Article published online: 2024-08-27

THIEME OPEN ACCESS

Spectrum of Surgico-Pathological Factors and Lymph Node Metastasis among Epithelial Ovarian Cancers: Experience of a Single Tertiary Care Institution from India

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South Asian J Cancer

Abstract

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Introduction Epithelial ovarian cancer (EOC) is one of the leading causes of mortality among women worldwide. The present study aimed to estimate the frequency of various histopathological types, clinical and surgico-pathological factors, and spectrum of lymph node (LN) metastasis in early and advanced EOC.

Material and Methods Women with EOCs who underwent cytoreductive surgery (CRS) between January 2019 and May 2022 were included. The distribution of Clinico-demographic parameters, histological type, stage, and LN metastasis were analyzed.

Results A total of 101 women with EOCs underwent CRS, out of which 5 (4.95%) with coexistent endometrial cancer were excluded ($N = 96$). Fifty women (52%) underwent primary CRS and 46 (48%) women underwent interval CRS. The mean age of the women was 48.42 ± 11.6 years. Initial serum cancer antigen 125 (CA 125) level was elevated (>35 U/mL) in 88 (91.67%) women and normal in 8 (8.33%) women. Complete cytoreduction was achieved in 75 (78.12%) cases. High-grade serous carcinoma was the most common histology (66/96, 68.75%), followed by mucinous carcinoma (15/96, 15.63%), endometrioid carcinoma (6/96, 6.25%), low-grade serous carcinoma (4/96, 4.17%), and carcinosarcoma (2/96, 2.08%). The majority of women, 69 (71.88%), were in stages III and IV at presentation. Most serous carcinomas were diagnosed at stage III (71.22%) or IV (13.64%). In contrast, the majority of endometrioid, mucinous, and clear cell carcinomas were diagnosed at stages I and II. Seventy-five women (78.13%) with EOC underwent pelvic

Keywords

- cytoreductive surgery
- epithelial ovarian cancer
- lymph node metastasis
- ovarian cancer
- surgico-pathologic factors

DOI https://doi.org/10.1055/s-0044-1789581 ISSN 2278-330X

How to cite this article: Bahadur A, Verma P, Rajaram S, et al. Spectrum of Surgico-Pathological Factors and Lymph Node Metastasis among Epithelial Ovarian Cancers: Experience of a Single Tertiary Care Institution from India. South Asian J Cancer 2024;00 (00):00–00.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

and/or para-aortic lymphadenectomy, out of which 23 (30.67%) were histologically positive. Three out of 23 patients (13%) with early-stage disease showed positive LNs.

Conclusion Serous carcinoma ovary is the most common histological subtype, presenting mostly in the advanced stage. A significant number of affected women were younger at presentation and diagnosis was made a decade earlier than the western population. A systematic pelvic and para-aortic lymphadenectomy in apparently early-stage (pelvic confined) ovarian cancer could detect additional LNs in 13% of women, especially in high-grade tumors and serous histology, suggesting the role of systematic lymphadenectomy for accurate staging in apparently early-stage ovarian cancer.

Introduction

Ovarian cancer (OC) constitutes 324,398 new cases and 206,839 deaths in year 2022 among women worldwide. In India, OC is the third most common cancer and a leading cause of death.[1] OC represents a heterogeneous disease with varied biological characteristics that share different histopathological phenotypes.[2] Epithelial ovarian cancers (EOCs) constitute majority of OCs; other less common pathological types are malignant germ cell and sex cord–stromal cell tumors. Based on histology, immunoprofile, and molecular analyses, at least five main types of EOCs are recognized in the revised 2020 World Health Organization classification[3]: high-grade serous carcinoma (HGSC, 70%), endometrioid carcinoma (EC, 10%), clear cell carcinoma (CCC, 6–10%), low-grade serous carcinoma (LGSC, 5%), and mucinous carcinoma (MC, 3–4%). Although some rare entities (mesonephric-like and mixed carcinoma) have been introduced, others (seromucinous carcinomas) have been removed due to significant morphological overlap with EC.[3] HGSC and LGSC represent two distinct tumor types with different morphologies, pathogenesis, molecular events, and prognosis.[4]

The standard treatment of OC consists of complete surgical staging, accurate diagnosis, and primary debulking surgery (PDS) followed by adjuvant chemotherapy. No gross residual tumor (R0) after PDS is considered the most important prognostic factor for survival.[5] Based on the predominantly metastatic pattern of intraperitoneal and lymphatic spread, complete pelvic and para-aortic lymphadenectomy (LND) has been an integral part of initial OC surgery for decades.

