THE THERAPEUTIC IMPACT OF LYMPHADENECTOMY IN THE MANAGEMENT OF EPITHELIAL OVARIAN CANCER: A SINGLE INSTITUTION EXPERIENCE

Kiran Abhijit Kulkarni[1], Premalatha T. S[1*], Sumangala G[1], Geeta Acharya[1], Sumithra Selvam[2], Vishakha C. Bidkar[1], Julian Crasta[3], Elizabeth Vallikad[1]

1 Department of Gynecologic Oncology, St. John's Medical College, Bengaluru

2 Department of Biostatistics, St. John's Medical College, Bengaluru

3 Department of Pathology, St. John's Medical College, Bengaluru

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ABSTRACT

Aim: To assess the impact of lymphadenectomy on overall survival (OS) and progression free survival (PFS) in patients with epithelial ovarian cancer (EOC).
Study design: Retrospective observational study
Place and duration of study: All patients diagnosed with epithelial ovarian, fallopian tube or primary peritoneal cancer treated in the Department of Gynecologic Oncology in a tertiary care hospital in South India from January 2012 onwards. All patients' follow up data was prospectively updated till 30 April 2017.
Methodology: We included 83 patients who met the inclusion criteria. The patients were classified into two groups based on the number of lymph nodes (LN) harvested (< 30 lymph nodes and ≥ 30 nodes). Lymphadenectomy was considered systematic (SLND) when the harvest was ≥ 30 nodes on the pathologic specimen.
Results: Out of the 83 cases, complete SLND was done in 43 (51.8%) cases and the median number of removed lymph nodes was 44 (IQR 25– 75%: 38–52). Among the women who underwent a complete SLND, the median OS was 55.7 months vs 49.0 months among those where the lymph node harvest count was < 30 (*P* value – 0.16). The median PFS in the complete SLND group was 49.0 months and 43.46 months for the other group with no significant difference *(P* value – 0.18). Though there was no significant difference in OS and PFS, there was a trend towards improved survival with complete SLND group beyond 500 days.
Conclusion: Complete SLND group showed a trend towards improved OS and PFS, though statistically not significant. Further investigation is warranted.

Keywords Systematic lymphadenectomy, epithelial ovarian cancer, survival, cytoreduction

E-mail address: premalatha_siddartha@yahoo.co.in

1. INTRODUCTION

Ovarian cancer is the most fatal of gynecologic malignancies [1] The disease is often diagnosed in advanced stage and long-term survival is 30%-40%. The common routes of spread of ovarian cancer are by peritoneal implantation and lymphatic dissemination [2,3]. Surgical staging in early cases and primary cytoreductive surgery followed by platinum-based chemotherapy is the standard treatment.

The clinical benefit of lymphadenectomy in women with early disease apart from providing more accurate staging is unclear [4] The effect of lymph node dissection on progression-free survival (PFS) and overall survival (OS) in patients with advanced ovarian cancer is still unknown. The benefit of complete cytoreduction, on the OS is well established [5-7]. Whether optimum surgery for epithelial ovarian cancer (EOC) should include retroperitoneal lymphadenectomy along with intraperitoneal procedures as part of maximal cytoreductive is not well defined. Various survival outcomes have been documented with systematic lymphadenectomy and with resection of only bulky nodes [8-11]. The practices are variable in different centers across the globe. There are very few Indian studies addressing the role of systematic lymph node dissection (SLND) in Epithelial ovarian cancer (EOC).

This study is an attempt to assess the impact of systematic pelvic and para-aortic lymphadenectomy on survival in EOC.

2. MATERIAL AND METHODS:

This was an observational study involving the record review of patients with a diagnosis of epithelial ovarian, fallopian tube or primary peritoneal cancer who underwent primary surgery or interval cytoreduction in the Department of Gynecologic Oncology from January 2012 onwards. The Institutional ethics committee approval was taken prior to beginning the study.

Follow up data of the patients was prospectively updated till 30 April 2017. Women who were operated elsewhere or who received less than three courses of chemotherapy in the adjuvant setting, when indicated, were also excluded from the study.

