of the internal iliac nodes, while others use this term for the entire internal iliac group[21], [22], [23].
Figure (2): Volume-rendered reformation of contrast-enhanced CT image showing location of named subgroups of internal iliac lymph nodes: 1 = lateral sacral, which are adjacent to lateral sacral artery (arrow); 2 = presacral; 3 = anterior, which are anterior to anterior division of internal iliac artery (arrowhead); 4 = hypogastric. [19]

3-The common iliac nodes:
Include the lymph nodes between the external iliac and para-aortic node groups mostly on the lateral surface of the corresponding vessel. This group is subdivided into three groups based on their anatomic location (fig.3):
The lateral subgroup lateral to the common iliac vessels, the medial subgroup medial to these vessels and the middle common iliac lymph node group located in the lumbosacral fossa, which is bordered posteromedially by the lower lumbar or upper sacral vertebral bodies, anterolaterally by the psoas muscle, and anteromedially by the common iliac artery and vein [19].

**Figure (3):** Volume-rendered reformation of contrast-enhanced CT image showing locations of named subgroups of common iliac lymph nodes: 1 = lateral, 2 = medial, 3 = middle. [19]
4-The obturator nodes:
Include the node-bearing tissue within the obturator fossa.

5-The para-aortic lymph nodes:
The lymphatic tissue of the para-aortic region which extends from the renal vessels to the aortic bifurcation and lies lateral to the aorta was divided arbitrarily into 2 parts according to the inferior mesenteric artery: Supra-mesenteric and infra-mesenteric para-aortic. Nodes present in front of the aorta were termed pre-aortic, whereas nodes located in front and lateral to the IVC were called precaval and paracaval respectively. Nodes lying between the IVC and aorta were termed intercavo-aortic and were divided into superficial and deep according to their relation to the lumbar vessels (fig.4)[24].
Fig(4)Para-aortic lymphatic regions [5]

6- Inguinal Lymph nodes:

These nodes were located inferior to the level of the inguinal ligament, and inferior to the external iliac node group. They are subdivided into superficial and deep inguinal nodes (fig.5). The superficial subgroup lies anterior to the inguinal ligament, the superficial femoral vessels, and the saphenous veins. The deep inguinal lymph nodes are within the femoral sheath and are usually located medial to the common femoral vein [25].
Data from the literature have suggested the presence of asymmetry along the left-right axis regarding the lymph node count. Results from previous studies have reported a significant right-sided prevalence in the distribution of pelvic lymph nodes, as well as other groups of lymph nodes including axillary, inguinal and mediastinal lymph nodes.
This may be explained by results of embryological studies that have shown that all the lymphatic primordia take their origin from discrete sprouts derived from the endothelial lining of the walls of veins. And the presence of the main venous axis of the human body in a paramedian right position may explain this right-sided predominance [26], [27], [28]. Several studies on pelvic lymphadenectomies showed an average nodal count that was higher on the right than on the left side [29], [30], [31].

**Pathways of ovarian lymphatic drainage:**

There are three main pathways of lymphatic drainage from the ovaries described:

The first pathway passes along the ovarian vessels through the infundibulopelvic ligament to the aortic area, terminating at the vena cava on the right side and between the aortic and renal vessels on the left side, and draining medially into the para-aortic, intercaval aortic, and paracaval lymph nodes [32]. The second pathway passes from the ovarian plexus to the obturator lymph nodes through the lymphatics of the broad ligament.
There is a rich anastomotic network of lymphatics between the obturator nodes and the external iliac, hypogastric, common iliac and para-aortic nodal basins. The third route, which was less significant, passes from the ovary through the round ligament to the external iliac and inguinal basins. Retrograde metastatic flow to the inguinal lymph nodes may occur secondary to the involvement of the external iliac nodes and obstruction of proximal drainage [24], [33].

Several studies have concluded that retroperitoneal lymph node involvement may follow the primary drainage pathways of pelvic organs invaded by locally advanced ovarian cancer such as the uterus, rectosigmoid, colon and peritoneum. An example was the paracolic lymph nodes which drain the rectosigmoid colon above the peritoneal reflection and follow the course of the superior rectal artery [34].
Mechanism of tumor dissemination via the lymphatic system

Harveit suggested the following explanations for the role of physical factors of the lymphatic system in tumor dissemination:

Lymphatics are optimally suited to the entry and transport of cells, this assists in the entry of tumor cells into the lymphatic circulation. This can be explained by four main reasons. First, lymph vessels are larger in caliber than small capillaries. Second, the physical movement of a tumor cell into a lymphatic is easier than its movement into a capillary due to the fact that lymphatics lack a basement membrane and have fewer intercellular junctions. Third, the flow velocity in lymphatics is slower than flow in the capillaries of the systemic circulation. Fourth, lymph is similar to interstitial fluid in terms of constituents and chemistry which helps in promoting cell viability [35].

In addition, it has also been suggested that these factors cause tumor cells to be subjected to weaker shear forces and lower serum toxicity in the lymphatics than in the hematogenous circulation [36].
Presence of a high lymphatic density through the growth of local lymphatic network can have an important impact in facilitating tumor metastases to lymph nodes. Over expression of some lymphangiogenic growth factors may play a role in the migration of tumor cells into the lymphatic system [37]. The vascular endothelial growth factor (VEGF) family of glycoproteins, which includes subtypes A, B, C, and D as well as VEGF receptors, were reported to have an important role in lymphatic and vascular proliferation [38].

Local stromal cells which are a subset of activated tumor-associated macrophages have been proved to be able to produce lymphangiogenic factors such as VEGF-C and VEGF-(7). These stromal cells expressed a panel of macrophage-specific markers including CD68, CD23, and CD14. They also expressed the VEGF- C– and VEGF-D–specific tyrosine kinase receptor VEGF receptor–3[38].

Advances in knowledge of the basis of node metastases may form an important substrate for the determination of the metastatic potential and treatment of ovarian tumors and play a role in future molecular imaging approaches.
[3] Pathology

Incidence:

Retroperitoneal lymphatic involvement by epithelial ovarian cancer is relatively common and should be considered one of the primary routes of spread [33]. However, the incidence of lymph node metastases in different stages of the disease varied widely in the literature, this is mainly related to the type of lymphadenectomy performed in these studies (sampling vs. systematic) [2].

Incidence of lymph node metastases varied according to the stage of ovarian cancer. The incidence of lymph node metastasis in patients with ovarian cancer presumed to be stage I has been reported to be 10% to 25%, and patients with stage II was 20-50% [39], [40], [41], [5]. Despite this high incidence of lymph node metastasis, two recent retrospective analyses of the Surveillance, Epidemiology and End Results (SEER) and the Centers for Disease Control and Prevention's National Program of Cancer Registries (CDC-NPCR) data showed that lymphadenectomy was omitted in 28% to 40% of early-stage ovarian cancer patients [42], [43].
The incidence of lymph node metastasis was higher in advanced stages, reportedly 60-70% for stage III and up to 88% in stage IV [41], [14]. In their series, Morice and colleagues found that 87% (41 of 47 patients) of patients with apparently enlarged lymph nodes had nodal involvement. Whereas lymph node involvement was observed in 35% (81 of 229) of patients who didn’t have macroscopically suspicious lymph nodes [5].

**Pattern of Lymph node involvement:**

Most studies have demonstrated that the incidence of positive para-aortic lymph nodes was greater than that of pelvic lymph nodes, with up to 50% having para-aortic lymph node metastases only in early stage ovarian cancer [44], [45], [46], [47]. With the reported incidence of positive high aortic nodes being 58% to 79% and of the lower aortic nodes (below the inferior mesenteric artery) being 33% to 71% [45], [4], [48].

As regards to contralateral nodal involvement in patients with unilateral epithelial ovarian cancer, it was initially indicated that the lymphatic spread was ipsilateral and that ipsilateral pelvic and aortic node dissection was therefore appropriate for staging especially for early stage tumors [24].
However, contralateral nodal involvement in EOC patients with unilateral clinical stage I disease has been reported to occur in as many as 30% of patients [46, 4, 48, 49]. More recent reports have suggested that bilateral pelvic and aortic lymphadenectomy should be undertaken for adequate retroperitoneal staging in the presence of unilateral EOC [50]. Ipsilateral lymphadenectomy has also been proved to be inadequate in patients with unilateral EOC, clinical stage II to IV [51].

In patients with unilateral EOC and clinical stage III, ipsilateral lymph node metastases has been documented in only 40% of patients with retroperitoneal nodal involvement with the rest having contralateral or bilateral disease [45]. Ipsilateral sampling in unilateral EOC may result in under staging in aortic lymphadenectomy by 7% to 16% and in pelvic lymphadenectomy by 0% to 7% [48].

Salani and colleagues analyzed in their study the incidence of mesenteric lymph node metastases in patients with advanced-stage ovarian carcinoma invading the rectosigmoid. Their results showed that 82% of 39 cases had one or more mesenteric lymph node metastases.
Accordingly, they recommended that in patients with advanced disease, lymph node sites in addition to the pelvic and/or para-aortic should be considered, especially when optimal debulking is attempted [52]. Similar results were also achieved by Baiocchi and colleagues with 70% of their 41 cases having mesenteric lymph node metastases [53].

Metastasis to inguinal lymph nodes are rare, and have been documented in literature with different patterns. Scholz and associates reported a case of ovarian carcinoma with inguinal lymph node metastasis as the only manifestation of lymphatic spread [54]. Ang and colleagues reported a case of ovarian cancer who presented with isolated contralateral inguinal lymph node metastasis [55], while Manci and colleagues reported a case of ovarian carcinoma who presented with bilateral inguinal lymphadenopathy as the primary sign [56].

Metastasis to axillary lymph nodes from primary epithelial ovarian carcinoma was rare, with most cases in the literature being of the serous type [57], [58], [59]. In those patients, it was important to exclude the presence of primary breast cancer as this may alter the treatment plan. Several tests have been proposed to help in confirming that the axillary nodal metastases is of ovarian origin.
Wilms Tumor gene (WT-1) which is a tumor suppressor gene located on chromosome 11 at p13 has been found in the literature to be positive in 94.7% of patients with ovarian carcinoma, and is tested for in axillary lymph nodes suspected to be of ovarian origin [60], [61].

Monteagudo and colleagues used Gross cystic disease fluid protein-15 (GCDFP-15) in distinguishing metastatic breast carcinoma from poorly differentiated ovarian carcinoma. Seventy one percent (10 of 14 cases) of metastatic breast cancers were positive for GCDFP-15 but none of the primary ovarian cancers were noted to be positive [62].

Goyal and colleagues reported a case, which was an ovarian cancer patient who underwent cytoreductive surgery and received adjuvant chemotherapy and presented during follow up with an enlarged axillary lymph node associated with an elevated level of CA-125 of 104 U/ml (CA-125 level dropped to 4.4 U/ml after chemotherapy). After excision of the axillary lymph node, CA-125 level dropped to 5 U/ml. The ovarian origin of the axillary lymph node metastases was also confirmed by positivity to WT-1 and negativity to GCDFP-15 [57].
Martinez and colleagues underwent a recent study to try to identify the prognostic relevance of celiac lymph node involvement in ovarian cancer. They concluded that patients who had celiac lymph node metastases were associated with adverse tumor biology and poor oncologic outcome. And in multivariate analysis, this was the only significant prognostic factor associated with resistance to platinum-based chemotherapy. They concluded according to their findings that celiac lymph node involvement was a high risk marker to select patients who will not benefit from maximal cytoreduction. However, more studies are needed to identify the effect of celiac lymph node metastases on survival [63].

In a study by Holloway and colleagues, 9 out of 78 patients with epithelial ovarian cancer had enlarged paracardiac lymph nodes. All these patients had CT evidence of associated disease in the abdomen and pelvis, with peritoneal metastases being the most common [64].

Zannoni and colleagues published a case report of ovarian serous carcinoma presenting with mediastinal lymphadenopathy 20 months before the appearance of the intra-abdominal mass [65].
Factors affecting lymph node metastases:

[1] Age:
Risk of lymph node metastasis has been reported to increases with age[45], [50].

[2] Histological type:
Serous histology has been demonstrated in to be the most common type of epithelial ovarian cancer associated with lymph node metastases with incidence ranging from 27-60% , and mucinous histology being the least common with incidence ranging from 0-9% [40], [41], [26], [50] .

[3] Grade:
Several studies have demonstrated that the rate of lymph node metastases increases with grade. Ayhan and colleagues showed in their results that lymphatic involvement in grade I, II, and III disease were 18.2%, 47.3%, and 65.7%, respectively (P = 0.001) [24], [49], [50]. However, other studies in the literature have illustrated that the rate of nodal involvement was lesser in grade 3 diseases than grade 2, and grade 2 involvement was less than grade 1 involvement [5], [40].
CA-125 level:
The normal level of CA-125 is 35U/ml. In their series, Ayhan and colleagues showed that a CA-125 level higher than 500 U/ml was significantly associated with lymphatic metastasis [50]. Preoperative CA-125 was also found to be a predictor of lymph node involvement in the study of Powless and colleagues (p=0.006). Using the value of 35 U/ml as cut-off, among patients with CA-125 more than 35 U/ml, 22.4% (19/85) had positive lymph nodes. Interestingly, none of the patients with a preoperative CA-125 level of less than or equal to 35 U/ml had positive nodes [40].

