Original Article

Prevalence and Pattern of Nodal Metastases in Ovarian Malignancy: A Perioperative Audit

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Abstract

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Keywords

► lymph node metastases
► ovarian cancers
► serous tumors
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► para-aortic lymph node

It is still unclear whether or not full nodal dissection and detailed staging offer any benefits. Little is known regarding the degree of nodal involvement based on histotype. We aimed to assess the lymphatic dissemination patterns and prevalence in early-stage epithelial ovarian cancer and identify the underlying risk factors for nodal metastases. This is a prospective study conducted over a period of three years. Institutional ethics committee approval has been obtained. A total of 157 consecutive patients with apparently early-stage ovarian cancer, who were treated at the Department of Gynecologic Oncology, Acharya Harihar Post Graduate Institute of Cancer (AHPGIC) from January 2020 to January 2023, were included. The most frequent grade was 3 (66.8%), and the most common histotype was high-grade serous ovarian cancer (HGSOC; 55.4%), followed by mucinous (16.5%) and endometrioid (14.01%) varieties. Seromucinous and clear cell ovarian cancers were found infrequently. The most common pattern was isolated pelvic nodal involvement in 48.9% of patients, followed by both para-aortic and pelvic nodal involvement in 25.5% of patients; 13 patients had isolated para-aortic nodal involvement. HGSOC was most commonly associated with isolated metastasis to the pelvic lymph nodes alone, while the endometrioid variety was prone to both pelvic and para-aortic spread. Out of the 55 patients with nonserous tumors, 12.72% exhibited nodal involvement. Most nonserous tumors showed affinity for both pelvic and para-aortic (42.85%) nodal metastases. Only grade 3 and serous histology showed a positive association with nodal metastasis. Approximately 45.2% of cases showed upstaging after surgical staging procedures. Multicentric studies are essential to analyze the prognostic impact of systematic lymphadenectomy in ovarian carcinoma patients, depending on the histotype and distribution pattern of nodal metastases.

Introduction

Approximately 30% of the epithelial ovarian cancer (EOC) patients present with clinically early-stage (i.e., International Federation of Gynecology and Obstetrics [FIGO] stage I–II) disease at initial evaluation The management of clinically early-stage EOC is determined by surgical staging, which provides a guidance for adjuvant treatment. Although surgical staging of ovarian cancer is recommended,[1] the

therapeutic benefit of lymph node dissection (LND) is still controversial. The incidence of nodal metastases reported in the literature is 10.6 to 24% for stage I, 23 to 50% for stage II, 53 to 74% for stage III, and 65 to 75% for stage IV ovarian cancer. The three main methods of EOC metastasis include implantation of exfoliated cells at distant intraperitoneal locations, direct dissemination to nearby organs, and spread through the retroperitoneal lymphatic channels.[1,2] Age, clinical stage at the time of laparotomy, serous histology, high grade histology, CA125 levels, and cytologic evidence of neoplastic cells have all been identified as risk factors for lymph node metastasis in the past.[3,4]

Advanced ovarian cancer (AOC) has a higher tendency to invade adjacent nodes.[5,6] Panici et al discovered that systematic nodal dissection had a better progression-free survival (PFS), but not an overall survival (OS), when compared with debulking of enlarged nodes. In another trial LION's trial by Harter et al, systematic pelvic and para-aortic LND in patients with AOC with both intra-abdominal complete resection and clinically negative LN neither improved OS nor PFS despite detecting (and removing) subclinical nodal metastases in 56% of the patients.[7] Hence, they concluded that systematic LND of clinical negative LN in patients with AOC and complete resection should be omitted to reduce postoperative morbidity and mortality. On the other hand, several investigations found that systematic lymphadenectomy improved OS in their study.[2]

Most of the studies have investigated the role of lymphadenectomy in AOC, but there is rarity of research in early-stage ovarian cancers. Therefore, it is still unclear whether or not full nodal dissection and detailed staging offer any additional benefits in early-stage ovarian malignancies. Based on the histotype, little is known regarding the degree of nodal involvement. We aimed to assess the lymphatic dissemination patterns and prevalence in early-stage EOC (apparent stage I and II) and identify the underlying risk factors for nodal metastases.