An informed written consent was obtained from patients who had completed treatment and were available for follow up. Telephonic verbal consent was obtained in women who had not visited the hospital for recent follow-up. The relevant information retrieved consisted of demographic data, clinical details, investigations, intraoperative findings, details of surgery, histopathology reports, postoperative period, adjuvant / neoadjuvant chemotherapy (NACT), follow up, recurrence and death. All the cases were staged as per the new FIGO staging (2014) for ovarian cancers. The FIGO stage for the cases operated prior to 2014 was reclassified according to the new FIGO staging (2014).

Systematic pelvic LND involved removal of all pelvic lymphatic tissues in front of, behind, between the iliac vessels up to the bifurcation of the aorta,down to the obturator fossa and the pelvic floor. Para-aortic lymphadenectomy extended up to the renal vessels, removing all lymphatic tissues around and between the aorta and vena cava. The number of LN harvested was considered as representative of the extent of dissection. Systematic lymphadenectomy (SLND) was defined as a complete procedure when at least 30 lymph nodes were reported in the pathologic specimen [12]. Surgery was performed by the same dedicated team over the period of study. The Surgical procedures were quantified using the Surgical Complexity Score (SCS) previously described by Aletti et al [13].

E-mail address: premalatha_siddartha@yahoo.co.in

OS was calculated as the number of months from the date of diagnosis to either the date of death or the date censored. PFS was calculated as the number of months from the date of diagnosis to either the date of recurrence or the date censored.

Descriptive statistics were reported using mean and standard deviation for continuous variables and number and percentages for the categorical variables. Kaplan -Meier curve, log rank test, univariate and multivariate Cox regression analysis were used to explore the impact of different covariates on OS and PFS. Probability value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS statistical package 23.

3. RESULTS

A total of 83 cases met the inclusion criteria for this study. Patient and tumor characteristics are shown in Table 1 and 2 respectively. Mean age of the study cases was 51.4 years +/- 12.8 with median follow up of 30.5 months. Sixty-nine (83.1%) were younger than 65 years. Fifty-two (62.7%) women were postmenopausal. Only eight were nulliparous (9.6%). Most of the patients (89.2%) did not have a family history of any malignancy. Thirty-seven (44.6%) women were in a good performance status (Eastern Cooperative Oncology group; ECOG 0). Forty-one women (49.4%) belonged to FIGO stage IIIC. Most of the patients had a high-grade carcinoma (n = 70; 84.3 %) and a serous histology (n =68; 81.9 %). The other histologies noted were mucinous (n = 7), endometrioid (n = 4), clear cell (n = 3) and carcinosarcoma (n =1). Lymphadenectomy was performed in 74 (89.2%) patients. Lymphadenectomy with a node count >/= 30 (complete systematic LND group) was found in 43 (51.8%) cases and the median number of removed lymph nodes was 44(IQR 25– 75%: 38–52). The median blood loss in this group was 600ml (IQR 25-75%: 500-1000ml). Among the rest of the patients (lymph node count < 30), the median number of dissected nodes was 23 (IQR 25–75%: 17-27). The median blood loss in this group was 700ml (IQR 25-75%: 400-1000ml). There was no significant difference in the number of cases which needed ICU care and blood transfusion in either group. The postoperative complications were seen in 14/43 cases (32.5%) in the complete SLND group and in 12/40 cases (30%) in the other group. Lymph node metastases was present in 27 of 74 (36.5%) patients, nine patients did not undergo lymphadenectomy. Among the node positive cases, 17 / 27 (62.9%) had normal sized non-suspicious nodes on intra-operative assessment. Complete gross cytoreduction (defined as no macroscopic tumor) was achieved in 52 (62.7%) cases, cytoreduction with gross residual disease of 1–10 mm in 22 (26.5%) and gross residual disease > 10 mm in nine (10.8%) patients.