The incidence of lymph node (LN) involvement in EOC varies widely in the literature. It depends mainly on the clinical stage of the disease, histologic subtype, and the extent of lymphatic dissection. Lymphatic involvement is found in 13 to 20% of women with clinical stage I EOC.[6] However, in advanced-stage intraperitoneal or extra-abdominal disease, nodal metastases are documented in 13 to 74% of women stage III EOC and in 33 to 88% of women with stage IV EOC.[7] Tumor spread to both the pelvic and para-aortic nodal chains is found in 53 to 73% of all women with positive nodes.[8] Approximately 75% of OCs are diagnosed at an advanced stage, with a 5-year survival rate of only 29%. This is in contrast to the 92% survival rate seen in early-stage cancers.[9]

Determination of various histological patterns and accurate staging, including LN metastasis, is essential for the management of women with EOC. Therefore, we have undertaken this study to determine the socio-demographic profile and clinical and surgico-pathological spectrum, along with incidence of LN metastasis in EOCs, including early and advanced cancers.

Methods

This observational study was conducted at AII India Institute of Medical Sciences (AIIMS), Rishikesh, India, from January 1, 2019 to May 30, 2022. Women with EOCs who underwent cytoreductive surgery, either primary or interval cytoreduction with age $\geq$18 years and Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2 at the time of surgery, were included in the present study. Women with diagnosis of nonepithelial/borderline tumors or recurrent OC were excluded from the study. Women with EOC who were treated with palliative intention, or diagnosed with other synchronous malignancies, were also excluded. The study was approved by our ethical research committee board (AIIMS/IEC/21/704; dated: December 24, 2021).

Women were recruited from the departments of Obstetrics & Gynaecology and Surgical Oncology after taking informed written consent. All the women with EOC who underwent staging laparotomy, which included ascitic fluid sampling or peritoneal washing, systematic exploration of the pelvic and abdominal cavity, hysterectomy with bilateral salpingo-oophorectomy (BSO), omentectomy, peritoneal biopsies from the suspected areas, pelvic and/or para-aortic LND, and removal of all gross disease with the aim of R0 resection, were recruited in the present study. The socio-demographic characteristics of the women, clinical parameters, tumor marker levels, preoperative imaging findings, surgical procedure, and LND details were recorded. Intraoperative details included the presence of ascites, laterality and size of tumor, any grossly enlarged (>1 cm) retroperitoneal LNs, peritoneal cancer index (PCI) scores, surgical complexity score (SCS), any residual disease, operative time, and blood loss including any complications as per modified Clavien–Dindo score were recorded.[10] Histopathological details, which included tumor grade, histological

type, involvement of LNs along with site, and final surgico-pathologic stage of the patients, were recorded and analyzed.

The primary outcome measures were frequency of various histotypes, grade along with the International Federation of Gynecology and Obstetrics (FIGO) stage of EOC studied, number of women who underwent pelvic and/or para-aortic LND, and LN positivity rate among all women with EOC and among various stages of EOC. The secondary outcome measures included PCI score, SCS, and extent of resection (completeness of cytoreduction [CC] score 0/1/2/3) in women who underwent cytoreductive surgery.

Statistical analysis: The categorical variables were presented as number and percentage (%). The quantitative data with normal distribution were displayed as the means ± standard deviation (SD), while data with non-normal distribution were displayed as median with the 25th and 75th percentiles (interquartile range). The association between quantitative variables, which were not normally distributed, was analyzed using the Mann–Whitney *U* test (for two groups) and the Kruskal–Wallis test (for more than two groups). The association between qualitative variables was analyzed using the chi-squared test. Fisher's exact test was applied in the cases where any cell had an expected value of less than 5. Final analysis was done using Statistical Package for Social Sciences (SPSS) software version 21.0 (IBM, Chicago, IL, United States). A *p*-value of less than 0.05 was considered statistically significant.

Results

A total of 103 women with EOCs who had undergone cytoreductive surgery between January 2019 and May 2022, were initially recruited for the study. Five of 101 (4.95%) EOC patients were diagnosed with a coexisting endometrial cancer. The most common histology was EC (►**Supplementary Material Table 1**, available in the online version only). Synchronous malignancy was considered an exclusion criterion in the present study; hence, 96 cases were considered for final data analysis.

►**Table 1** shows the clinico-demographic characteristics of all women with EOCs. The mean age (years) of the women with EOCs was 48.42 ± 11.6 with a median (25th–75th percentile) of 50 (40–57.25) years. The majority of the women (35.42%) were aged between 51 and 60 years, while 22.92% were 41 to 50 years, 20.83% were 31 to 40 years, and 13.54% were older than 60 years.

