International Research Journal of Multidisciplinary Scope (IRJMS), 2024; 5(2): 918-926 IRJMS

Original Article | ISSN (O): 2582-631X DOI: 10.47857/irjms.2024.v05i02.0683

Role of Lymph Node Dissection in Primary Staging Surgery of Early-Stage Mucinous Ovarian Cancer (mOC)- A New Insight

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Abstract

This study is done to evaluate whether it is necessary to do systematic retroperitoneal lymphadenectomy in all early-stage mucinous ovarian cancer (mOC) or do we need to change our routine practice according to new scientific clinical-based evidence. This is a single centre observational study where retrospective data of 81 patients of early stage mOC were prospectively analyzed into two groups depending on the systematic dissection of retroperitoneal lymph node i.e. 1. Lymph node dissection (LND+) group versus 2. Lymph node none-dissection (LND-) group. Log Rank (Mantle- Cox) test was used among these two groups to look for a comparison of outcome in terms of progression free survival (PFS) and overall survival (OS). During 2008-2016 out of 268 patients 123 had primary mOC and among them, 81 were early stage. Out of 81 patients, 48 were in LND+ and 33 patients in LND- group. The incidence of grade I mOC was 79.16% and 84.85% in LND+ and LND- group respectively. None of the LND+ cases came positive in the final report which shows very rare involvement of lymph nodes (LN)in early stage mOC. PFS was not statistically significant (p-value 0.061) in between the LND+(91.7%) and LND- (75.8%) groups. The same was true for a 5-year OS. There was no significant improvement of OS in between the LND+ (95.8%) and LND- (87.9%) groups. There was no lymph node recurrence even in LND- groups. This study has given us the insight that in early stage mOC routine systematic lymph node dissection (LND) can be omitted as it does not improve PFS and OS.

Keywords: Lymph Node Dissection, Mucinous Ovarian Cancer, Overall Survival, Progression Free Survival.

Introduction

According to GLOBOCAN 2022 worldwide, a total of 3,24,398 new cases of ovarian cancer were diagnosed and 2,06,839 cases of mortality were reported. The Surveillance, Epidemiology, and End Results (SEER) Program US data of National Cancer Institute from 2013- 2019 showed that the 5-year relative survival of ovarian cancer patients is only 50.8% which is almost similar to Cancer Research UK (45% 5-year survival). It shows poor outcomes and high mortality of ovarian cancer patients as most of the cases are presented in an advanced stage.

Most of the cases of ovarian cancers are epithelial in origin. Primary Mucinous Ovarian Cancer (mOC) is one of the less common variants of epithelial ovarian cancer. The incidence rate of mOC is 3-10% of all epithelial ovarian cancers (1). It may reach an enormous size, filling the entire abdominal cavity. For this reason, the majority of cases are diagnosed in the early stage. Incidence of bilateral tumors occurs in 8% to 10% of cases. As most contain enteric-type cells, it is difficult to distinguish metastatic carcinoma of the gastrointestinal tract based on histology alone. Primary mOC rarely metastasizes to the mucosa of the bowel, although they commonly involve serosa, whereas gastrointestinal mucinous cancer lesions frequently involve the ovary.

Generally, it is thought that in serous epithelial ovarian cancer, lymph nodes are more commonly affected than the mucinous variant (2).

Recently mOC has been further sub-classified into two types: expansile and infiltrative. Although infiltrative stage I mOC may be associated with lymph node metastasis (LNM) but the degree of differentiation was found to be unreliable in the prediction of recurrence or future LNM. For stage II and higher stage disease, differentiation between the

(Received 28th February 2024; Accepted 28th April 2024; Published 30th April 2024)

expansile versus infiltrative type seems to be less meaningful and the prognosis is more correctly determined by the stage (3).

Frozen section assessment (FSA) is thought to be helpful for intraoperative decision making to have tailored surgery for an individual early-stage ovarian cancer patient. Most of the mOC are very large-sized tumors with mixed heterogeneous components, hence the accuracy of FSA to determine the mOC is complex and challengeable (4). Diagnosis of malignancy by FSA for surgical staging decision may result in a substantial reduction in the number of cases and subsequent inadequate staging and less intervention. On the other way around, FSA can lead to over-diagnosis and thus necessitating extensive surgery and increased risk of morbidity (5).