E-mail address: premalatha_siddartha@yahoo.co.in

119

120

Variable	Number of patients	Percentage (%)
Total	83	100
Age		
< / = 64 yrs.	69	83.1
> 64 yrs.	14	16.9
Menopausal status		
Postmenopausal	52	62.7
Premenopausal	31	27.3
Treatment		
Primary surgery	58	69.9
Neoadjuvant chemotherapy	25	30.1
Performance status		
ECOG 0	37	44.6
ECOG 1	40	48.2
ECOG 2	06	7.2
FIGO stage		
I	21	25.2
II	3	3.6

E-mail address: premalatha_siddartha@yahoo.co.in

III	51	61.5
IV	8	9.7

Table 1. Patient characteristics

E-mail address: premalatha_siddartha@yahoo.co.in

154

Variable	Number of patients	Percentage (%)

155 Table 2. Tumor characteristics

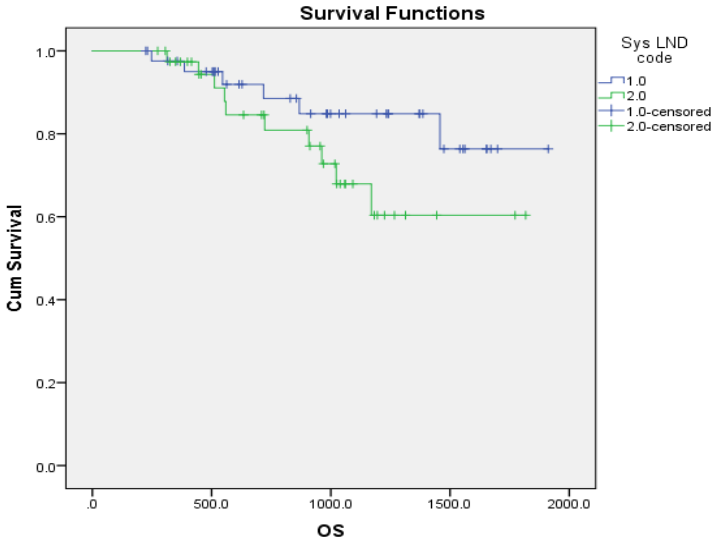
E-mail address: premalatha_siddartha@yahoo.co.in

Total	83	100
Grade		
Low	13	15.7
High	70	84.3
Histology		
Serous	68	81.9
Others	15	18.1
*p*N stage		
Nx	9	10.8
N0	47	56.7
N1	27	32.5
Lymph node resected		
< 30	40	48.2
≥ 30	43	51.8
Residual disease		
Nil	52	62.7
< / =10mm	22	26.5
> 10mm	9	10.8
Surgical complexity score		
Low	9	10.8

E-mail address: premalatha_siddartha@yahoo.co.in

Intermediate	68	81.9
High	6	7.3

Considering the outcome as mortality, the mean OS and PFS for all the patients was 52.4 months and 48.76 months respectively. Among the women who underwent a complete systematic lymphadenectomy, the median OS was 55.7 months vs 49.0 months among those where the lymph node harvest count was < 30 (*P* value – 0.16). Although median OS was slightly higher among women who underwent a complete systematic lymphadenectomy, especially with longer follow up, there was no significant difference as compared to women where the lymph node harvest count was < 30 (Fig 1).