The mean body mass index (BMI) was 24.06 ± 3.96 kg/m^2. Most women, 48 of 96 (50.00%), belonged to the lower middle class. The majority of the women, 51 of 96 (53.13%), were classified as P2–P3, followed by 32 women (33.33%) with higher than P3. Ten women (10.42%) were nulliparous, while 52 women (54.17%) were postmenopausal with a mean duration of menopause of 8.81 ± 5.79 years. Only 7 of 96 (7.29%) women had a history of infertility/ovulation induction. Forty-five (46.88%) women did not use contraception. Twenty-three (23.96%) women had barrier as a contraceptive measure, followed by tubal ligation in 17 women (17.71%) and intrauterine contraceptive device (IUCD) in 7 women (7.29%). Oral contraceptive pills (OCPs) as a contraceptive measure were used by only 4 of 96 women (4.17%). Only 7 of 96 women (7.29%) had a family history of cancer.

Sixty-five women (67.71%) had an ECOG performance status of 1, while 21 women (21.88%) had an ECOG performance status of 2 at the time of surgery. Among tumor markers, cancer antigen 125 (CA 125) is the most commonly raised among patients. Initial serum CA 125 level was elevated (>35 U/mL) in 88 (91.67%) women and normal in 8 (8.33%) women. The mean value of initial CA 125 of all the women was 2,861.72 ± 11,208.85 U/mL, with a median (25th–75th percentile) of 894 (312.55–1,907.2) U/mL. However, in the majority of women (69.57%), CA 125 was in the normal range after neoadjuvant chemotherapy (NACT).

PDS was done in 50 (52.08%) women, and NACT followed by interval debulking surgery (IDS) was done in only 46 of 96 (47.92%) women with EOC. In most women, 94 of 96 (97.92%), surgery performed was total abdominal hysterectomy (TAH) with BSO and omentectomy. In addition, other performed surgeries were pelvic peritonectomy in 23 women (23.96%), diaphragmatic peritonectomy in 5 women (5.21%), and complete peritonectomy in 10 women (10.42%). Rectosigmoid resection along with colorectal anastomosis was done in 10 women (10.42%). Other organ resections (appendix, gall bladder, and falciform ligament) were performed in 23 women (23.96%). Metastatic deposit removal at other sites was performed in 32 (33.33%) women.

Bilateral ovarian masses were seen in 61 (63.54%) women. The mean value of the amount of ascites and largest tumor dimension were 563.54 ± 1,027.95 mL and 12.26 ± 9.37 cm, respectively. LNs were enlarged in only 38 of 96 women (39.58%). Out of 38 women with enlarged LNs, 13 women (34.21%) had enlarged pelvic LN only, 12 women (31.58%) had enlarged para-aortic LN only, and 13 women (34.21%) had enlarged (both pelvic and para-aortic) LNs.

The CC score was 0 in 78.12% cases, 1 in 7.29% cases, 2 in 11.46% cases, and 3 in 3.13% cases. Reasons for failure to achieve a CC score of 0 in 20 (21.88%) women were bowel deposits in 7 (35.00%) women, mesenteric deposits in 5 (25.00%) women, mesenteric along with bowel deposits in 4 (20.00%) women, multivisceral deposits in 2 (10.00%) women, and deterioration of vitals in 2 (5.00%) women. The mean PCI score, SCS, and CC score of women were 4.71 ± 5.8, 4.08 ± 1.97, and 0.36 ± 0.77, with a range of 0 to 30, 2 to 11, and 0 to 3, respectively. Regarding postoperative complications, the majority of women, 57 of 96 (59.38%), had grade II as per the modified Clavien–Dindo score, followed by grade I in 28 (29.17%) women, grade IIIA in 7 (7.29%) women, and grade IIIB in 3 (3.13%) women. The modified Clavien–Dindo score was grade IVA in only 1 of 96 (1.04%) women. Although delayed bowel activity was seen in 21 (21.88%) patients, only 15 (15.63%) patients experienced paralytic ileus. Symptomatic lymphocele was seen only in three (3.12%) cases, necessitating ultrasound-guided percutaneous catheter drainage.

Table 1 Clinico-demographic characteristics of women with EOC ($N = 96$)

Baseline characteristics	Frequency	Percentage
Age (y)		
20–30	7	7.29
31–40	20	20.83
41–50	22	22.92
51–60	34	35.42
>60	13	13.54
Mean ± SD	48.42 ± 11.6	
Median (25th–75th percentile)	50 (40–57.25)	
Range	20–73	
Body mass index (BMI), kg/m^2		
18.5–24.9 (normal BMI)	43	44.79
25–29.9 (overweight)	21	21.88
>30 (obese)	32	33.33
Mean ± SD	24.06 ± 3.96	
Median (25th–75th percentile)	23.4(21.175–25.625)	
Range	18.6–40.3	
Occupation		
Unemployed	91	94.80
Unskilled	2	2.08
Semiskilled	1	1.04
Semiprofessional	1	1.04
Professional	1	1.04
Socioeconomic status (modified Kuppuswamy scale)		
Upper	8	8.33
Upper middle	30	31.25
Lower middle	48	50.00
Lower	10	10.42
Parity		
P0	10	10.42
P1	3	3.13
P2–P3	51	53.13
>P3	32	33.33
Mean ± SD	3.01 ± 1.61	
Median (25th–75th percentile)	3 (2–4)	
Range	0–8	
Prior menstrual history		
Irregular	15	15.63
Regular	81	84.38
H/0 infertility/ovulation induction	7	7.29
Menopausal status	52	54.17
Duration of menopause (y)		
Mean ± SD	8.81 ± 5.79	
Median (25th–75th percentile)	9 (4.75–10.25)	
Range	1–20	