Positive cytology and Ascites:
Powless and colleagues showed in their study that positive cytology of peritoneal washings was associated with an increased risk of lymph node metastasis (p=0.012). Lymph nodes were positive in 22.4% (13/58) of those with positive cytology. Presence of malignant ascites similarly was associated with an increased risk of lymph node involvement. Lymph node metastasis was noted in the presence of ascites in 11/39 patients (28.2%) compared to those patients without ascites where lymph node involvement was present 14/151 (9.3%) (p=0.002) [40].
Lymph node size:
Normal lymph node size varied from a few millimeters to 2.5 cm in diameter. Several studies have reported that nodal size had an effect on the likelihood of metastases: For nodes of less than 2 cm, the likelihood of metastasis was 24%, for those of 2 to 4 cm, 52.5%, and for nodes larger than 4 cm, 80%, indicating that intra-operative assessment of retroperitoneal lymph nodes by palpation is incorrect in 33% to 60% of patients [45, 51, 66].
Eisenkop and colleagues identified 31.1% of positive nodes by palpation, 26.2% by visual inspection, and 42.6% by dissection, which indicates that surgical dissection is necessary for full documentation of nodal disease [67].
Diagnosis

[1]CT:

Optimal identification of lymphadenopathy can be done using contrast enhanced CT of the abdomen and pelvis after the administration of low osmolar intravenous contrast (Fig 6) [68]. The following morphologic criteria have been suggested for differentiating benign from malignant nodes:

A. Nodal Size:
Although nodal size remains the primary criterion in assessing lymph nodes on cross-sectional imaging, yet it cannot be relied up on alone for diagnosis of nodal metastases [19]. This is due to the wide variation in the size of non metastatic lymph nodes which can overlap with the size of metastatic nodes [69].

In an attempt to establish a normal range for lymph node size, Vinnicombe and colleagues evaluated a group of healthy volunteers with CT with and without bipedal lymphangiography. In that study, the 95th percentiles for normal nodes’ short-axis diameter were 7 mm for internal iliac nodes, 8 mm for obturator nodes, and 10 mm for external iliac nodes [21].
A short-axis diameter of more than 10 mm is the most commonly used diagnostic threshold for a malignant node, although Koh and colleagues recommend the use of a size threshold of 8 mm (short-axis diameter) for pelvic nodes [22], [70].

B. Nodal Shape:
A normal lymph node is an oblong bean–shaped structure having a fatty hilum and a smooth outline except for small vessels at the hilum of the node. Malignant infiltration typically results in the node becoming round, with an increase of the short-axis to long-axis ratio [71].

C. Nodal Density/Signal Intensity:
The cortex of normal nodes has been reported to be uniform, homogeneous in density with many having a visible central fatty hilum. Whereas nodes with tumor deposits were irregular, with rim enhancement, and may have cystic areas within them. Central necrosis in a node, although not specific, has been reported with metastatic involvement [72].
D. Presence of Calcifications:
The presence of calcification in lymph nodes regardless of their size has been shown to improve sensitivity in diagnosing nodal metastases in a subset of patients with ovarian carcinoma in which the tumor calcifies [73].

Figure (6): Ovarian cancer. Axial contrast-enhanced CT image shows enlargement of inter-aortocaval lymph node (arrow) between aorta (a) and inferior vena cava (c). The para-aortic nodes are regional nodes for ovarian cancer; therefore, this represents N1-stage disease.[19]
MRI:
As with CT, studies for MRI also determined that nodal size was still the most important factor in predicting nodal metastases, MRI also had the additional ability to assess nodal signal intensity and dynamic contrast enhancement characteristics [74].

Malignant nodes tended to demonstrate similar signal intensity to the primary tumor on MRI. However, in attempting to differentiate between the different causes of nodal enlargement on MRI, the relaxation times of malignant nodes were not significantly different and even overlapped with those of benign nodes, which can lead to false positive results (fig 7) [75].

When nodal morphologic criteria were used with MRI, sensitivity and accuracy rates in assessing malignant lymph nodes have generally been demonstrated to be slightly better than CT in gynecologic malignancies but were still relatively low. Sensitivity rates for detecting metastatic nodes ranged from 38% (for ovarian cancer) to 73% (for cervical cancer) with specificity rates ranging from 75% to 98% [76].
Figure (7): Malignant nodes on MRI. (A) Axial T2-weighted image demonstrates large right pelvic side wall nodes (black arrows), which have the same signal intensity as the primary tumor (white dashed arrow). The metastatic left pelvic side wall node (black dashed arrow) has an irregular contour. (B) Axial T2-weighted image with fat saturation images show an enlarged left inguinal node (white arrow) that has a pocket of high signal intensity consistent with necrosis. [76]
Contrast-Enhanced MRI:
Contrast enhanced imaging using spin echo sequences showed no significant difference in enhancement characteristics between benign and malignant nodes as demonstrated by Kim and colleagues. [77]. Dynamic contrast-enhanced (DCE) sequences entail the fast acquisition of contrast-enhanced images at different time intervals and at different slice positions. Contrast transfer from vessels to tissue occurred more rapidly in lesions with increased neovascularity, such as tumors [78]. There is limited published literature regarding the use of DCE-MRI in assessing nodal status in gynecologic malignancies. Several authors have assessed its usefulness in differentiating benign from malignant lesions within the pelvis [79], [80]. Yang and colleagues obtained DCE pelvic sequences in patients with cervical cancer. They did not demonstrate any significant difference in the rate of enhancement or the time of peak enhancement between benign or malignant nodes [72]. Thus, to date, because of a lack of published data, DCE-MRI is not routinely used in the assessment of nodal status in gynecologic cancers.
Evolving Techniques

Diffusion-Weighted Imaging:
Diffusion-weighted imaging (DWI) is an MRI technique that measures differences in the mobility of water molecules within extracellular spaces. The extent of water diffusion is affected by cell organization and density, tissue microstructure, and capillary circulation [81]. DWI can be easily performed as an extra sequence to conventional MRI with a short acquisition time of approximately 2 to 6 minutes. It does not require intravenous contrast and can be performed in patients with impaired renal function.

The apparent diffusion coefficient (ADC) can be measured by placing a region of interest over the tissue of interest, giving a quantitative measure of the diffusivity of water in a tissue. Malignant lesions demonstrate high signal intensity on high b-value DW images and low mean ADC values [82],[83],[84],[85].

The use of DWI within the pelvis has been reported to lead to better discrimination of pelvic nodes that can be easily missed due to their proximity to adjacent structures, such as vessels and bowel.
These nodes present as discrete, non continuous high signal intensity lesions on a homogeneously suppressed background (Fig. 8 B, C) [82], [86]. Thus, DW can demonstrate small nodes more easily. However, Ichikawa and colleagues have noted that both benign and malignant nodes in colorectal cancer can demonstrate high signal intensities on DW images [87].
Figure 8 (A) T2-weighted axial image of pelvis demonstrates a large left pelvic side wall node with irregular contours (white arrow) that is high signal intensity on (B) DWI (b \_ 750) and low signal intensity on (C) corresponding ADC map. Note the restricted diffusion and heterogeneity in the primary cervical tumor (in white circle). [76]
Ultra small Particles of Iron Oxide (USPIO) and MR Lymphography:

Detection of malignant lymph nodes may be improved by combining the physiological function of lymph nodes with multiplanar MRI. Recently there has been progress in evaluating the use of lymphotrophic nanoparticles in MR lymphography via the use of dextran-coated USPIO [88]. The iron oxide nanoparticles are diluted in saline and administered by slow intravenous infusion. Then they reach lymph nodes by 2 routes: directly via transcapillary spread to the venules and into the nodal medullary sinus, or predominantly via the interstitial space where afferent lymphatics transport it into the lymph node [88]. Macrophages within normal lymph nodes phagocytose the nanoparticles, with peak uptake at 24 to 36 hours that manifests as a decrease in signal intensity on T2*-weighted sequences. Malignant nodes on the other hand have impaired ability to take up the nanoparticles and appear as areas of persistent high signal intensity on T2*-weighted images (fig 9) [89].
Several studies have demonstrated increased sensitivity (82%-93%) in comparison with conventional MR sequences (sensitivities of 38%-73%) without compromising on specificity in the detection of lymph node metastases with MR lymphography [89], [90], [91]. Some authors have marked some pitfalls to the technique: Micrometastases may remain undetected as they are below the spatial resolution of current scanners, magnetic susceptibility artifact can potentially obscure tiny metastatic deposits, the hila of granulomatous and fibrotic nodes can be devoid of macrophages causing a pattern of USPIO uptake similar to metastases, and also reactive hyperplastic nodes can result in a USPIO uptake pattern which can be confused with metastases [92], [93], [94].
Figure (9): MR lymphography with USPIO (A) Benign node. A small left inguinal node demonstrates normal uptake of USPIO and manifests as a decrease in signal intensity on the T2* image (white arrow). (B) Malignant node in the right groin, coronal T2* image. This small node did not demonstrate USPIO uptake, which manifested as persistently high signal intensity on T2* image (black arrow). Note adjacent uptake of USPIO in small benign nodes (white arrow). [76]
[3]US:
In rare cases of epithelial ovarian cancers with inguinal lymph node metastases, ultrasound features of abnormal metastatic nodes were suggested to be change to a circular (long to short axis ratio less than 2) or irregular configuration, loss of central hilar fat (Fig. 10B) and increased peripheral vascularity rather than hilar vascularity [95].
Figure (10): Ultrasound of inguinal lymph nodes. (A) Normal, ovoid lymph node. There is a hyperechoic fatty hilum and a thin, smooth hypoechoic cortex. (B) Malignant node which is round, with irregular margins and loss of central fatty hilum. (C) A malignant node. In this case, the cortex has developed an eccentric bulge (white arrow) which appears relatively more hypoechoic than the remainder of the cortex [76].
[4] Lymphoscintigraphy:
Lymphoscintigraphy has been rarely used in ovarian cancer because usually the large primaries make identification of sentinel nodes difficult. Also there is a theoretic risk of tumor dissemination during injection of dye and radiotracer in or around the primary tumor [96].

[5] PET scan:
PET scan has been shown to be a more accurate modality for detecting metastatic lymph nodes than CT and MRI. This has been concluded by Yual and colleagues in their meta-analysis of data from 882 patients with ovarian cancer [97], [98]. Yaun and colleagues also showed in their study that approximately 70.0% of metastatic lymph nodes and 97.1% of negative lymph nodes could be correctly diagnosed by PET or PET/CT [97].

Though significantly better than those of CT and MR imaging, the sensitivity of PET or PET/CT has been shown to be moderate. A possible explanation is that PET or PET/CT can only detect lesions with sufficient malignant cells to change the glucose metabolism and that FDG uptake may not be increased in low-grade tumors [99], [100], [101].
The greater specificity of PET or PET/CT has been shown to be statistically insignificant, which could have been due to the false-positive findings yield by PET from physiologic and inflammatory processes [97],[102],[103]. However, in suspected recurrent ovarian cancer, Bristow and colleagues have demonstrated that FDG-PET/CT has a high positive predictive value of 82.8% in identifying recurrence in retroperitoneal lymph nodes when conventional CT has been negative or equivocal (fig.11)[99].

There have also been case reports regarding the usefulness of FDG-PET/CT in identifying extra abdominal lymph node involvement during staging or in suspected recurrence [104],[74],[75],[105].
FIGURE (11). Images of 62-y-old woman with ovarian cancer who had a rising level of CA-125 and was being evaluated for recurrent disease. (A) Maximum-intensity projection coronal 18F-FDG PET/CT image (A) and transaxial CT images at 2 levels (B and C) show active disease in para-aortic and pelvic nodes (SUV, 4.3 and 5.8) and mesenteric disease. [106]

**Novel Techniques:**

The following imaging modalities and techniques of nodal assessment currently remain at an experimental stage.

**New Radiopharmaceutical Tracers:**

As discussed previously, 18F-FDG is not a selective radiotracer because other cell types in addition to tumor cells actively use glucose. More specific tracers are being explored for use in oncological imaging.
These include 11C-acetate, 11C-methionine, and F-18 fluoro-3’-deoxy-3-L-fluorothymidine. The degree of F-18 fluoro-3’-deoxy-3-L-fluorothymidine uptake is dependent on DNA synthesis and is most likely clinically useful in assessing response to treatment [107].