However, upcoming evidence shows that mOC very rarely metastasizes to the lymph nodes; therefore, the requirement of retroperitoneal lymph node dissection as a part of surgical staging for each and every case of early mOCs is questionable.

Here in this study, we tried to look into and validate the importance of the role of routine retroperitoneal lymph node dissection (RPLND) in the patients of our institute who were diagnosed with early stage mOC (Figure 1).

Methodology

This is a single-centre observational study conducted in a regional cancer centre in Western India. In this study, collected retrospective data were prospectively analyzed. Our Institutional review committee (The GCRI Institutional Review Committee-IRC) has evaluated and approved the study. Our study contains the patient's data of nine years (January 2008 to December 2016) who underwent surgery on that particular timeline. A total of 81 women with suspected mucinous ovarian tumors grossly confined to the pelvis who underwent comprehensive surgical staging during the study period were included. In this study, patients with early-stage mOC were analyzed into two groups: Group1-who underwent systematic lymph node dissection (LND+) versus Group 2-who did not undergo systematic lymph node dissection (LND-). All the patients included in the study group were well informed about this retrospective study and their consent had been taken retrospectively after counselling. All the patient's information had been taken from the hospital register with authority permission and the patient's confidentiality had been duly respected. All the clinical-radiological-surgical-pathological data were thoroughly reviewed wherever it was necessary to avoid misinterpretation and bias.

Inclusion Criteria

Post-primary staging surgery and histopathologically confirmed early-stage mOC consenting patients during the study period were included in this study.

Exclusion Criteria

1. Non-epithelial and Epithelial ovarian cancer other than mOC were excluded
2. Those patients who have received neo-adjuvant chemotherapy had been excluded
3. Discordance between FSA and final histology like final histopathology revealing benign or borderline mucinous ovarian tumors.
4. Metastatic disease from another primary origin
5. Evidence of advanced disease (beyond stage II) at surgical exploration.
6. Radiologically enlarged or intra-op palpable lymph node present
7. Abstraction of data that were Inconclusive.
8. Non-consenting patients

Wherever possible Frozen Section Assessment (FSA) was taken as a guide and determining factor to direct the surgeon to allocate patients for systematic lymphadenectomy to be performed or not.

Study Endpoint

The primary endpoint was overall survival (OS) which is calculated from the date of diagnosis to the date of death. So, the duration of the survival including disease recurrence was also included in OS. Secondary endpoints included progression-free survival (PFS) which was defined as the length of time during and after the treatment of a disease-to-disease progression or death from any cause. All the lost to follow up patients were censored from the statistical evaluation. Here, in this study we have statistically compared the primary and secondary

endpoint in terms of months in the two groups of LND+ and LND-.

Statistical Analysis

Outcomes evaluated including PFS, OS were compared in these two groups using Log Rank (Mantle- Cox) test. The p-value <0.05 was considered statistically significant. The Kaplan Meier method was applied to show the estimation of differences of the median survival curve among these two groups of patients.

All statistical analysis evaluation were performed with IBM SPSS (Statistical Package for the Social Sciences) version 26.

Table 1: Patient characteristics of two study groups(N=81)

Patients' characteristics	LND+ group (n=48)	LND- Group (n=33)
Median Age in years (Range)	45.5 (13-70)	55 (22-80)
Menopausal status-		
Pre-menopause	22(45.83%)	11(33.33%)
Post-menopause	26(54.16%)	22(66.67%)
Comorbidities-		
Hypertension	4(8.3%)	9(27.7%)
Diabetes Mellitus	0	3(9%)
Pre surgery Median CA 125 (Range)	44.5(7- 313)	48.04(7.9-906)
Pre surgery Median CEA (Range)	4.73(0.62-313)	3.78(0.73- 156.1)
Pre surgery Median CA 19-9 (Range)	18.28(1.69-2910)	83.67(6.36-48504)

Results

The primary outcomes of this study were OS and PFS. The secondary outcomes were recurrence, site of recurrence and lymphadenectomy associated complications.