Patients and Methods

This is a prospective study done over a period of 3 years (January 2020–January 2023). Institutional ethics committee approval has been done. Total of 157 consecutive patients with apparently early-stage ovarian cancer who were treated at the Department of Gynecologic Oncology, Acharya Harihar Post Graduate Institute of Cancer (AHPGIC), were included. Inclusion criteria in this study were apparent early-stage EOC who underwent primary surgical staging including systematic lymphadenectomy covering the pelvic and para-aortic regions. Apparently, early-stage patients were those who had disease confined only to pelvis, that is, stage I and II on imaging (contrast-enhanced computed tomography [CECT] abdomen and pelvis). Exclusion criteria were preoperative imaging suspicious for nodal metastases, any other histotype other than EOC, borderline tumors, patients incompletely staged at other medical centers, those who have had fertility sparing surgery, those with other concomitant cancers, and those who did not give consent.

Each patient in our study underwent surgical staging including exploration of entire peritoneal cavity, ascitic fluid cytology analysis, random peritoneal sampling or biopsy from suspicious areas, hysterectomy with bilateral

Table 1 Clinicopathologic features of surgically staged 157 patients

1	Age	Median (range)	52 years (18–70 years)
2	Grade	Low (Grade 1& 2)	52 (33.2)
		High (Grade 3)	105 (66.8)
3	Ascites	Nil	80 (50.9%)
		<1 L	47 (29.9%)
		>1 L	30 (19.1%)
4	CA125	≤ 35	28 (17.8%)
		35–250	56 (35.7%)
		>250	73 (46.5%)
5	CC	0	101 (64.3%)
		1	31 (19.7%)
		2	15 (9.5%)
		3	10 (6.3%)
6	Final assigned stage (pathological)	I	73 (46.5%)
		II	12 (7.6%)
		III	72 (45.9%)
7	Nodal metastases	Present	47 (29.94%)
		Absent	110 (70.06%)

salpingoophorectomy, infracolic omentectomy, and cytore-duction, as indicated. Systematic pelvic and para-aortic nodal dissection upto level of renal vessels was a part of the surgical staging. Pelvic nodes included all the node bearing fibrofatty tissue from distal circumflex iliac vein till the common iliac bifurcation. Para-aortic group included para-aortic, paracaval, and interaortocaval groups till renal vein. Final pathology results were obtained after the specimen were evaluated by a oncopathologist.

Results

One-hundred fifty-seven patients who fulfilled the inclusion criteria were enrolled. Identification of the clinicopathological variables related to nodal involvement, as well as the pattern of nodal metastases (pelvic or para-aortic), was done (►Table 1). Prior to being included in the evaluation, each patient gave their informed consent for the collection of data.

Statistical Analysis

SPSS Statistics Software version 21 was used to conduct the statistical analysis. Chi-squared analysis was used to estimate the differences between patients' lymph node status in terms of evaluated variables. The level for significance was chosen at $p < 0.05$.

Of the 157 enrolled patients, who characteristics are summarized in ►Table 1, the median age was 52 years in our study sample. Based on the histopathology reports, final assigned stages were: Stage1 = 73 (46.5%), Stage II = 12

Table 2 Pattern of nodal metastases

	Region involved	No. of patients
1	**Pelvic-/Paln−**	110
2	**Nodal disease+**	47
	Pelvic +/Paln−	23 (48.9%)
	Pelvic +/Paln+	11 (23.4%)
	Pelvic-/Paln+	13 (27%)

(7.6%), Stage III = 72 (45.9%). About 17.8% cases had CA125 levels in normal range, the most frequent histological grade was 3 (66.8%), and the most frequent histotype was high grade serous (55.4%), followed by the mucinous (16.5%) and endometrioid (14.01%) variety. The seromucinous and clear cell ovarian cancers were infrequently found. Metastases to the lymph nodes were found in 47 (29.93%) of the patients (►Table 1). The following was noted while looking at the afflicted lymph node regions: the most common pattern was isolated pelvic nodal involvement in 48.9% of patients, followed by both para-aortic and pelvic nodal involvement in 25.5% of patients; 13 patients had isolated para-aortic nodal involvement (►Table 2).