18F-methyl choline is being investigated as a specific tracer for prostate cancer. The estrogen analogue 16 alpha-[18F] fluoro-17-estradiol is being evaluated in gynecologic malignancies. Studies have so far concentrated on characterizing the primary tumor rather than nodal identification [108]. However, initial studies have demonstrated that estrogen receptor expression and glucose metabolism of uterine tumors measured on PET showed opposite tendencies, with decreased FES uptake but increased FDG uptake in malignant lesions. In benign lesions, for example, leiomyoma, there was an increased FES uptake but decreased FDG uptake as measured on standardized uptake values [108].
Sentinel lymph node:

Sentinel lymph node biopsy is still not widely used in the management of ovarian cancer. Among the possible causes is the difficult access to the primary tumor. In addition, for many patients the ovarian tumor masses are very large and heterogeneous, which poses problems regarding the sites of radiocolloid injection. In early stage disease, with an intact ovarian capsule, there would be theoretical concern about “injecting” tracer in or around the primary tumor for fear of rupture or spillage. Also, the anatomical nodal drainage region is very variable. Therefore, as with endometrial cancer, sentinel lymph node detection would most likely not alter clinical management and would not become part of routine clinical practice [96]. Nyberg and colleagues performed a study in 16 patients with high-risk uterine cancer in whom technetium and blue dye were injected into the right or left ovary [109]. Since patients with a high-risk uterine cancer undergo a staging procedure similar to that of patients with early stage ovarian cancer (total abdominal hysterectomy (TAH) with bilateral salpingio-ophorectomy (BSO) and a pelvic and para-aortic lymphadenectomy), these patients were selected to investigate whether injecting tracers in the ovary would render sentinel nodes.
After an incubation time of 15 minutes, a sentinel node was detected in 15 out of 16 patients, all in the para-aortic area [109]. Negishi and colleagues used activated charcoal solution to identify ovarian lymphatics in 11 patients. The charcoal was injected into the cortex of the ovary. The charcoal was deposited in (sentinel) lymph nodes of all patients. In both studies the tracer was injected into the ovary [110].

Some authors claim that injecting in the ovary can be difficult when bulky ovarian masses are present. Furthermore, it is claimed that there is a risk of tumor dissemination when tracers are injected into the ovarian capsule [111].

The injection of the tracer can be performed in the ovarian ligaments, not in the ovarian cortex, to avoid spillage and to be as close as possible to the draining lymph vessels in the ovarian ligaments, irrespective of the size of the ovarian masses. Therefore, in addition to including patients with high-risk endometrial cancer, the authors suggested that patients with an enlarged ovary can be included without risk of tumor dissemination [111].
Lymphatic mapping can be performed with blue dyes as well as with radioactive isotopes; both can be injected into the ovarian ligaments, which contain the main routes of lymph drainage. After the incubation time the sentinel nodes can be visualized by either colorization (blue lymph nodes can be identified) and/or with a gamma probe that detects the radioactive tracer $[^{109}]$. The blue dyes can cause an allergic reaction, exhibited with urticaria, erythema, hypotension and even cardiovascular collapse with bronchospasm $[^{112}]$. However, the incidence of allergic reactions is very low and varies between 0.07 and 2.7% $[^{113}, ^{114}]$. The radioactive isotope is safe for patients with no reports of allergic reactions $[^{115}]$. Recognition of sentinel nodes with blue dye and the gamma probe during surgery is less reliable than by making a scintigram. Therefore ideally, as in breast and vulvar cancer, a scintigram is made before surgery to recognize the sentinel nodes so that during surgery no sentinel nodes will be missed. This cannot be accomplished in patients with ovarian cancer, because the tracers have to be injected during surgery. However, the authors expect that missing sentinel nodes in patients with ovarian cancer should be uncommon since the area where the sentinel nodes can occur can easily be visualized.
Nevertheless, by making a scintigram 24 hours after surgery, at least an impression can be obtained on the incidence of unrecognized sentinel lymph nodes [116].
Impact on diagnosis:

Lymphadenectomy is still not routinely performed at the initial staging surgery, and when done varies from lymph node sampling to complete dissection. Goff and colleagues analyzed the surgical data of 10,432 women using hospital records from nine states. There were 4,057 patients with early ovarian cancer and only 53.1% of patients had lymph node biopsy or dissection \[117\]. Recently, Chan et al. and Cress et al. conducted a retrospective analysis of the SEER data of 8,372 patients and the CDC-NPCR data of 721 patients, respectively. All patients presented with early-stage disease and lymphadenectomy was performed in 60% and 70% of patients, respectively \[42\], \[43\]. The low rates of performing lymphadenectomy seem to be due to the fact that so far, no definitive answer has been given to the therapeutic benefit of lymphadenectomy \[44\]. Maggioni and colleagues published the results of a randomized study on the value of systematic lymphadenectomy for early ovarian cancer through assigning 268 patients to the lymphadenectomy group (n=138) and the lymph node sampling group (n=130).
There was no statistically significant difference in survival between the two groups, but the median operating time was longer and the morbidity was higher in the lymphadenectomy group [6]. Despite its prospective nature, the study may have lacked power to determine a survival impact of lymphadenectomy because of the small number of patients and inconsistent adjuvant chemotherapy to each group. Chang and colleagues also concluded that the progression-free and overall survival of patients undergoing lymphadenectomy did not differ from those of patients who had not had lymphadenectomy [44].

However, considering the small number of patients studied, it may be underpowered to detect a distinct survival difference between the two groups. On the other hand, several retrospective studies have shown that lymphadenectomy is associated with improved survival of patients with early ovarian cancer [12], [13], [42],[47].

One of the largest studies to assess the survival impact of lymphadenectomy in patients with early stage ovarian cancer was done by Chan and colleagues using information obtained from the SEER Program between 1988 and 2001. In this study 6,686 women had clinical stage I ovarian cancer.
Lymphadenectomy was associated with improved 5-year disease-specific survival of all patients from 87.0% to 92.6% (P<0.001). Also it was concluded that the completeness of lymphadenectomy increased the survival rates from 87.0% (0 nodes) to 91.9% (less than 10 nodes) to 93.8% (10 or more nodes), (P<0.001). On multivariable analysis, the extent of lymphadenectomy was a significant prognostic factor for improved survival, independently of other factors such as age, stage, histology, and grade of disease [12].

Timmers and colleagues retrospectively analyzed data which were collected for the European Organization for Research and Treatment of Cancer-Adjuvant Chemotherapy in Ovarian Neoplasm (EORTC-ACTION) trial on surgical staging and adjuvant chemotherapy for early-stage ovarian cancer. In this study of 135 patients with early ovarian cancer, both lymph node sampling and blind peritoneal biopsies were associated with improved progression-free and overall survival [47].
More recently, Cress and colleagues reviewed the medical records of 721 early ovarian cancer patients who resided in California and New York using population-based cancer registries. Of surgical procedures performed, only lymphadenectomy was strongly associated with improved survival [43].

**The role of lymphadenectomy in advanced stage ovarian cancer:**

Patients in whom intraperitoneal debulking result in residual tumors larger than 1 cm would not benefit at all from lymphadenectomy with respect to the maximum diameter of residual tumor matter. Patients with bulky nodes but complete or almost complete intraperitoneal debulking could benefit from removal of enlarged metastatic nodes by reducing the size of residual tumor. Lymphadenectomy in patients without clinically suspected lymph nodes and small residual intraperitoneal disease might not change the residual disease status but may reduce tumor burden that is possibly resistant to chemotherapy [118],[119] .
The latter hypothesis was tested by the International Multicenter Lymphadenectomy trial, which showed a beneficial impact of systematic lymphadenectomy with respect to progression-free survival (PFS) [14]. However, no survival benefit was reported in this trial, and some authors concluded that systematic lymphadenectomy should no longer be considered as standard therapy in advanced ovarian cancer [120].

The International Multicenter Lymphadenectomy trial indicated a 28% rate of clinically unsuspicious lymph nodes bearing metastatic disease. The poor reliability of intraoperative palpation for diagnosis of lymph node metastasis was confirmed by other trials [121], [122]. A possible reason for these findings maybe the similar size of metastatic and non metastatic lymph nodes [45], [123].

The role of complete lymphadenectomy as a staging procedure has been well established, providing information of prognostic relevance [14], [124], [125]. However, although suggested by many authors and retrospective single-institution series, the role of lymphadenectomy as a therapeutic procedure is less accepted.
A prospective international lymphadenectomy study compared systematic pelvic and para-aortic lymphadenectomy with removal of enlarged lymph nodes only in a cohort of mainly incompletely, but optimally debulked patients and found a significant benefit regarding PFS but not OS [14].

Du Bois and colleagues conducted a study to analyze the potential role of lymphadenectomy in advanced ovarian cancer. Their data indicated a survival benefit in specific subgroups defined by clinical lymph node status and residual intraperitoneal tumor. A significant impact for lymphadenectomy was observed in patients without residual disease but not in patients with small residual disease. There was also a significant survival benefit for patients who had pre- or intraoperative suspected lymph nodes, indicating a role for this operation as part of debulking by removing macroscopic tumor. This role was supported by their observation that more than 90% of patients with clinically suspect lymph nodes had histologically positive lymph nodes.
The combination of both residual disease and clinical lymph node status showed a significant impact of lymphadenectomy in patients with small residual disease and clinically suspect lymph nodes but not in patients with small residual tumor and clinically unaffected nodes [118].

This was in contrast to data by other studies that indicated a positive impact of lymphadenectomy even in patients with macroscopic residual disease [124], [125].

**Definition of systematic (complete) para-aortic node dissection**

Systematic (complete) para-aortic lymphadenectomy has been defined as the complete removal of all fat and nodal tissues surrounding the aorta, inferior vena cava and renal vessels from the left renal vein cranially to the midpoint of the common iliac vessels caudally [126]. Evidence of complete removal should facilitate the full and complete visualization of the adventitia of each of the aforementioned vessels, in addition to the full exposure of the anterior common vertebral ligament, anterior and lateral aspects of the vertebral bodies, psoas muscles and anterior sacrum.
It includes the separation and removal of all tissues lying between the arterial and venous vessels, and the clear identification of the origin/root of the ovarian vessels, inferior mesenteric artery, lumbar vessels and accessory vessels [126].

Pomel and colleagues proposed a classification system for para-aortic node dissection [126].

**Classification system for para-aortic node assessment**

(A) **Systematic para-aortic node dissection:**

- **A1:** Complete (includes infrarenal and suprarenal up to the celiac trunk to midpoint of common iliac vessels).

- **A2:** Infrarenal (as above, but does not include suprarenal dissection).

- **A3:** Infra-inferior mesenteric artery (IMA) (as above, but does not include dissection above IMA).
(B) Para-aortic node sampling

B1: Extensive (includes para-aortic areas, but does not allow full visualization of structures listed above, that is adventitia of vessels, renal vessels, anterior common vertebral ligament, psoas muscles and sacrum).

B2: Minimal (includes limited para-aortic areas, and does not allow full visualization of structures listed above).

(C) Non-excisional assessment

C1: Palpation (direct), following full exposure of para-aortic areas.

C2: Palpation (indirect), transperitoneal without any exposure.

C3: Radiological assessment by positron emission tomography (PET) / computed tomography (CT), CT or magnetic resonance imaging (MRI).

Nodal count is considered to be inaccurate in classification as it depends on other factors, including pathological assessment [126].
Technique of open para-aortic lymphadenectomy

The most common incision is the vertical midline incision [126], [127]. However Ayhan and colleagues in their study demonstrated that Pfannenstiel incision can be used for radical hysterectomy with pelvic and para-aortic lymphadenectomy in selected patients, without any negative influence on optimal resectability of tumor and surgical morbidity [128]. This was also concluded by Mendez and colleagues [129].

Pomel and colleagues proposed the following steps for undergoing a systematic para-aortic lymphadenectomy: [126]

1. Identification of the left renal vein

2. Freeing the right ureter medially

3. Identifying the left ureter medially behind the inferior mesenteric vein, above the level of the inferior mesenteric artery (fig 12).
4. Separating the fatty tissue anterior to the aorta, exposing the adventitia of the vessel along its full length and including the right common iliac artery, and mobilizing the nodal tissues laterally towards the left and right of the artery.

5. Dissecting the nodal tissues that have been mobilized towards the left of the aorta, starting cranially, without undue traction or mobilization of the aorta, in order to avoid injury to the posterior lumbar vessels.

The left para-vertebral sympathetic plexus is identified posteriorly.

6. Dissecting the nodal tissues along the right side of the aorta, allowing visualization of the anterior common vertebral ligament.

This dissection is continued to expose the left aspect of the IVC down to the level of the right common iliac artery.

7. Continuing the dissection to include the right side of the IVC with respect to the right paravertebral sympathetic plexus [126].
Chi and colleagues advised the identification and ligation of a fairly constant small vein ("fellow's" vein) within the lymphatics anterior to the IVC that inserts just above its bifurcation to prevent possible heavy bleeding which can result from its injury during dissection [127]. Chi also proposed the use of "split and roll technique." The vena cava is gently rolled medially and laterally. The lumbar veins are then doubly ligated and transected. Ligation of the lumbar veins allows for safe dissection behind the IVC and complete removal of the pericaval and retrocaval nodes. The lumbar arteries are doubly ligated, then transected. Ligation of the lumbar arteries allows safe dissection behind the aorta and complete removal of the periaortie and retroaortie nodes (fig13) [127].