As shown in the consort diagram, total mucinous ovarian tumors operated during the study period were 268. Out of those patients 109 were benign, 29 were borderline and 130 were malignant mucinous ovarian tumors. Among 130 malignant mucinous ovarian tumors, 7 were metastatic, 123 were primary mOC, 81 were early stage and 42 were an advanced stage with distant metastasis. In our study, we included only early-stage mOC and they were further divided into two groups depending on whether lymphadenectomy was done or not. Early stage of ovarian cancer is classically defined as a gross disease confined to the pelvis only (6).

In 48 patients, Lymph Node Dissection was done (LND +) and in 33 patients Lymph Node Dissection was not done (LND -). In LND+ and LND – groups, the median ages were 45.5 years and 55 years respectively. The median value of tumors markers for CA125, CEA, CA 19-9 in LND + was 44.5, 4.73, 18.25 and 48.04, 3.78, 83.67 in LND – group respectively (Table 1).

The mean duration of surgery in the LND+ and LND- groups was 182 minutes versus 150.5 minutes in these two groups respectively.

Ascites was present in almost half of the patients in both groups (LND+ 50% versus LND- 48.5%). The median diameter of the tumor was almost similar in both the groups LND+ 17cm versus LND- 16cm). In both the groups the adnexal disease was unilateral (LND+ 93.75% versus LND- 84.85%). Most of the tumors in both groups were grade I (LND+ 79.16% versus LND- 84.85%). There were no tumors of grade 3 in both groups (Table 2).

Peritoneal cytology was positive in only 4.16% in the LND+ group as compared to 6.06% in LND- group. In 95.84% in the LND+ group and 84.85% in LND- group optimal cytoreduction was achieved. In this study, we have included the patients in whom final histopathology was confirmed. In all the cases, we have reviewed slides and blocks for reconfirmation.