►Fig. 1 depicts nodal metastases in relation with histology. Most common was high-grade serous ovarian cancer (HGSOC; i.e., 38 of 87cases) followed by endometrioid histology (5 of 22 cases) that was associated with nodal metastasis. Though LN metastases is uncommon in mucinous

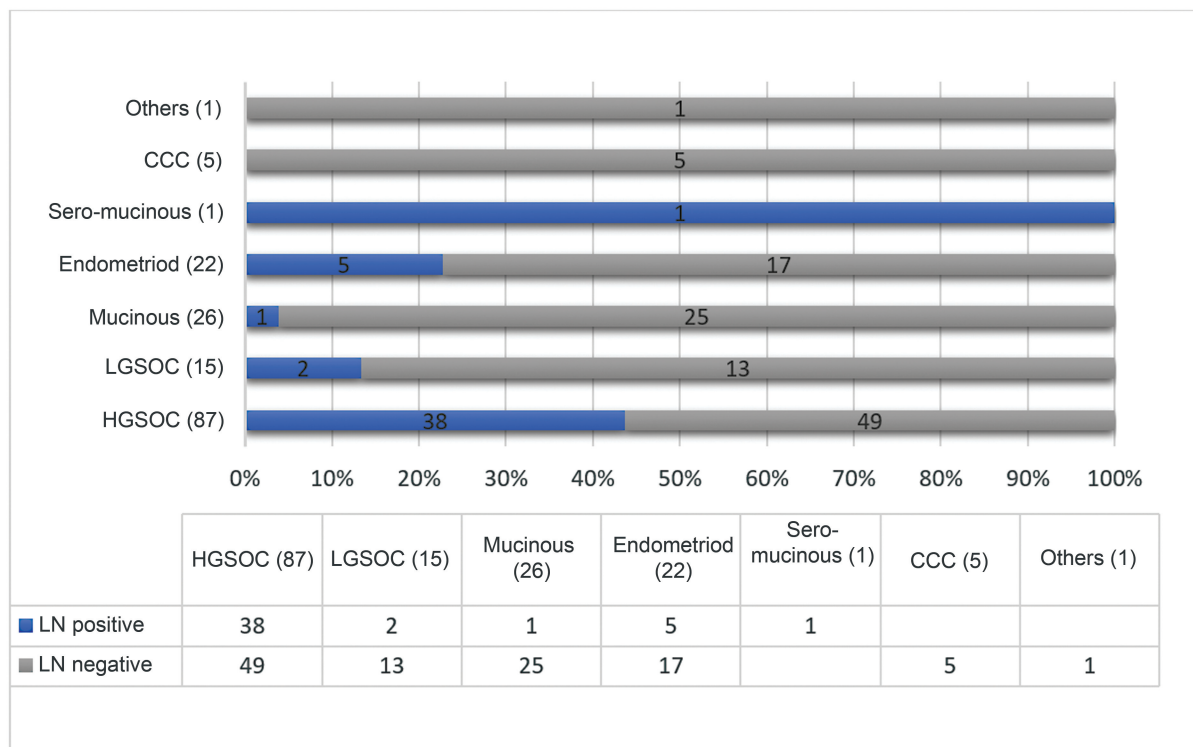|	HGSOC (87)	LGSOC (15)	Mucinous (26)	Endometriod (22)	Sero-mucinous (1)	CCC (5)	Others (1)
■ LN positive	38	2	1	5	1		
■ LN negative	49	13	25	17		5	1

Fig. 1 Nodal metastases in relation with histotype. HGSOC, high-grade serous ovarian cancer; LGSOC, low-grade serous ovarian cancer; LN, lymph node.

ovarian cancers (MOCs), we found 1 case of nodal metastases among 26 mucinous ovarian tumors. One case of seromucinous tumor reported in this study showed nodal positivity. We did not find any clear cell ovarian carcinoma case with nodal metastases in our study.

►Fig. 2 shows pattern of nodal metastases in relation with histology. HGSOC was most commonly associated with isolated metastasis to the pelvic lymph nodes alone. Endometrioid varieties were prone to both pelvic and para-aortic spread. The rare mucinous variety showed a predilection for PALN, without pelvic nodal metastases.

►Fig. 3 shows the comparison between nodal involvement of serous and nonserous tumors. Out of the 55 patients with nonserous histotype of ovarian tumors, 12.72% ($n = 7$) exhibited involvement of the lymph nodes. Most of the nonserous tumors showed affinity toward both pelvic and para-aortic (42.85%) nodal metastases.