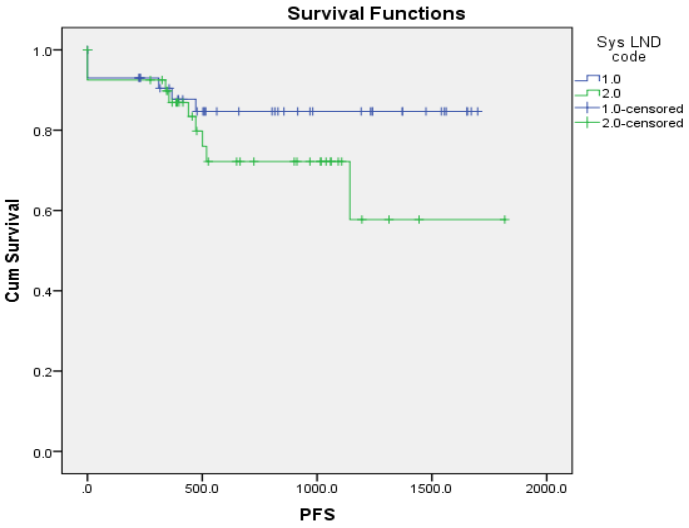


1.0 Lymph node count >/= 30 group
2.0 Lymph node count < 30 group

Fig 1. Overall survival (OS) in days. Kaplan - Meier

The median PFS in the group which underwent complete systematic lymphadenectomy was 49.0 months and 43.46 months for the other group with no significant difference (P value – 0.18) (Fig 2). However, a trend towards improved PFS was noted with the complete SLND group on longer follow up.

E-mail address: premalatha_siddartha@yahoo.co.in



1.0 - LN count >/= 30 group
2.0 - LN count < 30 group

206

Fig 2. Progression free survival (PFS) in days. Kaplan - Meier

OS was significantly different between performance status, nodal involvement (N stage), systematic lymphadenectomy and residual disease using Kaplan Meier analysis. Subjects with better performance status, negative nodes, who underwent complete systematic lymphadenectomy and had nil residual disease, had a higher survival as compared to other groups.

Univariate cox regression analysis revealed that performance status, N stage and residual disease were the significant predictors of mortality considering the overall survival. Subjects with poor performance status had 12.6 times higher hazards, positive nodes had 2.2 times higher hazards and residual disease had 27 times higher hazards as compared to other groups.

Multivariate cox regression revealed that none of the above variables were significant predictors of mortality. However, subjects with positive nodes had higher hazards of mortality as compared to negative nodes (*P* value=0.06). Similarly, when progression free survival was considered, performance status, N stage and residual disease were significant predictors of recurrence. Although none of the variables were significant in the multivariate analysis, N stage and residual disease had higher hazards of mortality (Table 3).

Variable	**N**	**Univariate analysis**	**Multivariate analysis**

E-mail address: premalatha_siddartha@yahoo.co.in

Variable	N	Univariate analysis			Multivariate analysis		
		HR	95%CI	*P* value	HR	95%CI	*P* value
Age (years)							
>64	69	1.56	0.50-0.856	0.43	1.07	0.29-3.93	0.91
<64	14	1	-	-	-	-	-
Performance status							
ECOG 0	37	1	-	-	-	-	-
ECOG 1	40	0.040	0.004-0.360	0.004	0.21	0.01-3.75	0.29
ECOG 2	6	0.428	0.136-1.348	0.14	-	-	-
***p*N stage**							
N0	47	1	-	-	-	-	-
N1	27	7.54	2.06-27.51	0.002	2.07	0.24-17.57	0.50
Nx	9	4.72	0.95-23.47	0.06	5.47	0.93-31.78	0.06
Lymph node count							
<30	40	2.13	0.76-5.97	0.14	-	-	-
≥30	43	-	--		-	-	-
Residual disease							
1. Nil	52	1	-	-	-	-	-
1-10 mm	22	3.7	1.04-13.1	0.04	1.52	0.35-6069	0.57

E-mail address: premalatha_siddartha@yahoo.co.in

Variable	N	Univariate analysis			Multivariate analysis		
> 10mm	9	7.56	2.12-26.83	0.002	3.55	0.77-16.35	0.10

Table 3. Univariate and multivariate analysis of prognostic factors

3.1 DISCUSSION:

Comprehensive surgical staging in early disease and optimal cytoreduction in advanced stage with platinum-based chemotherapy is the mainstay treatment of EOC [14-16]. Lymphatic spread is common in advanced EOC. Histopathology showed 27 (36.5%) positive nodes in our cohort, which is slightly less compared to other studies. This could probably be because of high number of early stage EOCs. In the present study 17 / 27 (62.9%) node positive patients had normal sized non-suspicious nodes on intraoperative assessment, emphasizing the inaccuracy of clinical assessment as noted in earlier studies [17].