Pomel and colleagues also recommended the use of clips or proper ligation when a large lymphatic duct has been identified [126].
Figure(12): Ureters dissected and retracted laterally. [127]
Figure (13): The left ovarian vein is ligated at the insertion into the renal vein (arrow); the lumbar vessels are ligated and the aorta mobilized. [127]
Pomel and colleagues proposed the addition of certain steps in case of dissecting bulky nodal masses to minimize possible blood loss. These include placement of vascular slings prior to the dissection of the bulky disease [126]. These slings are applied around the IVC at three locations: (1) suprarenal; (2) infrarenal; and (3) around the renal veins (fig.15).
These slings can be used to cut off the blood supply to the relevant areas of the vena cava during the dissection, to allow repair of any vessel injuries that may occur whilst minimizing blood loss and major hemorrhage [126].

**Figure (15):** Three slings are applied around the IVC at three locations: (1) suprarenal; (2) infrarenal; and (3) around the renal veins. [126]
**Technique of open pelvic lymphadenectomy:**

Pelvic lymphadenectomy is performed by incision of the posterior leaf of the peritoneum from the round ligament to the pelvic brim to allow adequate exposure to the retroperitoneum. After entering the retroperitoneal space, the ureter is identified as it crosses over the bifurcation of the common iliac artery.

Identifying and opening of the pararectal and paravesical spaces helps to define the anatomy of the region and to facilitate nodal dissection.

The pararectal space is bordered medially by the rectum, laterally by the internal iliac artery, anteriorly by the cardinal ligament and posteriorly by the sacrum, and can be opened by blunt dissection.

The paravesical space bordered by the superior vesicle artery medially, the external iliac artery laterally and the pubic ramus anteriorly, and is also opened with blunt dissection.
The lymphadenectomy is started with the external iliac nodes by grasping the node-bearing pad of fat over the external iliac vessels with forceps and freeing this nodal tissue from the underlying vasculature by scissor dissection from cephalad to caudal and from lateral to medial (fig. 16). Care should be taken to preserve the genitofemoral nerve which is present along the pelvic wall, lateral to the external iliac vessels. Small vessels can be clipped with vascular clips, and then transected.

The level of dissection is from the common iliac vessels to the deep circumflex iliac vein. Sometimes an abnormal obturator vessel arises near the distal aspect of the external iliac vessels and should be carefully identified and ligated.

After completion of the external iliac node dissection, the next step is obturator node dissection. The obturator space is entered by using a vein retractor to reflect the external iliac vessels away from the psoas muscle and the obturator nerve is identified by using a combination of blunt and sharp dissection. The lymphatics between the obturator nerve and external iliac vessels are cleared and the node-bearing tissue between the obturator nerve and obturator vessels gently released.
The obturator vessels lie below the nerve and should be visualized throughout the dissection to minimize risk of their injury which can lead to bleeding that is difficult to control. Bleeding from the obturator vein is best controlled with direct visualization and ligation of the vessel when possible. Otherwise, pressure and packing of the obturator space can be done if the bleeding source is not visible. The next step is dissection of the internal iliac nodes to the bifurcation of the common iliac vessels followed by removal of the common iliac nodes to complete the pelvic nodal dissection [130], [131].

Fig(16): Pelvic lymphadenectomy[131]
Laparoscopic Lymphadenectomy:

Although no randomized data exist for patients with ovarian cancer, the body of retrospective investigations suggests that these benefits can be extrapolated to include patients undergoing comprehensive staging for early ovarian cancer. The retrospective literature examining staging for ovarian cancer confirms that the laparoscopic approach has been associated with decreased estimated blood loss, shorter hospital stay, quicker return of bowel function, and shorter interval to adjuvant chemotherapy administration [132]. The existence of port site metastasis, a higher incidence of intraoperative tumor rupture, and an unknown rate of disease recurrence all represent tangible risks associated with laparoscopic staging [132].

An important drawback of using laparoscopy in the management of ovarian cancer is the potential for port-site metastases or tumor implantation. In a study by Vergote and colleagues on the role of laparoscopy in diagnosing ovarian cancer, trocar site implantation was observed in 5% of the 173 patients. An additional 12% of patients had subclinical trocar site metastases only discovered on pathological examination of the resected port-sites.
They concluded in their study that there was a high rate of port-site metastases after laparoscopy in patients with advanced ovarian carcinoma. However, prognosis was not worse in this group of patients [133].

Dottino and colleagues illustrated in their study that laparoscopic lymphadenectomy was a safe procedure with an adequate number of lymph node yield [134]. In the largest series to date consisting of 650 patients with gynecological cancers, Kohr and colleagues showed an excellent pelvic lymph node count (16.9-21.9). The number of para-aortic lymph nodes increased from 5.5 to 18.5 over the 9 years that the study lasted and the technique developed further.

Chi and colleagues evaluated 20 patients who underwent laparoscopic staging and 30 patients who had staging via laparotomy for apparent stage I ovarian cancers. Bilateral pelvic and para-aortic lymphadenectomy were done to all patients as part of their staging. There were no differences in numbers of lymph nodes removed between the two groups. The authors concluded that patients with apparent stage I ovarian and fallopian tube cancers can safely and adequately undergo laparoscopic surgical staging [135].
Similar results were concluded by Ghezzi and colleagues comparing 15 patients undergoing laparoscopic and 19 patients undergoing staging by open laparotomy. There were no significant differences between the two groups with regard to median number of lymph nodes and likelihood of identifying metastatic disease [136].

**Laparoscopic Extraperitoneal Lymphadenectomy**

The extra peritoneal laparoscopic approach for para-aortic lymph node dissection was first described by Vasilev and McGonigle [137]. Several authors have outlined their technique and assessed its safety and feasibility [138], [139], [140].

Generally, after the laparoscope is placed through the umbilicus and the abdomen is insufflated, an incision is made 2 cm medial to the anterior superior iliac spine along the McBurney line and carried down to the fascia. Blunt dissection is carried to the peritoneum. Once the retroperitoneum is identified and entered, dissection is performed to open the area above the psoas muscle.
A trocar is then placed in the retroperitoneum, CO2 gas is removed from the intraperitoneum, and the retroperitoneal space is insufflated to allow for para-aortic and common pelvic lymph node dissection [138].

Burnett and colleagues performed the procedure on 46 patients, with a median lymph node yield of 14 (range, 0–60). Only two patients had a disruption of their peritoneum such that transperitoneal lymphadenectomy had to be performed [139]. In the largest series, Sonoda and colleagues identified 111 patients who underwent an infrarenal aortic and common iliac lymph node dissection for bulky or locally advanced cervical cancer, the mean node count was 19 (+_12) [140].

**Robotic surgery in lymphadenectomy:**

Studies comparing robotic surgery to laparoscopy and laparotomy for cervical and endometrial cancer patients have shown comparable or superior outcomes to laparoscopy and advantages over laparotomy [141], [142], [143].
Studies regarding robotic surgery for ovarian cancer are still inadequate. Magrina and colleagues compared robotic surgery to laparoscopy and laparotomy in the management of ovarian cancer [144]. Their study consisted of 43 patients who underwent a robotic approach for the primary or secondary surgical treatment of ovarian cancer. These patients were compared to a similar group of patients matched by age, BMI, type and number of surgical procedures and treated by laparoscopy (N=27) or laparotomy (N=119) at the same institution. Patients in each surgical group were classified into type I, II or III debulking according to the extent of debulking surgery based on type and number of major procedures.

Type I debulking patients underwent primary tumor excision consisting of hysterectomy, salpingio-ophorectomy, omentectomy, pelvic and aortic lymphadenectomy, appendectomy and removal of metastatic peritoneal disease if present. Type II patients underwent a type I debulking and one additional major procedure. Type III patients underwent a type I debulking and 2 or more major procedures.
Included as major procedures were any type of intestinal resection, full thickness diaphragm resection, resection of liver disease, and splenectomy.

The average number of pelvic lymph nodes dissected was 13 for robotic, 14 for laparoscopic and 13 for laparotomy procedures. While the average number of para-aortic lymph nodes dissected was 12 for robotic, 7 for laparoscopic and 9 for laparotomy procedures. Magrina and colleagues concluded in their study that robotics and laparoscopy appeared preferable to laparotomy for the surgical treatment of ovarian cancer patients requiring primary tumor excision alone or with one additional major procedure. Laparotomy remains preferable for patients requiring primary tumor excision and 2 or more additional major procedures [144].

Zanagnolo and colleagues described their technique for Robotic para-aortic lymphadenectomy using Da Vinci System. An optical 12mm trocar was inserted 3 or 4 cm suprapubically and 1 or 2 cm to the left of the midline. Two robotic trocars were inserted 10 to 12 cm to the right and the left of the optical trocar, a third robotic trocar was placed 10 to 12 cm the left of the umbilicus.
Two of the robotic arms were used for the pelvic approach as well therefore reducing the total number of trocar sites (fig 17) [145].

A monopolar scissors was used on the right robotic arm or on the left one in case of a left handed surgeon, and a bipolar grasper was used on the left robotic arm or vice versa for a left-handed surgeon. For the first few cases two accessory trocars were placed 2 cm caudally and equidistant to the right and left of the optical trocar, afterwards only one accessory trocar was placed equidistant between the suprapubic optical trocar and the left robotic trocar [145].

The patient was placed in Trendelenburg position, and the robotic column was positioned at the patient’s head. The assistant stood between the patient’s legs and when 2 accessory trocars were used, the left hand was used to retract the duodenum and pancreas ventrally with a 10mm fan bowel retractor introduced through the left assistant trocar and the right hand for lateral retraction of the sigmoid mesentery [145].
Since they have started to use the 4th arm with a fenestrated grasper to retract the duodenum ventrally, the 2nd assistant trocar to the right of the optical trocar was not placed anymore and the assistant used the accessory port to the left. A small (3-4 cm) incision was made on the peritoneum overlying the midportion of the right common iliac artery and extended to the aortic bifurcation. A small tent was then created by gently elevating the peritoneum ventrally with the 4th arm gasping forceps, preventing the small bowel from sliding into the surgical field [145].

After identifying the right ureter the right aortic nodes over the vena cava were excised first, as well as the interaortic nodes. The dissection was extended cranially until no nodal tissue was present, usually at or above the level of the insertion of the right ovarian vein to the vena cava [145].

To access the inframesenteric left aortic nodes, the surgeon extended the peritoneal incision from the aortic bifurcation caudally and over the left common iliac artery for approximately 4 to 5 cm. The sigmoid mesentery was retracted laterally by the assistant surgeon, exposing the psoas muscle and the left ureter. The left inframesenteric nodes were then removed (fig.18) [145].
The inferior mesenteric artery, when necessary, was transected with a tissue-sealing device to increase exposure by allowing additional lateral mobilization of the left colon mesentery and facilitating the removal of the left infrarenal nodes.

The left ovarian vein and the cranial border of the left renal vein were the lateral and upper limits of left aortic dissection, respectively [145].

Figure (17): Trocar sites for para-aortic lymphadenectomy. TL: Telescope, RT: Robotic trocar, AT: Assistant trocar. [145]
Figure (18): (a) Dissection of inferior mesenteric nodes (b) Exposure of inferior mesenteric artery. [146]
COMPLICATIONS OF LYMPHADENECTOMY

1-Symptomatic postoperative lymphocyst:

Symptomatic postoperative lymphocyst may occur few weeks to few months after surgery. A study of the natural history of pelvic lymphocysts showed that 40% of 108 patients had lymphocysts detected by repeated routine ultrasonography, including 81% 2 weeks after surgery and none more than 6 months after surgery [147]. However, other studies have reported lymphocysts developing up to 2 years after surgery [148].

Kim and colleagues demonstrated in their study that a high BMI was significantly associated with lymphocyst formation. However, no cutoff value was determined for increasing the risk [149]. This finding wasn’t reported in a study done by Achouri and colleagues as their results showed that the mean BMI was not significantly higher in the patients with SPOL than in the other patients [150].
Results of previous studies showed lymphocyst formation was mainly related to pelvic lymph node dissection. And that the addition of para-aortic lymphadenectomy didn’t affect the risk of lymphocyst formation [150], [151],[152]. In their prospective randomized trial on 234 patients, Franchi and colleagues concluded that the number of lymph nodes removed during pelvic lymph node dissection did not affect the risk of symptomatic post-operative lymphocyst formation [152]. This finding was also concluded by Achouri and colleagues [150].