On analyzing for risk factors, only grade 3 and serous histology showed a positive association with nodal metastasis (►Table 3). Other risk factors like cytology, laterality, ascites, and CA125 were also analyzed in our study, but it did not show any significant association. Twenty patients of total 47 patients with positive lymph nodes had unilateral tumors. In patients with unilateral tumors, contralateral nodal spread was found in 10% of cases (2/20).

►Fig. 4 demonstrates upstaging of these tumors after complete surgical staging. Of total 157 cases, 71 cases (45.2%) showed upstaging after surgical staging procedures. Fourteen of 71 patients showed upstaging due to nodal involvement only. Of those 14 patients, 11 were HGSOC, rest were 1 each of LGSOC, endometrioid, and mucinous variety.

►Table 4 shows the intraoperative complications encountered while performing nodal dissection during surgical staging.

Discussion

A crucial initial step in managing patients with ovarian cancer is accurate surgical staging. The purpose of staging is to provide suitable, empirically supported adjuvant therapies. LND forms a "part and parcel" in surgical staging of early-stage EOC. Nodal dissection may be correlated with the prognosis in both early and advanced stages of illness, according to growing body of studies.[8–12]

Some preoperative radiological features are suggestive of nodal metastases like nodes with short-axis dimension more than 10 mm or with central necrosis and loss of fatty hilum. Other characteristic features like rounded (spherical) nodes, ill-defined, and irregular shaped nodes are suggestive of malignancy. Although preoperatively radiological features suggest the involvement of nodes, still complete surgical staging must be done even in apparently early-stage cancers. As in our study we had included 157 cases who did not show any nodal involvement on CECT imaging, but after surgical staging (including nodal dissection) 47 patients showed nodal metastases on final pathology report.[13–17]

Collective LN metastases were seen in 29.93% of the patients in this study (►Table 1). Results of a study by Takashima N et al and Panici B et al , regarding the involvement of the pelvic and/or para-aortic regions[10,18,19] were likewise supported by the findings of our study. (►Table 1).

In addition, the relationship between nodal metastasis and clinicopathological factors has been analyzed. Previous data on known risk factors for lymph node metastases have been enriched by the risk variables identified in our work. These results are in line with other research that showed a higher risk for serous EOC and a lower risk for mucinous histotypes.[3,13] According to earlier research, grade 3 EOCs also predicted nodal metastases.[12] In the current

	HGSOC	LGSOC	Endometriod	Mucinous	Seromucinous	CCC	Total
■ Pelvic only	20	0	2	0	0	0	23
■ Paln only	10	1	1	1	0	0	13
■ Both	8	1	2	0	1	0	11