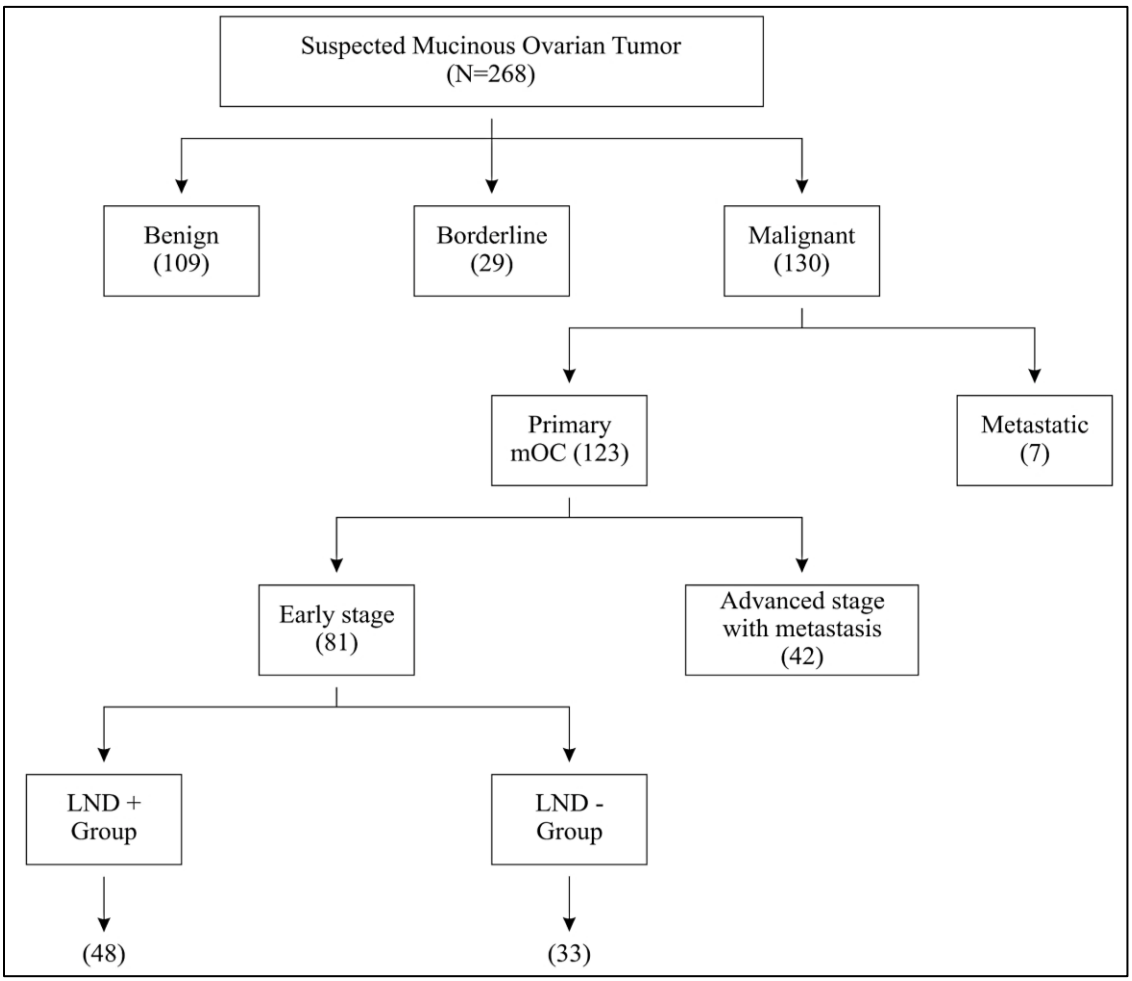

Figure 1: Consort diagram

FSA was corresponding to final histology in 81.39% and 78.57% in LND+ and LND- group respectively. In none of the LND+ cases
lymph node came positive for metastasis in the final histopathology report.

As our institute is a tertiary level cancer referral center, patient from remote corners of Gujarat and other states are referred for treatment. Thus, we kept the patients in the ward till suture removal leading to a long median hospital stay i.e. 13.5 days in LND+ and 16 days in LND- group.

22 out of 48 in the LND+ group (55%) and 20 out of 33 in the LND- group (60.60%) received adjuvant chemotherapy. Incidences of recurrence in these 2 groups were near similar (18.75% in LND+ versus 21.21% in LND-). It was interesting to see there was no lymph node recurrence in LND- group. Pelvis, Lung and diaphragm were common sites for recurrence in both groups.

91.7% of patients in the LND+ group and 75.8% of patients in the LND- group remained progression-free at the end of 24 months which is statistically not significant (p-value 0.061). The mean PFS was 16.5 months in the LND+ group and 15.5 months in the LND- group (Figure 2).

Overall survival at 5 years was 95.8% in the LND+ and 87.9% in the LND- group respectively which is not statistically significant (p-value 0.182). The mean OS in the LND+ group was 33.8 months, and the median OS was 37 months (Figure 3). The mean OS in the LND- group was 36.2 months and the median OS was 49.5 months. There was a statistically significant strong association (p-value 0.035) with fever in the LND+ group (9 cases) than LND- group (1 case).