Regarding the role of positivity of lymph nodes removed as a risk factor for lymphocyst formation, there were different results in the literature. Tam and colleagues have shown in their study that positive lymph nodes in the lymphadenectomy specimen was a risk factor for lymphocyst formation [147]. This was also demonstrated in the study by Petru and colleagues, [152]. In contrast, another study found no impact of node status on lymphocyst incidence [153].
Intraoperative drainage didn’t significantly influence the risk of lymphocyst formation in previous studies [150], [153]. In fact, it increased the risk of lymphocyst formation in some studies [151], [154].

2-Lower limb lymphedema:

Several studies have demonstrated that lower limb lymphedema following pelvic lymph node dissection occur during the first year [150], [155], [156].

There are different results regarding the role of the number of lymph nodes removed in increasing the risk of lower limb lymphedema. Some studies showed that the risk of lymphedema increased with increase in the number of lymph nodes dissected [157], [158]. Other studies showed that there was no difference [150].

The addition of para-aortic lymphadenectomy didn’t increase the risk of lymphedema in several studies [9], [150], [156]. Regarding the role of the surgical approach in increasing the risk of lower limb lymphedema, a number of studies demonstrated that there was no difference in the incidence of lymphedema between open laparotomy and laparoscopy [150], [157], [159].
3-Postoperative ileus:
Postoperative ileus can occur following para-aortic lymph node dissection because the abdominal aortic plexus related to the aorta is responsible for control of intestinal movement. Incidence of postoperative paralytic ileus following para- aortic lymphadenectomy ranged in the literature from 4.4 to 12.9 %. Fujita and colleagues evaluated in their study the incidence of postoperative ileus after para-aortic lymph node dissection in patients with malignant gynecologic tumors, the study consisted of 217 patients with malignant gynecological tumors, 39 of which were patients with ovarian cancer. The severity of ileus was classified into 3 classes according to its duration, i.e. mild (1 week or less), moderate (more than 1 week, but 1 month or less), and severe (more than 1 month). Postoperative ileus occurred in 28 (12.9 %) of the 217 patients. Twenty five patients had mild to moderate ileus, while only 3 had severe ileus. There was no significant differences in the incidence of postoperative ileus between patients that underwent para-aortic lymphadenectomy till the level of the left renal vein and those who underwent para-aortic lymphadenectomy to the level of the inferior mesenteric artery[10].
4-Thromboembolic Events:

The incidence of DVT and/or pulmonary embolism following pelvic lymphadenectomy has been reported to be 0-8%[160]. A study by Musch and colleagues highlighted the association between lymphocele and the increased risk of thromboembolic events. In that study, DVT and pulmonary embolism occurred in 8.3% and 2.8% respectively, compared with less than 1% of the patients without a lymphocele (P=0.001) [161].

5-Ureteral Injury:

Injuries to the ureter during pelvic lymphadenectomy is a relatively infrequent complication, occurring in less than 1% of large series [160], [161], [162].

6-Neurologic Injury:

The most common neurologic injury during pelvic lymphadenectomy is injury to the obturator nerve which can sustain either a transection or crush injury during lymphadenectomy [163].
Recent series have reported lower rates of injury during both open and laparoscopic pelvic lymphadenectomies ranging from 0% to 1.8% [164, 165].
Patients and Methods

A prospective study of 31 patients with epithelial ovarian cancer admitted to the surgical department at the National Cancer Institute, Cairo University in the period from May 2011 to April 2013.

The patients were included in the study according to the following inclusion: Patients with stage I, II and non bulky stage III, as well as patients who received neoadjuvant chemotherapy with good clinical response and were scheduled for interval debulking. Preoperative evaluation included patient’s history which consisted of the patient’s age, age of menarche and menopause, and family history of ovarian cancer. Physical examination included general, abdominal and pelvic examination. Laboratory investigations were in the form of complete blood picture, liver and kidney function tests, blood sugar, coagulation profile and tumor marker CA-125. Radiological investigations consisted of chest X-ray, CT abdomen and pelvis with oral and IV contrast. Others as MRI, IVP and colonoscopy were performed when indicated by clinical findings. Diagnosis of malignancy was done through (1) Patients with radiological criteria suspicious of malignancy:
Complex masses with solid component, omental masses, and peritoneal nodules. (2) Elevated CA-125 levels in postmenopausal patients. (3) In patients with uncertain malignancy, intra-operative frozen section was done for the ovarian masses. (4) Patients explored following neoadjuvant chemotherapy were diagnosed by cytology from ascites or biopsy from omental cakes.

**Intra-operative method:**

Patients underwent surgical staging in form of total abdominal hysterectomy, bilateral salpingio-ophorectomy, omentectomy, aspiration of ascites or peritoneal lavage for cytological examination, biopsy from peritoneal surface, maximal cytoreduction. Pelvic lymphadenectomy was done by removal of lymph nodes overlying and medial to the external iliac and hypogastric vessels, from the obturator fossa anterior to the obturator nerve, and overlying the common iliac artery. Some patients had pelvic lymph node sampling of only grossly suspicious nodes. Aortic lymph node dissection was done by stripping the nodal tissue from the vena cava and aorta bilaterally to the level of the inferior mesenteric artery and in some cases to the level of the renal vessels.
Some cases underwent para-aortic lymph node sampling by incising the peritoneum over the aorta and inferior vena cava. Lymph node specimen was labeled according to side (left and right) and groups of lymph nodes.

Pathological processing:
All lymph nodes were dissected from the surgical specimen and fixed in formalin. Each lymph node greater than 3 mm was bivalved or serially cut to between 2 to 3 mm along the transverse plane to have the widest surface. All lymph nodes were submitted in their entirety. The entire specimen was then dissected in a standard fashion, and fixed in formalin.

All lymph nodes dissections and primary tumors were examined as in a routine histologic examination. Pathologic analysis of the primary tumor included assessment of tumor type, stage, histologic grade and histologic response in case of preoperative chemotherapy.

The Histologic type and the grade of ovarian epithelial tumor were determined according to WHO classification of tumors of the female genital organs. The stage of tumor was determined according to FIGO staging system.
Statistical methods:

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 21.

Numerical data were summarized using means and standard deviations or medians and ranges. Categorical data were summarized as percentages.
Figure (19): Ovarian cancer composed of complex cystic mass showing soft tissue component.

Figure (20): Bilateral ovarian cancer with ascites
Figure (21): Total abdominal hysterectomy with bilateral salpingio-oophorectomy for bilateral ovarian cancer.

Figure (22): Total abdominal hysterectomy with bilateral salpingio-oophorectomy for right ovarian cancer.
Patients and Methods

Figure (23) : Total abdominal hysterectomy with bilateral salpingi-oophorectomy for left ovarian cancer

Figure (24): Para-aortic lymphadenectomy
Figure (25): Para-aortic lymphadenectomy.
Patients and Methods

Figure (26): Resected para-aortic nodes.

Figure (27): Pelvic lymphadenectomy.
Figure (28) : Resected pelvic lymph nodes .
**Results**

**Age:**
Mean age of patients was 52.7 years, the oldest patient was 74 years and the youngest 29 years. Mean age of patients with positive lymph nodes was 55.2 with the oldest patient aged 67 years and youngest 35 years.

**Menopausal status:**
Of the 9 patients with positive lymph nodes, 7 were post-menopausal (77%) while 2 (22%) were pre-menopausal.

**Laterality:**
Thirteen patients had bilateral ovarian tumors, 10 patients had left ovarian tumors and 8 patients had right ovarian tumors. Regarding patients with positive lymph nodes, 5 patients had left ovarian tumors, 2 patients had right ovarian tumors and 2 patients had bilateral ovarian tumors. There were no contralateral nodal metastases.
Ascites:
Ten patients had ascites, 2 of them had positive lymph nodes. Three patients had positive cytology.

Clinical stage:
The most prevalent clinical stage was stage IA which was present in 11 patients, followed by stage IIIC in 7 patients, stage IIB and IIIB both in 5 patients, stage IC in 2 patients and stage IIC in one patient.
Patients with positive lymph nodes:

Three patients with clinical stage IA, 2 patients with stage IIB, 2 patients with stage IIIB and 2 patients with stage IIIC had positive lymph nodes.

Figure (30): Clinical stage of patients
Results

Final staging:

The most common stage after pathological assessment was stage IIIC which was present in 14 patients, followed by stage 1A in 9 patients, stages IC and IIIB both in 3 patients, and finally stage IIB which was present in 2 patients.

![Final Staging](image)

Figure (31): Final staging of patients

Types of lymphadenectomy:

Ten patients had pelvic and para-aortic lymphadenectomy, 14 patients had only pelvic lymphadenectomy and 5 patients had only para-aortic lymphadenectomy.
Four patients had lymphadenectomy of pericolic lymph nodes because of colonic invasion by the ovarian tumor.

Figure (32): Types of lymphadenectomy

Pelvic lymphadenectomy:

Twenty four patients in total had pelvic lymphadenectomy, 21 of these had bilateral pelvic lymphadenectomy, 2 had only right lymphadenectomy and one had only left lymphadenectomy.
Of the 24 patients, 6 had positive nodes. 4 of them bilateral positive nodes and 2 had positive left pelvic nodes. All positive nodes were on the same side of the primary tumor.

Total number of dissected pelvic nodes was 259 nodes with a mean of 10.7 nodes. Total number of positive pelvic nodes was 50. Total number of dissected right pelvic nodes was 142 nodes, of which 24 were positive. Total number of dissected left pelvic nodes was 117 nodes, of which 26 were positive.

Figure (33): Pelvic lymphadenectomy
Para-aortic Nodes:
Fifteen patients had para-aortic lymphadenectomy, 3 of them had positive para-aortic nodes. Total number of dissected nodes was 97 with a mean number of nodes of 6.4. Total number of positive nodes was 11.

Pericolic Nodes:
Four patients had dissection of the pericolic nodes due to colonic invasion by the primary ovarian tumor. Three patients had positive pericolic nodes. Total number of dissected pericolic lymph nodes was 38 nodes with a mean number of nodes of 9.5, of this total number, 15 were positive.

Histological types:
The most predominant histological type was serous cystadenocarcinoma which was present in 20 patients, other histological types included mucinous type in 5 patients, endometrioid type in 3 patients and clear cell type in 3 patients.
Among patients with positive nodes, serous histology was the most common histological type and was present in 5 patients, followed by mucinous type in 2 patients, and endometrioid and clear cell types in one patient each.

![Bar chart showing histological types of tumors]

Figure (34): Histological types of tumors
**Results**

**Grade:**

Most frequent grade was grade 2 which was present in 17 patients, followed by grade 3, found in 11 patients and grade 1 found in 3 patients.

None of the patients with grade I had lymph node metastases, whereas 4/17 (23%) patients with grade 2 and 5/11 (45%) patients with grade 3 had lymph node metastases.

![Bar chart showing grade distribution and lymph node positivity](chart.png)

*Figure (35): Grade of tumors*
Neoadjuvant chemotherapy:
Ten patients with advanced ovarian tumors received neoadjuvant chemotherapy. Two of them had positive lymph nodes (20%).

CA-125 level:
All patients included in the study had CA-125 level above normal value except for one patient. Tumor marker CA-125 levels in patients with positive lymph nodes ranged from 97 to 14554 u/ml. Patients with less than 10 positive nodes had a level ranging from 80-523 u/ml, while patients with more than 10 positive nodes had a level ranging from 97 to 14554 u/ml.
Lymphatic drainage of the ovary is known to follow the gonadal blood supply. The dominant lymph channels coalesce in the infundibulopelvic ligament, where they travel with the pampiniform plexus of the ovarian veins, and then drain into the inferior pole of the kidney and move medially into the para-aortic and precaval lymph nodes[24]. An ancillary lymphatic pathway from the hilus of the ovary traverses the broad ligament draining into the obturator, external, and common iliac nodes [11], [13].

The pattern of lymph node spread in ovarian cancer has long been an area of interest. In 1985 the staging of ovarian cancer by FIGO was modified to incorporate the more aggressive biologic behavior associated with lymph node spread. This is due to the fact that lymph nodes are major sites for metastatic involvement and because accurate information on nodal status is essential in determining disease stage.

Retroperitoneal lymph node dissection aims at ensuring the following advantages: proper staging of disease, prediction of patient prognosis, and improvement of patient survival [166].
In this study we tried to answer questions regarding the factors that were possibly associated with the risk of developing lymph node metastases as well as the distribution of those lymph nodes.