Table 1 (*Continued*)

Baseline characteristics	Frequency	Percentage
Family history of cancer		
No	89	92.71
Yes	7	7.29
Contraception		
No	45	46.88
Barrier	23	23.96
IUCD	7	7.29
OCP	4	4.17
Tubal ligation	17	17.71
Addiction		
Yes	1 (bidi smoker)	1.04
No	95	98.96
Comorbidities		
Diabetes mellitus	6	6.25
Hypertension	15	15.63
History of tuberculosis	4	4.17
Hyperthyroidism	9	9.38
History of pulmonary thromboembolism	4	4.17
Others	8	8.33
ECOG performance status		
0	10	10.42
1	65	67.71
2	21	21.88
Initial CA 125 (U/mL)		
0–35	8	8.33
>35	88	91.67
Mean ± SD	2,861.72 ± 11,208.85	
Median (25th–75th percentile)	894 (312.55–1,907.2)	
Range	4.2–108,290	
Post-chemo (NACT) CA 125 (IU/L)		
0–35	32	69.57
>35	14	30.43
Mean ± SD	200.96 ± 776.41	
Median (25th–75th percentile)	23.75 (13.5–50.575)	
Range	2–5,105	
CEA (IU/L)		
0–5	79	82.29
>5	17	17.71
Mean ± SD	20.75 ± 156.05	
Median (25th–75th percentile)	1.46 (1.068–2.858)	
Range	0.02–1,525	

(*Continued*)

Table 1 (*Continued*)

Baseline characteristics	Frequency	Percentage
CA19.9 (IU/L)		
0–37	77	80.21
>37	19	19.79
Mean ± SD	317.2 ± 2,065.94	
Median (25th–75th percentile)	10.88 (4.965–19.54)	
Range	1.06–20,041	
Neoadjuvant chemotherapy (NACT)		
No	50	52.08
Yes	46	47.92
PDS/IDS		
PDS	50	52.08
IDS[a]	46	47.92
Surgical procedure performed		
TAH + BSO	94	97.92
Salpingo-oophorectomy (SO)	2	2.08
Omentectomy	94	97.92
Pelvic peritonectomy	23	23.96
Peritonectomy	10	10.42
Diaphragmatic peritonectomy	5	5.21
Small bowel resection	2	2.08
Rectosigmoid resection	10	10.42
Colorectal anastomosis	10	10.42
Appendix/gall bladder/falciform ligament removal	39	40.63
Other metastatic deposit removal (Pouch of Douglas (POD)/peritoneal/bowel serosal/ mesenteric/bladder/liver capsule deposit)	32	33.33
Laterality of tumor		
Unilateral	35	36.49
Bilateral	61	63.54
Ascites		
No	48	50.00
Mild	29	30.21
Gross	19	19.79
Ovarian mass consistency (solid/cystic)		
Normal	14	14.58
Cystic	3	3.13
Cystic with small solid component	10	10.42
Solid	15	15.63
Solid cystic	54	56.25
Ovarian surface		
Irregular	51	53.13
Regular	45	46.88

Table 1 (*Continued*)

Baseline characteristics	Frequency	Percentage
Growth over surface/capsule breach		
No	68	70.83
Yes	28	29.17
LN enlarged on intraoperative clinical examination		
No	58	60.42
Yes	38	39.58
Enlarged LN site		
Pelvic LN	13	34.21
Para aortic LN	12	31.58
Pelvic and para-aortic LN	13	34.21
Completeness of cytoreduction score (CC score)		
0	75	78.12
1	7	7.29
2	11	11.46
3	3	3.13
Amount of ascites (mL)		
Mean ± SD	563.54 ± 1,027.95	
Median (25th–75th percentile)	200 (100–500)	
Range	50–5,000	
Size of tumor (cm)		
Mean ± SD	12.26 ± 9.37	
Median (25th–75th percentile)	10 (5–18)	
Range	3–60	
PCI score		
Mean ± SD	4.71 ± 5.8	
Median (25th–75th percentile)	3 (0–6)	
Range	0–30	
CC score		
Mean ± SD	0.36 ± 0.77	
Median (25th–75th percentile)	0 (0–0)	
Range	0–3	
Surgical complexity score		
Mean ± SD	4.08 ± 1.97	
Median (25th–75th percentile)	4 (3–4)	
Range	2–11	
Total surgery time (min)		
≤240	42	43.75
>240	54	56.25
Mean ± SD	290.62 ± 93.69	
Median (25th–75th percentile)	270 (240–360)	
Range	90–660	