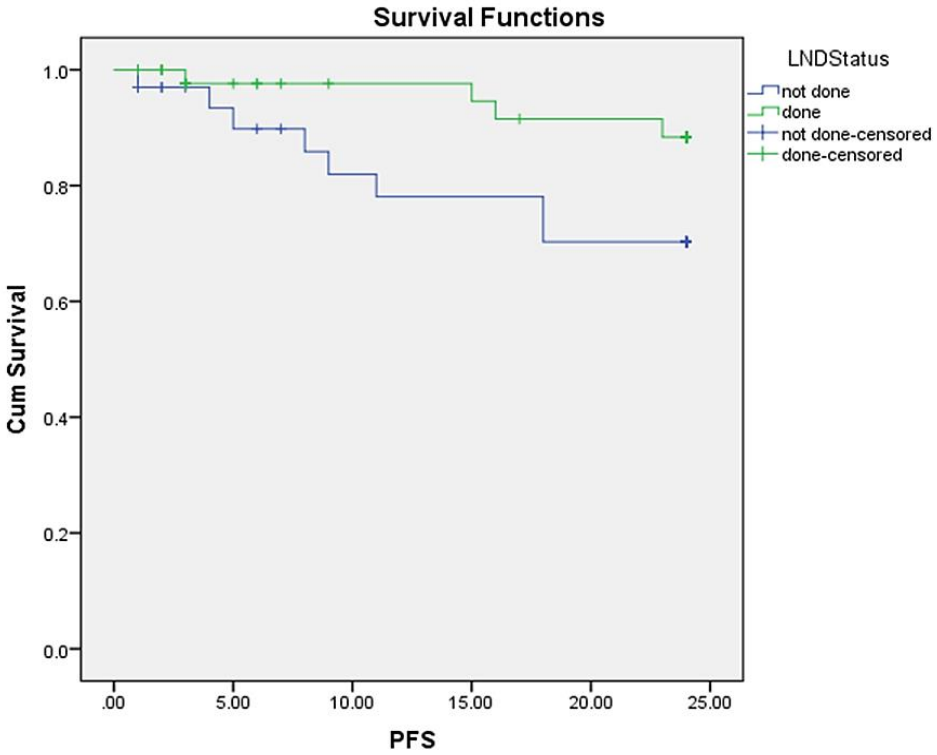

Figure 2: Progress free Survival in LND+ group 91.7% and LND- group 75.8% P value-0.061

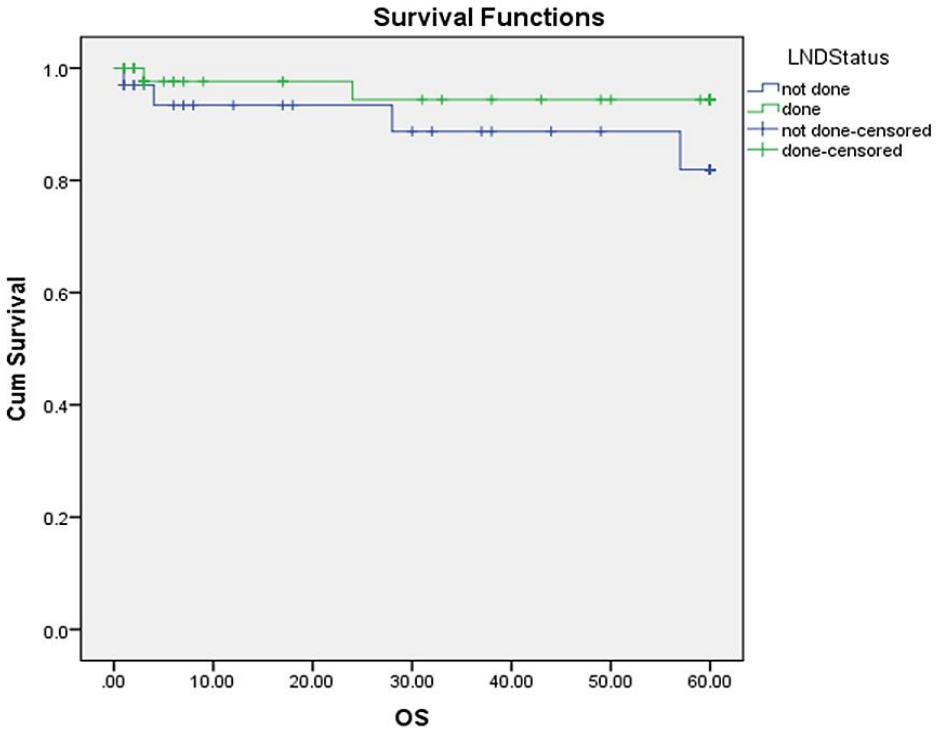

Figure 3: Overall survivals in LND+ group 95.8% and LND- group 87.9% P value-0.182