Number of metastatic nodes:

There are numerous published data evaluating the clinical predictors and importance of lymphatic metastasis [5], [40],[41], [45], [50]. However, few of the studies had previously analyzed the number of metastatic lymph nodes (Table 1).
Discussion

Table (1) Review of the literature about the number of resected metastatic lymph nodes[167]

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Threshold (Number of metastatic nodes)</th>
<th>Correlation</th>
<th>Prognostic value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burghardt et al.</td>
<td>1991</td>
<td>91</td>
<td>1 vs ≥1</td>
<td>Clinical stage, residual disease</td>
<td>Yes</td>
</tr>
<tr>
<td>Benedetti-Panici et al.</td>
<td>1993</td>
<td>35</td>
<td>-</td>
<td>Clinical stage</td>
<td>-</td>
</tr>
<tr>
<td>Petru et al.</td>
<td>1994</td>
<td>9</td>
<td>1 vs ≥1</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Di Re et al.</td>
<td>1996</td>
<td>194</td>
<td>-</td>
<td>Clinical stage, residual disease</td>
<td>No</td>
</tr>
<tr>
<td>Onda et al.</td>
<td>1998</td>
<td>38</td>
<td>1-4 vs ≥4</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>Suzuki et al.</td>
<td>2000</td>
<td>5</td>
<td>-</td>
<td>Clinical stage</td>
<td>-</td>
</tr>
<tr>
<td>Morice et al.</td>
<td>2000</td>
<td>122</td>
<td>1 vs ≥1</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>Ayhan et al.</td>
<td>2007</td>
<td>328</td>
<td>≤4 vs ≥4</td>
<td>High CA-125 levels</td>
<td>No</td>
</tr>
</tbody>
</table>

Kleppe and colleagues undertook a meta-analysis to compare the results of 14 studies on lymph node metastases in stage I and stage II ovarian cancer. Of these studies, 2 were randomized controlled studies and 12 were retrospective cohort studies.
Mean number of removed para-aortic and pelvic lymph nodes ranged from 15 to 46 and 14 to 74 respectively [33]. Carnino and colleagues saw 3.9 times more lymph node metastases when the node yield was more than 10 as compared to the removal of one to five nodes (95% confidence interval (CI) 1.0–15) [3].

The mean number of lymph nodes in our study was less than other studies, with a mean of 10.7 pelvic and 6.4 para-aortic lymph nodes dissected. In a study by Morice and colleagues the mean number of nodes resected was 14 pelvic and 15 para-aortic, whereas in another retrospective study by Pereira and associates, the mean number of resected pelvic and para-aortic nodes was 24 and 13 respectively [5], [45]. The variation in number of pelvic (1 to 25) and para-aortic (1 to 15) nodes dissected in our patients which made the mean number of nodes in our study less than other studies could be due to the fact that our patients were operated upon by a variety of surgeons from all units of our surgical department. This lead to different degree of expertise and discrepancy in surgical experience among the different operators.
There was a moderate correlation between total number of pelvic nodes and positivity (p=0.01), and also between total number of right pelvic nodes and right pelvic node positivity (p=0.003). Whereas there was a weak correlation between total number of left pelvic nodes and left pelvic node positivity (p=0.012) and total number of para-aortic lymph nodes and node positivity (p=0.098).

In their study on pelvic and para-aortic lymph node metastases in epithelial ovarian cancer which included 116 patients, Periera and colleagues proposed that for documenting lymph node metastases in EOC, about 25 dissected pelvic lymph nodes and 13 aortic lymph nodes were adequate [45]. Pereira and colleagues also recently tried to define the optimal lymphadenectomy cut-off value in epithelial ovarian cancer staging surgery utilizing a mathematical model of validation. The mean number of lymph nodes and metastatic nodes removed were 35 and 7.8 respectively. The optimal point of each fitting curves were: 7 nodes for unilateral aortic nodal sampling (at least 3 infrarenal or 5 inframesenteric) and 15 nodes for unilateral pelvic lymphadenectomy (at least 5 external iliac).
They concluded that they managed to mathematically predict the probability to obtain a positive node in EOC surgical staging by dissection of at least 22 pelvic and para-aortic lymph nodes [168].

In our study, mean number of lymph nodes dissected in premenopausal patients was greater than that in postmenopausal patients, 14 vs 9.6 nodes. Although our results were not statistically significant, other studies showed similar significant results. Harema and colleagues conducted a retrospective study to assess the factors influencing the number of pelvic and para-aortic lymph nodes removed in surgical treatment of endometrial and ovarian cancer. The number of lymph nodes removed was correlated with age, year of surgery, the operating surgeon, pathologist, height, body weight, body mass index (BMI), body surface area, histology, clinical stage, operating time, blood loss, and LN metastasis [169].
The results of their study showed a significant correlation between number of lymph nodes removed and age (≤49 years: 80 LNs [range, 48-140 LNs]; 50-64 years: 69 LNs [range, 32-139 LNs]; (P = 0.036), histology (clear: 79 LNs [range, 50-140 LNs]; serous: 67 LNs [range, 32-117]; (P = 0.015), and BMI (≤25: 69 LNs [range, 32-140]; ≤25: 90.5 LNs [range, 54-137];( P =0.0001) in ovarian cancer. Multivariate linear regression analysis confirmed that age and BMI were independent risk factors for removed LN counts (Table 2). There was no significant correlation between number of lymph node removed and other factors [169].

Table (2). Multiple linear regression analysis of number of pelvic and para-aortic LNs removed in ovarian cancer. [169]

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>SE</th>
<th>β*</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.386</td>
<td>0.184</td>
<td>-0.168</td>
<td>5.411</td>
<td>0.038</td>
</tr>
<tr>
<td>BMI</td>
<td>1.187</td>
<td>0.468</td>
<td>0.203</td>
<td>-2.096</td>
<td>0.012</td>
</tr>
<tr>
<td>Histology</td>
<td>-2.532</td>
<td>0.468</td>
<td>0.203</td>
<td>2.537</td>
<td>0.091</td>
</tr>
<tr>
<td></td>
<td>77.664</td>
<td>14.354</td>
<td></td>
<td>5.411</td>
<td>≤0.0001</td>
</tr>
</tbody>
</table>

B: Unstandardized regression coefficient. SE: Standard error
β : Standardized regression coefficient, Y = 77.664Y0.386 _ age + 1.187 _ BMI.. t : t-statistic. P: P-value
A possible explanation to the decrease in number of metastatic nodes in older patients is the decrease of immunologic reactions to cancer and inflammatory processes associated with old age [170], [171]. Whereas Fournier and colleagues didn’t find age as an independent risk factor [155].

**Histology:**

The commonest histological type associated with lymph node metastases in the literature is the serous type [16], [26]. This was also the most common type in our study (55%) followed by mucinous type (22%) then clear and endometrioid types (11%). Kleppe and colleagues studied in their review the results of 8 prospective and retrospective cohort studies that included 574 patients and concluded that the incidence of metastatic lymph nodes was higher in serous (23.3%) and lowest in mucinous tumors (2.6%) [33]. Similar results were shown by Morice and colleagues in their retrospective study that included 276 patients. The frequency of nodal involvement according to the histologic subtype of the tumor was: 57% (90 / 157) for serous tumors, 13% (4 / 30) for mucinous tumors, and 28% (16 / 56) for endometrioid tumor [26].
The results of their study also showed that none of the patients with stage I mucinous tumors had lymph node involvement, this observation was previously highlighted in the literature [15], [40, 49, 172]. According to these results, Morice and colleagues suggested that lymphadenectomy may be spared in patients with stage I unilateral mucinous tumors [26]. Another finding in the study was that none of the patients with stage I endometrioid tumors had lymph node involvement. However, lymph node metastases in the literature varied from 0-9% [49]. So it was proposed that further studies were needed to evaluate the precise risk of lymph node metastases in stage I endometrioid tumors [5].

One of our patients had stage I endometrioid tumor and she had negative nodes, but only para-aortic lymph nodes were dissected in this patient without pelvic nodes. The role of intra-operative frozen section analysis for diagnosis of ovarian cancer has been previously highlighted in the literature, Cross and colleagues showed in their study that included 1439 cases of suspected early-stage ovarian cancer that intra-operative frozen section had a sensitivity and specificity of 91.2% and 98.6%, respectively [173].
This was in accordance with another study by Wootipoom and colleagues which included 229 patients and showed sensitivity and specificity for malignant tumors of 96.4%, 98.5% respectively [174]. In our study, 4 patients underwent intra-operative frozen section. All 4 patients were confirmed to have ovarian cancer, the histological types were 3 serous and one endometrioid.

Takeshima and colleagues undertook a study to compare the difference in lymph node metastases between serous and non-serous tumors (table 3). Their results showed that in case of serous tumors, 86.4% (19/22) of patients with metastatic lymph nodes had metastases in the para-aortic region, with 14 patients having positive nodes located above the inferior mesenteric artery and 5 below it [41]. These findings suggested that the dominant lymphatic drainage from serous tumors was directed to the para-aortic lymph nodes, with the region above the inferior mesenteric artery being the most common site [41]. However, the results were different in non-serous tumors, where positive nodes were detected throughout the pelvic and para-aortic regions, with only 53.8% (7/13) of the metastatic lymph nodes located in the para-aortic region.
They concluded according to their results that it could be possible to determine the extent of lymph node dissection according to the histological type of the primary tumor.

Serous tumors caused nodal metastases more than non-serous tumors, with the para-aortic region above the inferior mesenteric artery being the most common site of nodal metastases. Therefore they proposed that lymph node dissection in this area alone maybe a valid option, especially that serous tumors were chemosensitive and adjuvant chemotherapy has been shown to be comparable to performing lymphadenectomy in other regions in previous studies. Whereas non-serous tumors didn’t have a special pattern for nodal metastases and were generally chemoresistant, therefore they proposed that a systemic lymphadenectomy was appropriate for non-serous tumors (fig.36) [41].
Table (3): Lymph node involvement in relation to tumor histology [41]

<table>
<thead>
<tr>
<th>Histology</th>
<th>Nodal disease+</th>
<th>Only Para-aortic+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Only pelvic+</td>
<td>Both+</td>
</tr>
<tr>
<td>Serous (n = 60)</td>
<td>22 (36.7%)</td>
<td>14 (23.3%)</td>
</tr>
<tr>
<td></td>
<td>2 (3.3%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Non-serous (n = 148)</td>
<td>25 (16.9%)</td>
<td>6 (4.1%)</td>
</tr>
<tr>
<td></td>
<td>4 (2.7%)</td>
<td>15 (10.1%)</td>
</tr>
<tr>
<td>Clear (n = 71)</td>
<td>12 (16.9%)</td>
<td>4 (5.6%)</td>
</tr>
<tr>
<td></td>
<td>1 (1.4%)</td>
<td>7 (9.9%)</td>
</tr>
<tr>
<td>Endometrioid (n = 32)</td>
<td>5 (15.6%)</td>
<td>2 (6.3%)</td>
</tr>
<tr>
<td></td>
<td>2 (6.3%)</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Mucinous (n = 26)</td>
<td>2 (7.7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>0 (0%)</td>
<td>2 (7.7%)</td>
</tr>
<tr>
<td>Mixed (n = 12)</td>
<td>4 (33.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>0 (0%)</td>
<td>4 (33.3%)</td>
</tr>
<tr>
<td>Other (n = 7)</td>
<td>2 (28.6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>1 (14.3%)</td>
<td>1 (14.3%)</td>
</tr>
</tbody>
</table>
Fig (36). Distribution of 35 metastatic lymph nodes from 25 patients with up to 3 positive nodes. In patients with serous tumor, 86.4% (19/22) of metastatic lymph nodes were found in the para-aortic region, with 14 of the positive nodes located above the inferior mesenteric artery and 5 below it, whereas metastases from non-serous tumors were found throughout the pelvic and para-aortic regions. [41]

From the above conflicting results of different studies, we cannot conclude that there is clear evidence that there are subgroups of patients with certain histopathology or grade that wouldn’t benefit from nodal dissection.
And those 2 variables have not been adopted as determinants for lymphadenectomy by the current NCCN guidelines [7].

In our study, from the 5 patients with serous type and positive nodes, 3 patients had positive bilateral pelvic and para-aortic lymph nodes. The other 2 patients had positive ipsilateral pelvic nodes, yet no para-aortic lymphadenectomy was done.

The 3 patients in our study that had positive mesenteric lymph node metastases due to colorectal invasion by the primary ovarian tumor all had different histological types, serous, mucinous and endometrioid. Whereas other studies showed higher incidence in serous tumors such as the study conducted by Gouy and colleagues which included 52 patients who underwent debulking surgery for advanced ovarian cancer with bowel resection, and a study by Park and colleagues that included 60 patients with advanced primary and recurrent ovarian cancer that underwent low anterior en bloc resection as part of cytoreductive surgery [34].
Discussion

Since both studies included only patients with advanced ovarian cancer that necessitated bowel resection, in order to accurately compare our results, a further study including only patients with advanced ovarian cancer who underwent bowel resection as part of cytoreductive surgery should be conducted.

Stage:

Most studies in the literature illustrated that incidence of lymph node metastases increased with clinical stage. Incidence of lymph node metastases in a study by Morice and colleagues that included 276 patients was 20% for stage I, 40% for stage II and 55% for stage III [5]. Also in a study by Takeshima and associates which included 208 patients this incidence was 12% for stage I, 48% for stage II and 60% for stage III (table 4)[41]. Whereas in a study by Fournier that included 355 patients the incidence was 10% for stage I, 27% for stage II and 62% for stage III [5, 41, 175].