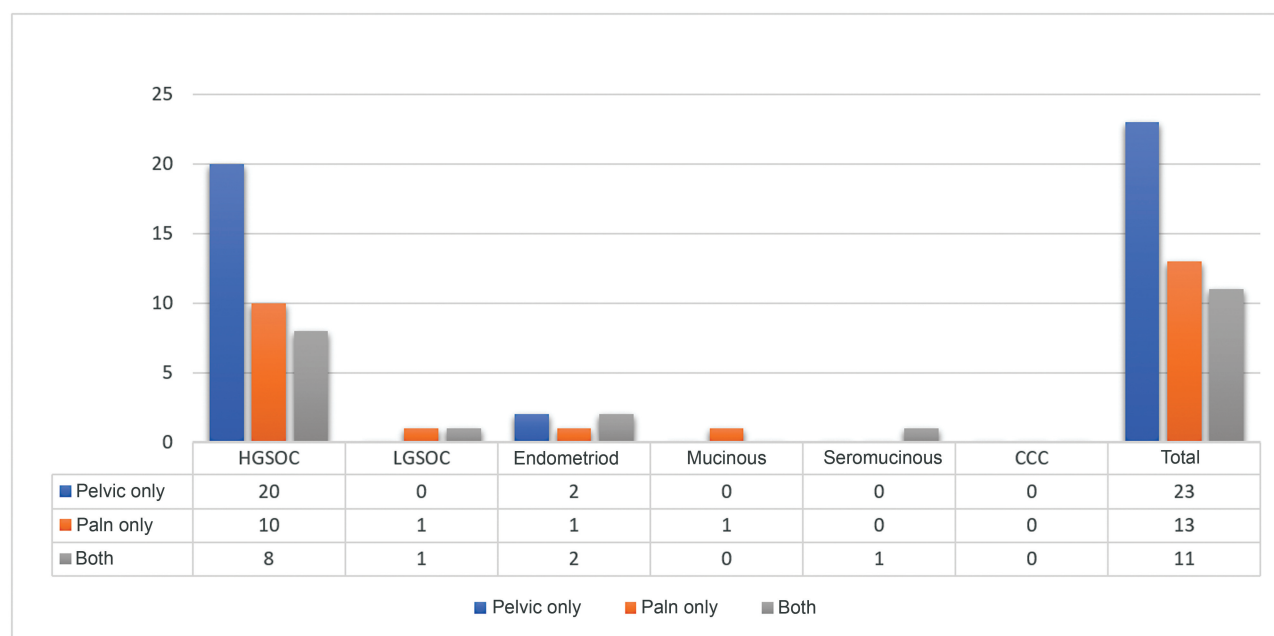■ Pelvic only ■ Paln only ■ Both

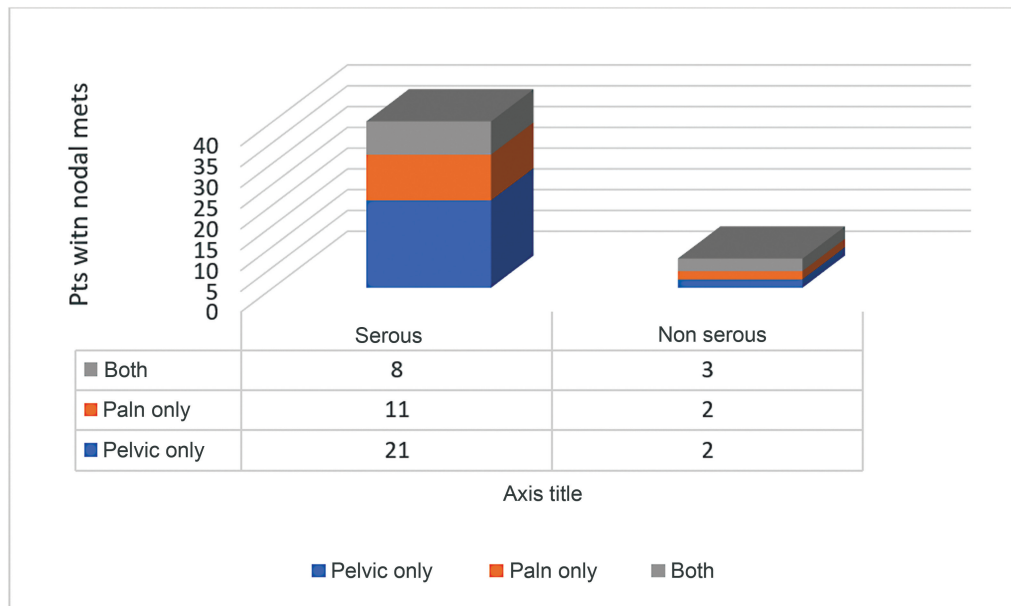**Fig. 2** Pattern of lymph node metastases in relation with histology.

Fig. 3 Pattern of distribution—serous versus nonserous tumors.

Table 3 Risk factor analysis

Sl. no.	Risk factors		Total	Node negative (%)	Node positive (%)	p-Value
			n = 157	110	47	
1	Laterality	Unilateral	64	44 (68.7)	20 (31.25)	NS
		Bilateral	93	66 (70.9)	27 (29.1)	
2	Cytology	Negative	111	77 (69.3)	34 (30.6)	NS
		Positive	46	33 (71.3)	13 (28.2)	
3	Ascites	Absent	80	62 (77.5)	18 (22.5)	NS
		Present	77	48 (62.3)	29 (37.6)	
4	Histology	Serous	102	62 (60.7)	40 (39.3)	$p < 0.05$
		Nonserous	55	48 (87.3)	7 (12.7)	
s5	Grade	Low	52	48 (92.3)	4 (7.6)	$p < 0.05$
		High	105	62 (59)	43 (40.9)	
6	CA125	≤ 35	28	21 (75)	7 (25)	NS
		>35	129	89(68.9)	40 (31.1)	

Abbreviation: NS, not specified.

investigation, other risk factors such laterality, cytology, and CA125 levels did not demonstrate any significant association. Suzuki et al[15] described a cohort of patients with low-grade stage I malignancies and mucinous tumors. These patients were not likely to have nodal spread based on risk factors. Similar outcomes were observed in our investigation, where we observed just one case of infiltrative MOC with nodal metastases. No case of expansile MOC was found with positive nodes.