(*Continued*)

Table 1 (*Continued*)

Baseline characteristics	Frequency	Percentage
Blood loss >500 mL		
No	43	44.79
Yes	53	55.21
Total	96	100.00
Intra-/postoperative blood products transfusion		
No	40	41.67
Yes	56	58.33
Total	96	100.00
Intraoperative complication		
No complications	87	90.63
Bladder wall injury	1	1.04
Duodenal injury	1	1.04
Rectal/sigmoid wall injury	3	3.13
Ureter injury repair	1	1.04
Vessel injury	3	3.13
Total	96	100.00
ICU stay		
No	85	88.54
Yes	11	11.46
Total	96	100.00
Time to bowel activity		
Delayed	21	21.88
Normal	75	78.13
Total	96	100.00
Total hospital stay (d)		
<7	72	75.00
≥7	24	25.00
Mean ± SD	6.58 ± 4.4	
Median (25th–75th percentile)	5 (4–6.25)	
Range	3–35	
Modified Clavien–Dindo score		
Grade I	28	29.17
Grade II	57	59.38
Grade IIIA	7	7.29
Grade IIIB	3	3.13
Grade IVA	1	1.04
Total	96	100.00

Abbreviations: BSO, bilateral salpingo-oophorectomy; CA 125, cancer antigen 125; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; EOC, epithelial ovarian cancer; ICU, intensive care unit; IDS, interval debulking surgery; IUCD, intrauterine contraceptive device; LN, lymph node; OCP, oral contraceptive pill; PCI, peritoneal cancer index; PDS, primary debulking surgery; SD, standard deviation; TAH, total abdominal hysterectomy.
[a]Two cases of IDS treated with HIPEC (hyperthermic intraperitoneal chemotherapy).

►Table 2 shows that the most common histology was HGSC, which was detected in 66 women (68.75%), followed by MC in 15 women (15.63%), EC in 6 (6.25%) women, LGSC in 4 (4.17%) women, and carcinosarcoma in 2 (2.08%) women. The histological type CCC, squamous cell carcinoma (SCC), and mixed carcinoma (serous + transitional) were only 1 case each out of 96 (1.04%) women. Out of 96 women with EOC, 62 women (64.58%) had high-grade EOC and 16 (16.67%) women had low-grade EOC. The grade was not specified in 18 (18.75%) cases. As shown in ►Table 2, of the 96 women diagnosed with EOC, 24 (25%) were in FIGO stage I, 3 (3.12%) in stage II, 60 (62.51%) in stage III, and 9 (13.64%) in stage IV. The commonest stage of presentation was FIGO stage IIIC, observed in 47 (48.96%) women. Out of 66 women with HGSC of the ovary, most women, 41 (62.12%), were in stage IIIC, followed by 5 women (7.58%) in stage IVB, and 4 women (6.06%) in stage IVA. Out of four cases of LGSC, two women (50%) were in stage IA and one woman each was in stages IIIA and IIIC. Out of 15 cases of MC, 8 cases (53.33%) were in stage IA, followed by 3/15 (20%) cases in stage IIIC, and 1/15 case each in stages IIIA2 and IIB (6.67%). Out of eight cases of EC, two cases (33.33%) each were in stages IA and IB and one case (16.67%) each was in stages IIIB and IIIC (►Table 3).

As shown in ►Table 4, LNs (pelvic/para-aortic) were positive on histology in only 23 of 75 women (30.67%). Para-aortic LNs were positive in only 16 of 75 women (21.33%). Pelvic LNs were positive in only 17 of 75 (22.67%)

Table 2 Histological types and grade of women with EOC ($N = 96$)

Histological type and grade	Frequency	Percentage
Histological type		
High-grade serous carcinoma (HGSC)	66	68.75
Low-grade serous carcinoma (LGSC)	4	4.17
Mucinous carcinoma (MC)	15	15.63
Endometrioid carcinoma	6	6.25
Clear cell carcinoma (CCC)	1	1.04
Squamous cell carcinoma (SCC)	1	1.04
Mixed carcinoma (serous + transitional)	1	1.04
Carcinosarcoma	2	2.08
Histological grade		
Low grade	16	16.67
High grade	62	64.58
Not specified	18	18.75
FIGO stage		
Stage I	**24**	**25**
IA	14	14.58
IB	5	5.21
IC1	1	1.04
IC2	4	4.17
IC3	0	0.00
Stage II	**3**	**3.12**
IIA	1	1.04
IIB	2	2.08
Stage III	**60**	**62.5**
IIIA1	3	3.13
IIIA2	4	4.17
IIIB	6	6.25
IIIC	47	48.96
Stage IV	**9**	**9.38**
IVA	4	4.17
IVB	5	5.21