Table 2: Clinical, surgical and pathological characteristics of two study groups (N=81)

	LND+ group (n=48)	**LND- Group (n=33)**
Ascites	24 (50%)	16 (48.5%)
Tumour diameter (Median)	17 (3.8-35cm)	16 (2.5-24 cm)
Laterality of adnexal disease		
Ipsilateral	45(93.75%)	28(84.85%)
Bilateral	3(6.25%)	5(15.15%)
Stage		
IA	26(54.16%)	12(36.36%)
IB	0	1(3%)
IC	21(43.75%)	15(45.45%)
II	1(2%)	5(15.15%)
Grade		
1	38(79.16%)	28(84.85%)
2	10(20.83%)	5(15.15%)
3	0	0
Peritoneal washing (Cytology) Positive	2(4.16%)	2(6.06%)
Duration of Surgery (Mean)	182(90-450min)	150.5(60-410 min)
Frozen section done	43(89.58%)	28(84.84%)
Frozen correspond with final histopathology report	35 out of 43(81.39%)	22 out of 28 (78.57%)
Lymph node positive in histopathology report	0	-
Total Amount of Blood loss (Mean)	303(100-600ml)	443(100-1600ml)
Blood transfusion	18(37.5%)	17(51.51%)
Immunohistochemistry done	10(20.83%)	7(21.21%)
Median Hospital Stay (range)	13.5 (7-20 days)	16(8-30 days)
Adjuvant Chemotherapy received	22(55%)	20(60.60%)
Recurrence	9(18.75%)	7(21.21%)
Site of Recurrence		
Lung	2	1
Colon	0	2
Diaphragmatic surface of Liver	2	1
Cerebral metastasis		1
Peritoneum	1	1
Retroperitoneal nodes	0	0
Pelvic mass	3	1
Gall bladder mass	0	1
Bone	2 (1 patient had both bone and lung and other had bone and liver metastasis)	0 (1 patient had both gall bladder and colon mass. 1 patient had both liver and cerebral metastasis)

Lung complications were seen in one patient of the LND+ and three patients of the LND- groups. The renal complications were equal in two of these groups. Three patients in LND+ and two patients in LND- had GI Complications. Wound dehiscence in

LND+ and LND- groups were three and four patients respectively.

In LND+ group one patient had Vesico-Vaginal Fistula (VVF) whereas in LND- group, one patient had both VVF and Recto Vaginal Fistula (RVF). Only one patient in the LND+ group had neutropenia (Table 3).

Table 3: Postsurgical complications and primary systemic treatment (N=81)

	LND+ group (n=48)	LND- group (n=33)	P Value
Fever>38'C	9	1	0.035 Significant
Pelvic lympho-cyst collection	1	0	0.41 NS
Total Lung Complications-	1	3	0.15 NS
Pulmonary Embolism	0	1	
Pleural Effusion	1	0	
Requiring Ventilation	0	1	
Requiring Tracheostomy	0	1	
Total Renal Complications-	2	2	0.73 NS
AKI treated with Dialysis	0	1	
DJ Stenting for gross HU/HN	1	1	
	1	0	
GI complications-	3	2	0.97 NS
Paralytic Ileus	1	0	
Diarrhoea	1	1	
Bowel obstruction	1	1	
Wound Dehiscence	3	4	0.36 NS
Fistula	1	2	0.35 NS
VVF	1	1	
RVF	0	1	
Neutropenia	1	0	0.41 NS

Discussion

As there is no randomized control trial and lack of systemic review of literature on LND in early stage mOC so there is no clear-cut consensus on it. Here in this study, we are looking into the role of retroperitoneal lymph node dissection in early stage mOC and whether we can omit this step with its associated complications in primary staging surgery.

In our study patients with early stage mOC who underwent primary staging surgery did not benefit from systematic lymphadenectomy with respect to both PFS and OS.