Benedetti-Panici et al[16] discussed the significance of ipsilateral pelvic LND for unilateral ovarian malignancies; however, further research[14,15,20] has shown that isolated contralateral nodal involvements are not uncommon. In this

study, of the 20/47 node positive patients who had unilateral tumors, 18 patients had ipsilateral nodal involvement, 1 patient had bilateral nodal involvement, and 1 patient of unilateral right ovarian tumor had isolated contralateral pelvic nodal (left) metastases in our study, hence, under-scoring the fact that bilateral lymphadenectomy should be performed.
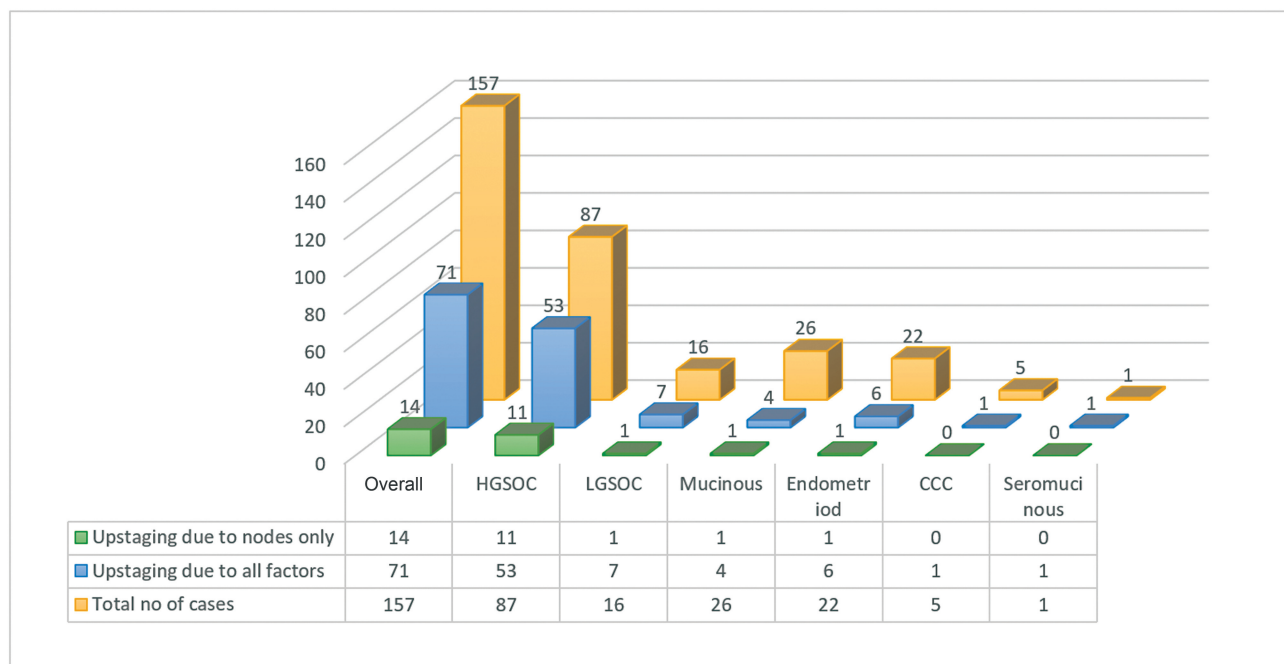
Lymph node locations have been studied in connection with ovarian cancer. In 48 ovarian cancer patients who were to be confirmed node-positive, Onda et al[12] looked at the vital locations for lymph node sampling. They came to the conclusion that if the biopsy was only performed at a single site, the area above the Inferior Mesentric Artery (IMA)