Table 3 Association of FIGO stage with histological subtype ($N = 96$)

FIGO stage	HGSC ($n = 66$)	LGSC ($n = 4$)	Mucinous ($n = 15$)	Endometrioid ($n = 6$)	CCC ($n = 1$)	SCC ($n = 1$)	Mixed carcinoma ($n = 1$)	Carcinosarcoma ($n = 2$)	Total	*p*-value
I	9 (13.65%)	2 (50%)	8 (53.33%)	4 (66.66%)	1 (100%)	–	–	–	24 (25%)	< 0.0001[a]
IA	1	2	8	2	1	–	–	–	14	
IB	3	–	–	2	–	–	–	–	5	
IC1	1	–	–	–	–	–	–	–	1	
IC2	4	–	–	–	–	–	–	–	4	
II	1 (1.52%)	–	1 (6.67%)	–	–	–	–	1 (50%)	3 (3.12%)	
IIA	1	–	–	–	–	–	–	–	1	
IIB	–	–	1	–	–	–	–	1	2	
III	47 (71.22%)	2 (50%)	6 (40%)	2 (33.34%)	–	1 (100%)	1 (100%)	1 (50%)	60 (62.51%)	
IIIA1	1	1	–	–	–	–	–	1	3	
IIIA2	2	–	1	–	–	–	1	–	4	
IIIB	3	–	2	1	–	–	–	–	6	
IIIC	41 (62.12%)	1	3	1	–	1	–	–	47 (48.96%)	
IV	9 (13.64%)	–	–	–	–	–	–	–	9 (13.64%)	
IVA	4	–	–	–	–	–	–	–	4	
IVB	5	–	–	–	–	–	–	–	5	
Total	66	4	15	6	1	1	1	2	96 (100%)	

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; HGSC, high-grade serous carcinoma; LGSC, low-grade serous carcinoma; SCC, squamous cell carcinoma.
[a]Fisher's exact test.

Table 4 Final histopathology of lymph nodes (LNs) of women with EOC who underwent lymphadenectomy ($n = 75$)

LN histology	Frequency	Percentage	
Distribution of positive LN on HPE			
Total LNs (pelvic/para-aortic) positive			
Negative	52	69.33%	
Positive	23	30.67%	
Para-aortic LNs positive			
Negative	59	78.67%	
Positive	16	21.33%	
Pelvic LNs positive			
Negative	58	77.33%	
Positive	17	22.67%	
No. of positive LNs of EOC women with LND			
No. of positive LNs	**Mean ± SD**	**Median (25th–75th percentile)**	**Range**
Total no. of positive LNs	3.57 ± 2.8	3 (1.5–4.5)	1–11
No. of positive para-aortic LNs	3.5 ± 2.78	3 (1.75–3.5)	1–9
No. of positive pelvic LNs	2.06 ± 1.75	2 (1–2)	1–8

Abbreviations: EOC, epithelial ovarian cancer; HPE, histopathological examination; LND, lymphadenectomy; SD, standard deviation.

women. However, 12 of 17 (70.59%) patients with positive pelvic nodes also had positive para-aortic LNs. The mean number of total positive LNs, positive para-aortic LNs, and positive pelvic LNs were 3.57 ± 2.8, 3.5 ± 2.78, and 2.06 ± 1.75 with a median (25th–75th percentile) of 3 (1.5–4.5), 3 (1.75–3.5), and 2 (1–2), respectively.

►Table 5 shows the distribution of positive pelvic and para-aortic LNs among various stages of disease. Among apparent early-stage OC (T1/T2), 3 of 23 (13.04%) patients were found to have LN metastasis (upstaged/diagnosed as FIGO stage IIIA). The proportion of patients with positive total LNs was significantly higher in stages IIIA1 (100%) and IVB (75%; $p = 0.009$).

Discussion

This study evaluated the sociodemographic data, surgicopathological characteristics of EOC, and LN profile among women with EOC who underwent cytoreductive surgery at a single tertiary care institution.

In the present study, 5 of 101 women (4.95%) were diagnosed with synchronous endometrial cancer. Matsuo et al reported a similar incidence of synchronous ovarian and endometrial cancer in their retrospective observational study based on the Surveillance, Epidemiology, and End Results (SEER) program in 2018.[11] Synchronous endometrial and OC is not an uncommon clinical entity; it has been found in 3 to 10% of ovarian malignancies and 3 to 5% of endometrial cancers. The commonest histology among synchronous malignancies was low-grade endometrioid adenocarcinoma, similar to the present study.