In contrast, lymphadenectomy resulted in statistically significant more febrile morbidity in the LND+ group. In LND+ group, no lymph node came positive for metastasis in the HPE report. There was no single case of lymph node recurrence in the LND- group. Jesica M. Gillen et al. conducted a retrospective review of mOC patients at the University of Oklahoma from 1996 to 2014. The study showed that occult metastasis to clinically stage l mOC is very rare (only 1 out of 46 patients) and isolated metastasis to lymph node is very unlikely when a tumor is confined to the ovary (7).

Most of the studies in the literature search showed similar findings except one Japanese study in 2005 conducted by Nobuhiro Takeshima et al. which suggested that non-serous ovarian cancer should undergo systematic LND as 7.7% of the mOC cases had nodal metastasis. This study also concluded that the likelihood of pelvic node and para-aortic node involvement is almost equal in the case of non-serous ovarian tumors versus serous ovarian tumors (8).

However, there is increasing evidence coming up that primary mOC stages I and II do not have lymph node involvement and consequently no significant

impact on staging (9). Besides shortening the total duration of operation omitting LND would reduce 2-3% risk of complications, such as vascular, neurological, ureteric, bowel injuries, lymphedema, lymphocyst and chylous ascites formation (10). JOAM van Baal et al. conducted a retrospective cohort study in the Netherlands between 2002 and 2012. The study shows lymph node metastases is rare (2.1% in grade I and 0.9%in grade II) in early-stage Grade I and II mOC without clinical suspicion hence lymph node sampling can be omitted (11). Similar conclusions have been drawn by M. Kleppe et al. review of literature which analyzed total 14 numbers of well-conducted studies. Their review favors omitting a systematic lymphadenectomy can only be done in grade 1 mOC (12).

A similar retrospective study was conducted on the patient data of 23 years (1985 to 2007) in M.D. Anderson Cancer Center by Pedro T. Ramirez et al. in which 93 out of 107 patients had mOC confined to the ovary. Among these 93 patients, 51 patients (55%) had LND and of these 51 patients, none of them had retroperitoneal metastasis.

There was no significant difference in PFS and OS between LND+ and LND- groups of patients. As no case of isolated lymph node metastases in early-stage mOC was found in that study hence, the study concluded that early-stage mOC may be subjected to skip LND from primary staging surgery (13).

Our study result should be analyzed and interpreted in the context of the limitation of single-center and retrospective data which were analyzed prospectively. Surgeons' discretion to perform LND or not was dependent on his/her philosophy, perception, and practice. In a few cases, FSA unequivocal results or inability to conduct FSA could be another limitation. It is undeniable to say that this study has raised the complex issue of our conventional practice of routinely doing LND in early stage mOC without any strong scientific evidence of therapeutic benefit.

Conclusion

This study revealed that early stage mOC with non-suspicious nodal status systematic retroperitoneal lymphadenectomy was not associated with better outcomes than no lymphadenectomy and was associated with a higher incidence of postoperative febrile morbidity. In the LND+ group, all the lymph nodes came metastasis negative. Our study findings may be helpful to give hypothesis-generating information to guide for the formation of future study design for this group of mOC. Further well designed multi-centric prospective randomized control trials with a larger sample size should be conducted to reach meaningful advances and to end the practice of routine lymph node dissection as standard care of treatment on the early stage mOC.

Abbreviation

LND- Lymph Node Dissection; mOC- Mucinous Ovarian cancer; FSA- Frozen Section Assessment; VVF- Vesico-Vaginal Fistula; RVF- Recto Vaginal Fistula; OS-Overall Survival; PFS- Progression Free Survival; RPLND-Retro Peritoneal Lymph Node Dissection; LNM- Lymph Node Metastasis.

Acknowledgement

The authors express their gratitude to the all the participating patients and Pathology, Medical Oncology departments of The Gujarat Cancer and Research Institute Ahmedabad, Gujarat, India.

Authors Contribution

All authors contributed to the study conception and design.

Conflict of Interest

The authors declare no conflict of interest.

Ethics Approval

The study protocol was approved by the Institutional Review Committee of The Gujarat Cancer and Research Institute Ahmedabad, Gujarat, India.

Funding

This research received no specific grant from public, commercial, or non-profit funding agencies.

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