The incidence of lymph node metastases in our study according to stage was 23% for stage I and 33% for both stage II and III.
Discussion

Although the incidence of nodal metastases was similar in both stage II and III, yet the mean number of dissected para-aortic nodes which is the most common site of nodal metastases in epithelial ovarian cancer was less in stage III patients (2.8 nodes) than in stage II patients (6.4 nodes). This may explain the lower incidence of nodal metastases in stage III patients compared to the literature.

Table (4) Lymph node involvement in relation to clinical stage [41]
The incidence of occult lymph node metastases in clinical stage I disease varies in the literature from 4 to 27% [5], [24],[ 49], [121], [176]. The rate of nodal involvement in our study for patients with apparent stage I tumors was 23%, all of them being stage IA which correlates with other series in the literature.

In an attempt to highlight the importance of proper surgical staging in clinically early stage ovarian cancer, Young and colleagues performed systemic restaging laparotomy for 100 patients referred to them with early ovarian cancer. Thirty-one percent of patients were found to have upstaged disease and 77% of these patients had stage III disease. The most frequent sites of extra pelvic involvement were para-aortic nodes (19%) and peritoneal washings (19%) [177].

Grabowski and colleagues also restaged 35 patients referred to their institution with presumed early ovarian cancer limited to the pelvis. After comprehensive restaging surgery, 50% of patients were upstaged and 65% of upstaged patients had stage IIIC disease. Pelvic peritoneum (34%) and para-aortic lymph nodes (32%) were the most commonly involved sites [178].
Discussion

With the difference in timing of the 2 studies being almost 3 decades, it shows that up till now not all patients with apparent early ovarian cancer undergo comprehensive surgical staging procedures, as that was also apparent in our study. Also, a considerable number of upstaged patients have stage III disease with para-aortic lymph nodes being one of the most commonly involved sites.

Many authors suggested that the detection of metastatic disease varies with the type of surgical procedure. Di Re and colleagues defined a lymphadenectomy as yielding at least 20 nodes, and a lymph node sampling as yielding between 5 and 20 nodes [179]. In all our patients with clinical stage 1 tumors, the number of pelvic and para-aortic lymph nodes dissected was less than 20. Three patients out of 11 had both pelvic and para-aortic lymph node sampling, yet none of them had positive lymph nodes. The 3 cases that had positive lymph nodes all had pelvic lymph node sampling only.

Previous studies have demonstrated that neoadjuvant chemotherapy didn’t have an effect on lymph node metastases in advanced ovarian cancer [16], [119].
Morice and colleagues conducted a retrospective study that included 205 patients with epithelial ovarian cancer who underwent bilateral pelvic and para-aortic lymphadenectomy during initial surgery, during chemotherapy (interval debulking) and after chemotherapy (second look surgery). The rates of lymph node involvement in patients who had stage III disease was 53% (15/28) for initial surgery, 58% (15/26) for interval debulking and 48% (20/42) for second look surgery.

Among our patients with stage III tumors, 7 out of 12 patients received neoadjuvant chemotherapy; only 2 patients out of 7 had positive lymph node metastases after neoadjuvant chemotherapy, one in the pelvic and the other in the mesenteric nodes. In both patients there was tumor regression after neoadjuvant chemotherapy, which does not correlate with previous studies [16], [119]. In patients with no nodal involvement, the mean number of dissected lymph nodes was 7.2 pelvic and 5.2 para-aortic nodes. While in patients with positive nodes who underwent only pelvic lymph node dissection the mean number of dissected nodes was 23 nodes.
These numbers show that in order to precisely assess the effect of neoadjuvant chemotherapy on lymph node metastases, a larger number of lymph nodes should be dissected.

**Grade:**

Most of the studies in the literature demonstrated that the rate of lymph node metastases increased with increasing grade. In a meta-analysis, Kleppe and colleagues reviewed the results of 6 different studies including 361 patients with stages I-II and demonstrated that the incidence of lymph node metastases was 4.0% in grade 1 tumors, 16.5% in grade 2 tumors and 20.0% in grade 3 tumors [33].

In the series by Baiocchi and colleagues the rate of nodal involvement in stage I, grade 1, 2, and 3 were, respectively 3.9%, 7.7%, and 38.5%. In the report of Sakurai and associates those rates were, respectively: 1.4% (grade 1), 22.2% (grade 2), and 33.3% (grade 3). And in the series by Petru and colleagues, 5.8% (grade 1), 25% (grade 2), 45.4% (grade 3).

Although as previously mentioned that most of the studies in the literature demonstrated that the rate of lymph node metastases increased with increasing grade, yet some studies showed different results.
Although Powless and colleagues demonstrated in their study that patients with grade 3 had the highest incidence of lymph node metastases, 23.2\%, yet their study also showed that grade 1 tumors had higher incidence than grade 2 tumors with respective percentages of 2.7\% for grade 1 disease and 1.9\% for grade 2 disease ($p \leq 0.001$). Similar results were concluded by Desteli and colleagues in their study where 11 patients had grade 1 disease (33.0\%), 8 patients (24.2\%) had grade 2 and 14 patients (42.4\%) had grade 3 disease [2, 40].

Morice and colleagues demonstrated in their study that the rate of lymph node metastases in patients with grade 2 tumors was higher than in both grade 1 and 3 tumors. The rate of nodal involvement was: 24\% in grade 1, 51\% in grade 2, and 47\% in grade 3 disease [5].

None of the patients in our study with grade 1 tumors had lymph node metastases. Incidence of metastases in grade 2 and 3 tumors was 23.5\% and 45.4\% respectively. Absence of lymph node metastases in patients with grade 1 could be due to the fact that grade 1 patients constituted a low percentage in our study of the total patients (9\%) compared to other studies (18-33\%).
To analyze the results statistically we combined grade 1 and 2 together and compared them to grade 3. However, the results were statistically insignificant (p ≤ 0.210). Our results showed that grade 2 tumors were associated with increased incidence of para-aortic lymph node involvement than grade 3 tumors (50% vs 20%). This was in accordance to the work done by Ayhan and colleagues who also found grade 2 to be a significant determinant of para-aortic lymph node metastases. However, Tsuruchi and associates in discordance with other authors reported in their study that grade 3 had a significantly higher incidence of para-aortic involvement than grade 1-2 tumors, with an incidence of 45% vs 20% [50], [180]. This difference of results in the literature shows that there is still no sharp conclusive evidence regarding the relation between the tumor grade and site of lymph node metastases.

Cass and colleagues found that all patients with stage IIIC tumors were exclusively grade 3 (14/14). Moreover, Grade 3 tumors were more commonly seen in lymph node positive than in lymph node negative patients (P = 0.001) [46].
In this study the rate of nodal involvement in different grades was: 24% in grade 1, 51% in grade 2, and 47% in grade 3 disease. The rate of nodal involvement in our series is higher in grade 2 disease than that reported by others but in grade 3 it was similar to that observed by other studies.

In our series none of 15 patients with stage IA grade 1 disease had nodal involvement. So, this finding consolidates the recommendation postulated by Sakuragi and Petru that lymphadenectomy may be omitted in patients with stage IA grade 1.

**CA-125 level:**

In our study, the level of CA-125 in patients with positive lymph nodes ranged from 80-14554 U/ml (p=0.199). Patients with positive pelvic lymph nodes had a higher median level of CA-125 than those with positive para-aortic lymph nodes, 375 vs 317 U/ml.

CA-125 level has been investigated in previous studies to assess its role in predicting lymph node metastases in EOC. In a retrospective study by Powless and colleagues which included 190 patients, preoperative CA-125 was also found to be a predictor of lymph node involvement (p=0.006).
In patients with CA-125 level more than 35U/ml, 22.4% (19/85) had positive lymph nodes. While none of the patients with a preoperative CA-125 level of less than or equal to 35 U/ml had positive nodes [40]. Ayhan and colleagues conducted a study on lymphatic metastasis in epithelial ovarian carcinoma with respect to clinicopathological variables. In multivariable analysis, CA-125 level of more than 500U/ml was significantly associated with lymph node metastases (P = 0.04), occurring in 101 out of 145 patients [50].

A similar result was seen by Kim and colleagues who underwent a study to evaluate the significance of preoperative serum CA-125 levels in the prediction of lymph node metastases in EOC. The cut-off value of 535 U/ml was significantly associated with lymph node metastases (p≤0.05) and was associated with the highest sensitivity (70%) and specificity (83%) [181]. In our study we couldn’t determine a cut-off value for CA-125 level associated with lymph node metastases.
Distribution:
Plentl and Friedman described the lymphatic drainage for EOC through 3 main routes: First route was along the infundibulopelvic ligament to the aortic area, terminating at the vena cava on the right side and between the aortic and renal vessels on the left side, and draining medially into the para-aortic, intercaval aortic, and paracaval lymph nodes. The second route was through the broad ligament and parametrial lymphatic channels to the internal iliac lymph nodes. And finally the third route along the round ligament to the external iliac and inguinal lymph nodes [32]. The pattern of lymph node spread in ovarian cancer has long been an area of interest, in 1985 the staging of ovarian cancer by FIGO was modified to incorporate the more aggressive biologic behavior associated with lymph node spread. In 1974, Knapp and Friedman described a 19% incidence of para-aortic lymph node spread in clinical stage I disease, which they suggested was the dominant lymphatic pathway of the ovary[182] . Subsequent clinical studies of patients with stage I–III disease have confirmed the importance of both pelvic and para-aortic lymphatic drainage pathways, with some debate as to the most
common site of lymph node involvement in ovarian carcinoma [24],[26],[31], [46]. Although the distribution of pelvic and para-aortic lymph node metastases had a lot of variation in the literature, most data suggested that para-aortic lymph nodes were the most common site of lymph node metastases[5] , [24], [32], [5, 24, 121, 175].

The incidence of pelvic lymph node metastases in our study was higher than para-aortic metastases, with incidence of 25% (6/24) compared to 20 % (3/15). These results are similar to those of Petru and colleagues who found a higher prevalence of pelvic lymph node metastases, but more patients had pelvic than para-aortic lymphadenectomies [49]. Burghardt and colleagues performed para-aortic and pelvic lymphadenectomies in 105 patients with different stages of ovarian cancer and found an equal distribution of para-aortic and pelvic metastases [176].

Onda and colleagues performed a study to assess pelvic and para-aortic lymph node metastases in EOC and to try to identify the essential sites of lymph node biopsy.
The lymph nodes were classified into 5 subgroups: the aortic lymph nodes above the inferior mesenteric artery (A1), the aortic lymph nodes below the inferior mesenteric artery (A2), the common iliac and sacral lymph nodes (P1), the internal and external iliac and obturator lymph nodes (P2), and the suprainguinal (the lowest external iliac) lymph nodes (P3). The incidence of metastases to A1, A2, P1, P2, and P3 was 79%, 71%, 46%, 77%, and 40%, respectively. Provided that 2 of the 5 lymph node subgroups were selected for biopsy, the combination of A1 and P2 gave the best results in sensitivity (94% [45 of 48 patients]) and negative (95% [62 of 65 patients]) predictive value for detection of lymph node metastases [4].

The incidence of metastases in the aortic nodes above the inferior mesenteric artery was also shown in other studies to be the most common site of metastases as shown in a study by Tsumura and colleagues[48]. Morice and colleagues demonstrated in their study that even in unilateral right ovarian tumors, the lymph nodes between the left renal vein and inferior mesenteric artery were involved in 38% of patients with positive nodes [5].
Some authors have suggested performing selective lymph node sampling as a staging procedure in this area alone in serous tumors [41]. However, a staging procedure limited to the para-aortic area missed 11% of the node-positive patients in the series of Harter and colleagues and 24% of patients in another series by Fournier and associates [121],[175]. Also, in a study by Pereira and colleagues 14% of patients had negative aortic nodes but positive pelvic nodes, and 22% of patients had negative pelvic nodes but positive aortic nodes [45]. Harter and colleagues in 70 early stages and 125 advanced stages observed isolated pelvic involvement in 0% and 9% of the cases, respectively [121]. Benedetti-Panici and associates described solitary para-aortic lymph node metastases in 6% and only pelvic involvement in 8% in 35 patients with FIGO-stage I ovarian carcinoma [10]. Morice and colleagues in a series of 276 patients with lymph node dissection observed isolated pelvic involvement in 8% of the cases [5]. This percentage was 2.9% in a series of 208 patients with lymph node dissection from Takeshima and colleagues [41]. Fournier and colleagues concluded in their study that isolated pelvic involvement was always rarer than isolated para-aortic involvement or involvement of both sites [175].
In our study we couldn’t detect the incidence of isolated pelvic lymph nodes metastases because patients with positive pelvic nodes either had concomitant positive para-aortic nodes or didn’t perform para-aortic lymphadenectomy. One of our patients had isolated para-aortic lymph node metastases. All these results together with the fact that studies have failed to identify sentinel lymph nodes in early stages highlight the importance of undergoing a systematic pelvic and para-aortic lymph node dissection [4, 110].