The present study showed the mean age of women with EOC at the time of diagnosis was 48.42 years ± 11.6 (median = 50 years), with peak prevalence in patients between the ages of 51 and 60 years. The prospective Million Women Study conducted by Gaitskell et al reported a mean (±SD) age of women at the time of diagnosis of 65.6 ± 6.5 years.[12] Another study from India conducted by Jindal et al reported a mean age at diagnosis of EOC of 52.1 ± 8.96 (median: 52) years.[13]

Coburn et al stated that incidence rates before ages 35 to 39 years remained relatively low for all subtypes of EOC. After that, incidence increased steadily with age, reaching a peak at age 70 to 74 years and a slight decrease in women aged 75 to 79 years for serous and mucinous cancers. Incidences of endometrial and CCC were markedly parallel in all age groups, reaching a plateau around 55 to 59 years.[14]

Comparatively lower age of cancer diagnosis in the present study, in contrast to most western studies, may suggest an earlier onset or more prevalence of high-grade tumors and aggressive course of the disease in Indian women. This corroborates with other Indian studies, warranting a high index of suspicion in women aged 31 to 60 years since a significant number of women were in this age range in the present study.

The mean BMI in this study was 24.06 ± 3.96 kg/m^2. Similar to our study, Gaitskell et al reported a BMI of 26.2 (4.7) kg/m^2 in women with EOC.[12] In the present study, 10 (10.42%) women with EOC were nulliparous, although increasing parity did not show any decline in OC. In the study by Jindal et al, 10.5% of women with OC were nullipara. A history of infertility was present in 7.29% of women.[13] Gaitskell et al concluded that parous women, on average, had a 26% reduced risk of OC than nulliparous women.[12] In the present study, 52 (54.17%) women with EOC were menopausal, with a mean (SD) duration of 8.81 ± 5.79 years. A study by Jindal et al reported 65% of cases of EOC in postmenopausal women.[13]

Table 5 Association of positive lymph nodes with stage among women with EOC

TNM stage	T1a	T1b	T1c1	T1c2	T2a	T2b	T1/T2	T3a2	T3b	T3c	Any T, M1a	Any T, M1b	Total		*p*-value
FIGO stage	IA	IB	IC1	IC2	IIA	IIB	IIIA1	IIIA2	IIIB	IIIC	IVA	IVB			
No.	9	3	1	4	0	2	3	2	4	40	3	4	75		
Total lymph nodes positive															
Negative	9 (100%)	3 (100%)	1 (100%)	4 (100%)	0	2 (100%)	0 (0%)	1 (50%)	3 (75%)	25 (62.50%)	3 (100%)	1 (25%)	52 (69.33%)		0.009[a]
Positive	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0	0 (0%)	**3** (100%)	1 (50%)	1 (25%)	**15** (37.50%)	0 (0%)	3 (75%)	23 (30.67%)		
Para-aortic lymph nodes positive															
Negative	9 (100%)	3 (100%)	1 (100%)	4 (100%)	0	2 (100%)	1 (33.33%)	2 (100%)	4 (100%)	29 (72.50%)	3 (100%)	1 (25%)	59 (78.67%)		0.046[a]
Positive	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0	0 (0%)	2 (66.67%)	0 (0%)	0 (0%)	11 (27.50%)	0 (0%)	3 (75%)	16 (21.33%)		
Pelvic lymph nodes positive															
Negative	9 (100%)	3 (100%)	1 (100%)	4 (100%)	0	2 (100%)	1 (33.33%)	1 (50%)	3 (75%)	28 (70%)	3 (100%)	3 (75%)	58 (77.33%)		0.28[a]
Positive	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0	0 (0%)	2 (66.67%)	1 (50%)	1 (25%)	12 (30%)	0 (0%)	1 (25%)	17 (22.67%)		

Abbreviations: EOC, epithelial ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; TNM, *tumor size, node involvement, and metastasis status.*
[a]Fisher's exact test.

In the present study, seven (7.29%) women had a family history of cancer. In the study by Jindal et al, 6.15% women had a family history of cancer.[13] According to Webb and Jordan, women with a family history of OC are more likely to develop the disease themselves.[15] Those with one affected first-degree relative have a threefold increase in risk than women with no affected relatives.

Among EOC subtypes, the most frequent histological subtype was 68.75% HGSC, followed by 15.63% MC, 6.25% EC, 4.17% LGSC, 2.08% carcinosarcoma, and 1.04% each CCC, SCC, and mixed carcinoma (serous + transitional). Similar to our study, in the prospective Million Women Study,[12] during 16.7 million person-years of follow-up (an average of 14.6 years per woman), 8,719 incident OCs were reported, with various histotype distribution as 67% serous carcinoma, 15% MC, 11% EC, and 7% CCC.