Table 4 Morbidity associated with lymphadenectomy

A	Intraoperative complications	No of patients
1	**Vascular injury**	
	External iliac vein	2
	External iliac artery	1
	Accessory obturator vein	1
	Obliterated umbilical artery	3
2	**Nerve injury**	
	Obturator nerve injury	3
3	Ureter injury	1
B	**Postoperative complications**	No of patients
	Postoperative ileus	5
	Lymphocele	11
	Lymphorrhea	14
	Lymphedema	6
	Thromboembolic events	4

would be the most preferable location, and if it was performed at two sites, the combination of the obturator lymph nodes, internal and external iliac with the aortic lymph nodes above the IMA would produce the best results in terms of sensitivity and negative predictive value. Other studies[8,18,21] have demonstrated that the incidence of nodal disease in the para-aortic region and the pelvic region is almost similar or even comparable. The findings of these studies are similar to the results derived in our study i.e., most common pattern of spread was isolated pelvic nodal metastases (23/47 node positive cases) followed by spread to isolated PALN region (13/47 cases), (►Fig. 2). Additionally,

stage I tumor patients with isolated pelvic nodal metastases are frequent,[6,8,17] supporting the idea that an ovarian lymphatic channel drains to the pelvic nodes. All of these results could be helpful in deciding whether patients be subjected to systematic lymphadenectomy or other nodal dissection procedures. However, it would be beneficial to be aware of the most common nodal involvement sites, particularly when lymph node sampling is being done. In our study, we observed that a significant prevalence of PALN dissemination (i.e., 51% cases showed PALN involvement), and hence, comprehensive surgical staging in apparent early-stage EOC should include both pelvic and para-aortic LND.

	Overall	HGSOC	LGSOC	Mucinous	Endometriod	CCC	Seromucinous
Upstaging due to nodes only	14	11	1	1	1	0	0
Upstaging due to all factors	71	53	7	4	6	1	1
Total no of cases	157	87	16	26	22	5	1

Fig. 4 Upstaging of cases after surgical staging.

We observed a strong trend in upstaging among those with complete staging; overall 45.22% cases showed upstaging in our study. About 8.9% cases showed upstaging due to nodal metastases alone (►Fig. 4).

The categorization of patients according to the primary tumor's histologic type makes this study distinctive. The initial tumor's histologic type may influence the lymphatic routes. The most important conclusion of this study was that the histologic type of the tumor greatly influences the nodal involvement. Nodal metastases are more common in serous tumors than in nonserous tumors with a typical pattern of dissemination.[22,23] Similar outcomes were discovered in this study. Nodal dissemination is seen five to six times more commonly in serous tumors than nonserous tumors and the former group has a specific metastatic pattern (50% cases showed isolated pelvic nodal metastases in our study) Therefore, LND may be a valid clinical option in the context of serous tumors. In contrast, there is no specific pattern in the distribution of nodal disease, and the risk of nodal disease is substantially lower with nonserous tumors. We have reported seven cases of nonserous type of tumors with nodal metastases with nonspecific pattern of spread. Additionally, nonserous tumors are typically resistant to chemotherapy, and it is unknown if postoperative chemotherapy works to treat nodal illness that persists after surgery. As a result, we currently believe that systematic LND is appropriate for nonserous tumors.

Although pelvic LND is generally considered a relatively safe procedure, few complications may occur and may vary considerably in their severity. ►Table 4 shows some of the morbidity associated with lymphadenectomy during our staging procedures. Both intraoperative and post-operative complications were seen but the incidence was not high (only 8% cases had Clavien Dindo grade 3 complications) and the complications have been managed conservatively. Similar findings have been reported in a study by He et al.[24]

Our research suggests that a vital element in the surgical evaluation of early stage of EOC is bilateral pelvic and paraaortic LND up to renal vessels. A thorough evaluation, which includes meticulous LND, allows for accurate staging and the possibility of finding occult node metastases. Planning for restaging operations should take the tumor's grade and histotype into consideration. (Our study revealed a favorable correlation between tumor histotype and grade in cases of nodal metastases) When patients are recommended for completion staging procedures, these data may be useful. Nevertheless, multicentric analysis is necessary.

Some of the limitations of this study are that positron emission tomography-computed tomography (PET-CT) imaging has not been utilized and it is a single-center study. PET-CT facility was not available at our institute during this study period.

Conclusion

Multicentric studies are quintessential to analyze the prognostic impact of systematic lymphadenectomy in early-stage ovarian carcinoma patients, depending on the histotype and distribution pattern of nodal metastases. Based on histology, this subset of node-positive EOC may be stratified, which may have prognostic significance and provide clarity for therapeutic decision making.

Conflict of Interest
None declared.

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