Another debated point is the performance of unilateral para-aortic lymphadenectomy in patients with unilateral early stage ovarian tumors. Such a procedure was recommended after the work of Benedetti-Panici and colleagues, in which all 35 patients with stage I disease had ipsilateral involvement [24]. Our study showed similar results where all our patients with positive lymph nodes in all different stages had ipsilateral lymph node metastases. However, other authors have reported on cases of contralateral positive nodes: Onda and coauthors reported one case of contralateral positive pelvic node from 110 patients[4].
Suzuki and associates reported two cases of contralateral pelvic positive nodes in 47 patients with stage I intra-abdominal ovarian cancer [172]. Cass and colleagues observed three cases of isolated contralateral pelvic or para-aortic lymph nodes in their retrospective study that included 96 patients, one had isolated contralateral para-aortic nodes, another had contralateral pelvic and para-aortic nodes, and the last patient had an isolated pelvic node [46]. In another study by Morice et al, 11.1% of 85 patients with unilateral stage I disease had contralateral para-aortic node involvement [5].

This very small number of patients with contralateral lymph node metastases from different studies which included a larger number of patients than our study may explain absence of patients with contralateral nodal metastases in our study. These results highlight the necessity of a complete bilateral lymphadenectomy, even in patients with unilateral apparent stage I EOC.

There are several studies in the literature which studied the incidence of mesenteric lymph node involvement in advanced ovarian carcinoma invading the colorectum [34, 52], [183].
Salani and colleagues underwent a retrospective study that included patients who underwent rectosigmoidectomy during surgical management of advanced ovarian carcinoma. Of the 53 patients included in this study, 39 patients had an adequate mesenteric resection suitable for nodal analysis. In the study, 2 prognostic factors for mesenteric lymph node involvement were observed. First, invasion beyond the serosa of the rectosigmoid colon which was present in 31 of 39 cases (79.5%). The second factor was concurrent tumor spread to retroperitoneal nodes (p=0.025) [52].

Our study showed different results with 2 of the 3 patients with mesenteric lymph node involvement had colonic invasion limited to the serosal layer with intact mucosa. Our results are in accordance to studies by Gouy et al. and Lax et al. who also didn’t find a significant correlation between the depth of intestinal wall infiltration and the rate of mesenteric node involvement. They suggested according to their results that mechanical involvement of the intestinal wall may not be the factor influencing mesenteric nodal involvement. And that the nodal involvement could be related to tumor biological characteristics (table 5) [34].
Also in our study, only one patient with positive mesenteric lymph nodes had positive pelvic nodes, so there was no correlation between mesenteric lymph node involvement and retroperitoneal nodal spread. This was also in accordance with the results of a study conducted by Gouy and colleagues [34].

Table (5) Histological characteristics in both groups [34]

<table>
<thead>
<tr>
<th></th>
<th>Involved Mesenteric Nodes (n=19)</th>
<th>No involved_mesenteric nodes (n=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of bowel involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serosa</td>
<td>10(53%)</td>
<td>19(58%)</td>
<td>NS</td>
</tr>
<tr>
<td>Muscularis propria</td>
<td>4(21%)</td>
<td>5(15%)</td>
<td>NS</td>
</tr>
<tr>
<td>Submucosa</td>
<td>2(10%)</td>
<td>1(3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mucosa</td>
<td>3(16%)</td>
<td>3(9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Uninvolved</td>
<td>0</td>
<td>5(15%)</td>
<td>NS</td>
</tr>
<tr>
<td>Positive pelvic nodes</td>
<td>12(63%)</td>
<td>19(54%)</td>
<td>NS</td>
</tr>
<tr>
<td>Positive para-aortic nodes</td>
<td>11(58%)</td>
<td>21(60%)</td>
<td>NS</td>
</tr>
<tr>
<td>Median number of mesenteric nodes removed</td>
<td>15 (range,1-36)</td>
<td>4 (range,1-45)</td>
<td>NS</td>
</tr>
<tr>
<td>Median number of mesenteric nodes involved</td>
<td>4(1-12)</td>
<td>-</td>
<td>NS</td>
</tr>
</tbody>
</table>
The aim of this study was to study the distribution and evaluate possible predictive factors of lymph node involvement in epithelial ovarian cancer, as well as studying the impact of lymph node involvement in the upstaging of early ovarian cancer.

We undertook a prospective study of 31 patients with epithelial ovarian cancer admitted to the surgical department at the National Cancer Institute, Cairo University in the period from May 2011 to April 2013. Patients with stage I, II, and non bulky stage III tumors were included. Pre-operative evaluation included history, physical examination, and investigations including CT abdomen and pelvis with oral and IV contrast, and CA-125 level.

Diagnosis of malignancy was established through presence of radiological criteria of malignancy, elevated CA1-25 level in post-menopausal women or frozen section examination. Patients explored following neoadjuvant chemotherapy were diagnosed by cytology from ascites or biopsy from omental cakes. Patients underwent complete surgical staging including pelvic and para-aortic lymph node sampling or dissection.
The most prevalent clinical stage was stage IA which was present in 11 patients, followed by stage IIIC in 7 patients, stage IIB and IIIB both in 5 patients, stage IC in 2 patients and stage IIC in one patient.

Regarding patients with positive nodes, 3 patients with clinical stage IA, 2 patients with stage IIB, 2 patients with stage IIIB and 2 patients with stage IIIC.

The incidence of pelvic lymph node metastases in our study was higher than para-aortic metastases. None of our patients had contralateral lymph node metastases.

The most predominant histological type was serous cystadenocarcinoma.

The 3 patients in our study that had positive mesenteric lymph nodes had different histological subtypes. Two of the 3 patients with mesenteric lymph node involvement had colonic invasion limited to the serosal layer with intact mucosa.

None of the patients with grade I tumors in our study had lymph node involvement. Grade 2 tumors where associated with increased incidence of para-aortic lymph node involvement than grade 3 tumors.
Patients with positive pelvic lymph nodes had a higher median level of CA-125 than those with positive para-aortic lymph nodes.
From our results we conclude that the only significant factor affecting distribution is the laterality of the tumor. Although the number of included patients in our study was small, such conclusion is worth further investigation for the possibility of avoiding unrequired dissection and its morbidity in rarely affected sites.

As it has been shown through our discussion that the number of lymph nodes affected the yield of positive nodes, this might have biased our results regarding a comprehensive pelvic lymphadenectomy which resulted in yields similar to the literature, while the non-standardized para-aortic lymphadenectomy resulted in discrepancy in the yield.

Other factors that we noted maybe of importance in special circumstances such as invasion of the serosal layer of the colon which may cause lymph node affection in unusual sites (mesenteric nodes). These are also worth further investigation, which was beyond the scope of this study. Such study is needed to determine those sites, their frequency and the relevance of removal of such nodes.
Changing the policy of managing ovarian cancer that minimally invades intestine from peeling off to resection with the mesenteric lymph nodes, may prove necessary in the future.

We could not describe results that agree with the literature regarding the relation between the histological type and distribution of nodal metastases and this could have been due to the limited number of patients with each histologic type and the non-standardized technique of lymph node dissection. But we still recommend the complete para-aortic and pelvic lymph node dissection with all histologies till we have undisputed evidence proving otherwise for special histologic types.

Although we are aware that in other several studies, stage I low grade mucinous tumors showed no nodal spread, which coincides with our own results, still we cannot recommend leaving out lymph node dissection for those tumors based on this factor only.

Regarding the risk factors, we could not conclude that there are dependable predictive factors for lymph node metastases, but we still consider the small number of patients included in this study as a limiting factor for this conclusion.
On the other hand, we found that the yield of positive lymph nodes significantly increased with the increase in number of nodes dissected, and hence we recommend a complete meticulous nodal dissection, and that sampling or partial dissection should be avoided with ovarian cancer.

We finally conclude that the surgical management of ovarian cancer requires systematic detailed comprehensive and evidence based approach to the para-aortic and pelvic lymph nodes, which in turn requires proper training of surgeons aiming at a standardized operative technique.


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استئصال الغدد الليمفاوية في أورام المبيض الطالبية: التوزيع والعوامل التنبوية لتأثير الغدد الليمفاوية

الهدف من هذا البحث هو دراسة التوزيع والعوامل التنبوية لتأثير الغدد الليمفاوية في أورام المبيض الطالبية.

فاستئصال الغدد الليمفاوية يساعد على تحديد مرحلة الورم بدقة وبالتالي تستطيع المريضة أن تتلقى العلاج الكيميائي الملائم بعد الجراحة حسب المرحلة النهائية للورم، كما تبين من خلال العديد من الدراسات ان استئصال الغدد يساعد على تحسين فترة بقاء المريض على قيد الحياة.

لكن نظرًا لأن استئصال الغدد الليمفاوية كجزء من العلاج الجراحي يزيد من إمكانية حدوث مضاعفات جراحية، فقد تمت مؤخرًا بعد الدراسات لمحاولة معرفة العوامل التنبوية لتأثير الغدد الليمفاوية لتحديد المرضى الذين يمكنهم تفادي استئصال هذه الغدد.

نظراً لضعف استجابة السرطان المنتشر بالغدد الليمفاوية للعلاج الكيميائي فقد أثبتت عدة دراسات أن استئصال الغدد الليمفاوية في حالات أورام المبيض المتقدمة يساعد على تحسن استجابة المريضة للعلاج الكيميائي بعد العملية.

تمت الدراسة في الفترة من مايو 2011 إلى إبريل 2013 وتضمنت مرضى أورام المبيض الطالبة بالمراحل الأولى والثانية والثالثة والمرضى الذين تم إعطائهم علاج كيميائي قبل الجراحة مع وجود استجابة للعلاج وتقلص في حجم الورم.
تقييم المرضى تم عن طريق أخذ التاريخ الطبي والكشف وعمل فحوصات وأشعات تتضمن دلالات أورام CA-125 وأشعة مقطعية على البطن والحوض.

العلاج الجراحي اشتمل استئصال الرحم والمبيض ومنديل البطن مع أخذ عينات في حالة وجود استسقاء بالبطن أو انتشار للورم للغشاء البريتوني.

تم استئصال الغدد الليمفاوية بالحوض والحارج أورطية مع تسميتها حسب الجانب والمكان المستثاث منه. كما تم استئصال الغدد الليمفاوية بجانب القولون في حالة انتشار الورم من المبيض للقولون.

الدراسة اشتملت على 31 مريضة، 10 مرضى كان الورم بالمبيض الأيسر و 8 بالمبيض الأيمن و 13 بالجانبين. بعد استئصال الغدد وتحليلها تبين انتشار السرطان بالدد في 3 مرضى بالمرحلة الأولى و 2 بالمرحلة الثانية و 4 بالمرحلة الثالثة.

في حالة عدم استئصال الغدد لم يكن سيعرف المرحلة الحقيقية للورم وبالتالي كان سيغوت على المرضى أخذ العلاج الكيميائي المناسب.

من نتائج الدراسة أنه كلما زاد عدد الغدد المستثاثة زادت نسبة وجود ورم منشور بها مما يؤكد أهمية تعلم الاستئصال الجراحي الكامل للدد للمساعدة على تحديد المرحلة الفعلية للورم. ومن نتائج الدراسة أيضاً تبين أن نسبة انتشار السرطان بالدد الليمفاوية بالحوض كانت أعلى من الغدد الجارج أورطية، ولكن هذا قد يكون بسبب أن عدد الغدد الليمفاوية المستثاث بالحوض كان أكبر من عدد الغدد الجارج أورطية مما قد يكون له تأثير على هذه النتيجة.
ومن نتائج الدراسة أيضاً أن انتشار الورم للفم والشفاء كان بنفس جانب الورم (أيمن وأيسر) ولكن للتأكد على هذه النتيجة يجب عمل دراسة لعدد أكبر من المرضى.

أهم النتائج التطبيقية التي تتم الوصول إليها: أهمية دور استئصال الفم والشفاء بالحوض والجارأورطية كجزء مهم من العلاج الجراحي لأورام المبيض الطلاطية وأهمية تعلم الأسلاط الجراحي الصحي استئصال الفم والشفاء بالحوض والجارأورطية للوصول لأعلى معدلات الدقة في تقييم مراحل الورم. أهمية الاستئصال الكامل للغدد بجانب القولون في حالة انتشار أورام المبيض للقولون. كلما زاد عدد الغدد الفم والشفاء المستقلة زادت نسبة وجود ورم سرطاني بها. إمكانية الاستئصال للغدد الفم والشفاء بنفس جانب أورام المبيض ولكن يجب عمل دراسات أكبر لتأكيد ذلك. يمكن التغاضي عن استئصال الفم والشفاء في حالات أورام المبيض الطلاطية ذات الدرجة الأولى ولكن يجب عمل دراسات أكبر لتأكيد ذلك.
استئصال الغدد الليمفاوية في أورام المبيض الطلابية: التوزيع والعوامل التنبؤية لتأثر الغدد الليمفاوية

رسالة مقدمة من

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ماجستير جراحة الأورام

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