High-grade EOC was seen in 64.58% women and low-grade EOC was found in 16.67% women. The grade was not specified in 18.75% women. In a retrospective study by Ivanova et al, among 2,041 patients of EOC, low-grade (51.4%), moderate-grade (48.65%), high-grade (28.8%), and unspecified grade (25.1%) EOCs were found.[16]

The heterogeneity in epithelial histologies and grade distribution may be explained by differences in population in terms of genetic and environmental risk factors, which affect each histological subtype differently. Coburn et al studied the variation in the pattern of OC by histotypes worldwide. They concluded that it may be linked to differences in the prevalence of modifiable reproductive factors such as nulliparity/low parity, menopausal hormone therapy use, oral contraceptive use, and other familial/genetic predispositions.[14]

In the present study, the majority of women, 60 of 96 (62.5%), were in stage III, 24 women (25%) were in stage I, 9 women (9.38%) were in stage IV, and 3 women (3.15%) were in stage II at presentation. The stage at diagnosis varies substantially by the epithelial subtype. Most serous carcinomas were diagnosed at stage III (71.22%) or IV (13.64%), reflecting the aggressive nature of predominant HGSCs. In contrast, the majority of endometrioid, MC, and CCCs were diagnosed at stage I. This is in concordance with the previous study done in 22,240 women with EOC by Torre et al.[17] There was a difference in the percentage of women diagnosed with stage III EOC in a study conducted by Ivanova et al compared to the present study.[16] The reason could be a high number of unstaged tumors in that study (31.3% in serous tumors and 36.15% in mucinous tumors).

Regarding the spectrum of LN involvement, we found the involvement of pelvic or para-aortic LNs in 23 of 75 (30.67%) women, while pelvic LNs were involved in 17 of 75 (22.67%) women. Out of 57 women who underwent para-aortic LND, para-aortic LN involvement was found in 16 (28%) women. In a retrospective study of 114 women with EOC done by Widschwendter et al, 59 women (51.8%) had LN metastasis (pelvic and/or para-aortic), 39 (34.8%) women had pelvic LN metastasis, and 51 (46.8%) women had para-aortic LN metastasis with a median number of total positive LNs of 5 (1–48), pelvic (median: 3; range: 1–26) and para-aortic (median 2,

range 1–22).[18] Similar to our study, Zhou et al observed 32.8% LN metastasis in a retrospective analysis of 256 women with EOC.[19]

The present study showed an interesting finding that 3 of 23 patients (13%) with apparently pelvic confined disease (early stages) showed positive LNs (upstaged). Van de Vorst et al found 18.7% upstaging in a meta-analysis of 5,194 patients of early EOC.[20] Erdem et al inferred 12.9% upstaging rate in a retrospective analysis of 163 women with EOC due to LN metastasis.[21] Bachmann et al found 8% upstaging in a prospective study of 75 women with EOCs.[22] In a retrospective analysis of 190 women with EOC, Powless et al found an upstaging rate of 13%.[23] According to a meta-analysis by Kleppe et al, the rate of LN metastasis is 14.2% (pelvic only: 3.3%; para-aortic only: 6.7%; and both pelvic and para-aortic: 4.3%).[24] Lymphatic dissemination is significant in OC, even if the tumor is confined to the ovary or the pelvis.

Our study showed that out of 60 women with a FIGO stage III EOC, 20 (33.3%) women had a positive LN status, with 13 (21.7%) women showing at least one positive para-aortic node. A FIGO stage IV EOC was found in nine women, and three (33.3%) of these women had positive nodes; all three (33.3%) women had at least one metastasis in para-aortic nodes, whereas only one patient (11.1%) had pelvic LN metastasis along with para-aortic LN metastasis. In contrast to our study, Widschwendter et al showed that 47 (72.3%) of the 65 women with a FIGO stage III tumor had a positive LN status, with 40 (61.5%) of them having at least one positive para-aortic node. A FIGO stage IV tumor was observed in 14 women, with 12 (85.7%) having positive nodes and 11 (78.6%) having at least one positive para-aortic node.[18] The lower number of LN metastasis in advanced stage EOC may be due to NACT followed by IDS in 40 of 75 women (53%) who underwent LND in our study. No significant association was found between LN metastasis and NACT.

Integration of clinical, radiological, and surgico-pathological characteristics and biomarkers of individual tumors is of utmost importance to predict tumor behavior and response to therapy, thereby helping the clinician to decide the management of cancer patients within a multidisciplinary tumor board.

Conclusion

The findings from this research suggest that a systematic pelvic and para-aortic LND in apparently early-stage (pelvic confined) OC could detect additional LNs in 13% of women, especially in high-grade tumors and serous histology, suggesting the role of systematic LND for accurate staging in apparently early-stage OC. Hence, accurate surgical staging is a cornerstone in the management of women with EOC.

Conflict of Interest

None declared.

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