The role of lymphadenectomy for staging procedure is well established though the therapeutic role is debated [18,19]. The impact of lymphadenectomy in advanced ovarian cancer is less clear and guidelines are lacking whether systematic pelvic and para aortic lymphadenectomy be performed with debulking surgery [20-23]. The decision to perform systematic lymphadenectomy is by the surgeon's discretion or the policy of the hospital.

In advanced ovarian cancer there is a high rate of involved nodes and survival benefits are documented with systematic aortic and pelvic lymphadenectomy [9]. Studies also have shown that removal of bulky nodes improved OS in optimally debulked ovarian carcinoma and there are studies showing no advantage in resection of clinically negative nodes [20-23,25]. No standardized techniques were mentioned in most of the studies and number of nodes dissected were also variable. The node count for systematic verses incomplete nodal dissection was also not uniform. The lymphadenectomy in ovarian neoplasms (LION) is the only prospective randomized trial which demonstrated no significant benefit of either PFS or OS and endorsed omitting routine lymphadenectomy in clinically node negative advanced ovarian cancer patients with macroscopic complete tumor resection [25].

Kim et al in 2010, conducted a meta-analysis comparing the impact of systematic lymphadenectomy and non-systematic lymphadenectomy (random removal or less removal or no removal of pelvic and para aortic nodes). They found an increased OS in all stage disease with systematic lymphadenectomy. But sub-analysis of the two RCTs included in their study showed no difference in OS between systematic and non-systematic lymphadenectomy [9]. In a study by Gao et al, 5-year OS in systematic lymphadenectomy group was higher than the non-systematic lymphadenectomy group. In their analysis of 14 studies, the difference was seen in observation studies and advanced stage disease and no difference was seen in the RCT, early stage disease and residual disease </= 2cm. The definition of unsystematic lymphadenectomy was inconsistent even in this study [26].

In the present study, in women who underwent a complete systematic lymphadenectomy, the median OS was 55.7 months vs 49.0 months among those where the lymph node harvest was < 30 but was not statistically significant. OS was significantly different between performance status, N stage, systematic lymphadenectomy and residual disease using

E-mail address: premalatha_siddartha@yahoo.co.in

Kaplan Meier analysis. Subjects with better performance status, negative nodes, who underwent complete systematic lymphadenectomy and nil residual disease, had a higher survival as compared to other groups.

In our study there is not much of a difference between overall and progression free survival as the number of events ha still not happened at the time of analysis and the analysis was time bound.

The limitation of the present study is that it is a retrospective study with less numbers and hence no sub group analysis could be done.
We included cases with a follow up as short as one month after completion of treatment. A study with larger numbers and longer follow up would throw better light in this matter.

4. CONCLUSION

Systematic lymphadenectomy does not have a significant impact on improving overall or progression free survival in epithelial ovarian cancers. However, N stage and residual disease had higher hazards of mortality. Complete SLND group showed a trend towards improved OS and PFS, though statistically not significant. Further investigation is warranted.

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COMPETING INTERESTS

The authors did not receive any funding for the research work. The authors declare that no conflict of interest exist in the submission of the manuscript.

AUTHORS' CONTRIBUTIONS

The first author (KK) and corresponding author (PTS) contributed to patient care, intellectual content, conception and design of the work, data collection, analysis, literature review, drafting and editing. The authors (SG, GA and VB) were involved in the patient care, documentation and record keeping, editing, referencing. The author (SS) did the statistical analysis. The author (JC) was involved in review of histopathology and contributed to the intellectual content. The author (EV) was involved in patient care, conception and design of the work.

CONSENT

An informed written consent was obtained from patients who had completed treatment and were available for follow up. Telephonic verbal consent was obtained in women who had not visited the hospital for recent follow-up.

ETHICAL APPROVAL

The study was approved by the institutional ethical committee.

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E-mail address: premalatha_siddartha@yahoo.co.in

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E-mail address: premalatha_siddartha@yahoo.co.in

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E-mail address: premalatha_siddartha@yahoo.co.in