Effect of lymph node dissection on overall and disease free survival in early epithelial ovarian cancer (EOC)

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Abstract

Objectives: The aim of this study was to evaluate the effect of systemic lymphatic dissection on overall and disease free survival in early epithlial ovarian cancer in our institute.

Introduction: Ovarian cancer is potentially curable by surgery; the cure rate is, however, poor because in most patients the disease is diagnosed at an advanced stage when overall five-year survival is only about 30%. Even when the tumor is seemingly limited to the gonads or with pelvic extension only the spread to retroperitoneal nodes is not uncommon. Retrospective study to assess the impact of lymphadenectomy on survival in patients with clinical stage I ovarian cancer and suggested that lymphadenectomy significantly improved the survival of such patients. Randomized study was conducted to investigate the effect of systematic lymphadenectomy in patients with pT1 and pT2 ovarian cancer, which showed that systematic lymphadenectomy had no influence on either progression free survival or overall survival.

Patients and methods: From December 2014 to January 2019 we collect date of one hundred and forty seven female patients with clinically FIGO stage I and II epithelial ovarian cancer underwent primary surgical treatment from a total of 520 patients with different stages of ovarian cancer that were admitted and operated at South Egypt Cancer Institute, Assiut University, Egypt.

Results: Mean age of patients in the study was 59.21 ± 10.121years with range 35 – 76 years. 44.2% of patients had comorbidities as diabetes, hypertension and others some patients may had more than one disease. Patients were ranged from 0 to two ECOG performance; most of patients had zero performance (51%). 60(40.8%) patients had received adjuvant chemotherapy. In our study overall survival and DFS was 74% and 68.7% respectively while mean time of survival and recurrence was 65.9456 ± 21.9450 with range of 36 – 120 months and 56.76 ± 23.927 with range of 10 – 120 months respectively.

Conclusion: Systemic lymphadenectomy even if have significant effect on DFS but it has multiple operative and post-operative morbidities and no significant effect on overall survival.

Keywords: Ovarian cancer, Survival, Lymph node dissection, early ovarian tumor.

Objective:

The aim of this study was to evaluate the effect of systemic lymphatic dissection on overall and disease free survival in early epithelial ovarian cancer in our institute.

Introduction:

Ovarian cancer is potentially curable by surgery; the cure rate is, however, poor because in most patients the disease is diagnosed at an advanced stage when overall five-year survival is only about 30% (Jemal et al, 2005).[1] While the surgical procedures and the requirements for optimal intra-peritoneal surgical staging of cancers apparently confined to the pelvis (International Federation of Gynecologic and Obstetrics (FIGO) stage I and II disease) (FIGO Committee on Gynecologic Oncology, 2000) are well established, the surgical approach to retroperitoneal nodes is controversial. Even when the tumor is seemingly limited to the gonads or with pelvic extension only the spread to retroperitoneal nodes is not uncommon.[2] Involvement of pelvic nodes have been reported to occur in 8– 15% (Piver et al, 1978; Burghadt et al, 1991) and of Para-aortic nodes in 5–24% of patients with stage I disease (Burghadt et al, 1991).[3][4] Recently, Chan et al. conducted a large-scale, retrospective study to assess the impact of lymphadenectomy on survival in patients with clinical stage I ovarian cancer and suggested that lymphadenectomy significantly improved the survival of such patients.[5] In addition, a randomized study was conducted to investigate the effect of systematic lymphadenectomy in patients with pT1 and pT2 ovarian cancer, which showed that systematic lymphadenectomy had no influence on either progression free survival or overall survival.[6]

Patients and Methods:

Eligibility

In the period from December 2014 to January 2019 we collect date of 520 patients with different stages of ovarian cancer that were admitted and operated at South Egypt Cancer Institute, Assiut University, Egypt in collaboration with obstetrics and gynecology department, Al-Alzhar University. One hundred and forty seven female patients with FIGO stage I and II epithelial ovarian cancer underwent primary surgical treatment in the form of abdominal total hysterectomy, bilateral salpingo-oophorectomy, total omentectomy, peritoneal wash and removal of all macroscopic tumors with or without L.N clearance. According to lymph node dissection these group of patients were classified to three groups; group (A) including 74 patients that not underwent lymph node removal, or just lymph node sampling for bulky pelvic lymph nodes (B) those underwent pelvic L.N dissection (48 patients) and (C) including patients underwent both PLN and PAN dissection. **Excluded** from this study; patients with incomplete data, patient with previous chemo or radiotherapy. Patients missed follow up are considered dead. Data which collected include age, BMI, associated diseases, performance of patients, tumor characteristics (as grade, histopathology, laterality, cytology, ascites, CA 125), L.N dissection, number of L.Ns and patients with positive L.Ns operative time, blood loss, hospital stay, perioperative deaths, recurrences and overall survival.

The protocol of our study was revised and accepted by our local ethical committee.

Informed consent was obtained from all patients previous to surgery according to local and national legislation.

Follow up and adjuvant treatment

According to postoperative pathological staging, patients with **FIGO** stage IIb and above were given first and second lines of platinum-based chemotherapy. Patients were followed up every 3 months in the first 3 years after surgery then six monthly after that, using radiological (sonar, C.T, MRI and/or PET scan) and tumor markers; to asses recurrence and survival.

Statistical analysis:

Statistical analysis was done using IBM SPSS Statistics v16. Percent and numbers were expressed for continuous variables while categorical variables expressed as means ± standard deviation. Chi-square test was used to assess statistical significance and Kaplan-Meier test for survival assessment.

Results:

From December 2014 to January 2019 we collect date of one hundred and forty seven female patients with clinically FIGO stage I and II epithelial ovarian cancer underwent primary surgical treatment from a total of 520 patients with different stages of ovarian cancer that were admitted and operated at South Egypt Cancer Institute, Assiut University, Egypt.

Firstly we discuss parameters of the whole study then we compare between the three groups of patients.

Table 1: Patient characters

		Number	Percent
Age			
-	Mean ± SD	59.21 ± 10.121	
-	Range	35 - 76	
BMI			
-	Mean ± SD	29.6998 ± 5.37555	
-	Range	22 - 43	
Associated condition			
-	Healthy	82	55.8%
-	D.M	13	8.8%
-	Hypertension	24	16.3%
-	Cardiac	9	6.1%
-	Hepatic	5	3.4%
-	Renal	3	2.0%
-	Multiple	11	7.5%
Performance			
-	0	75	51%
-	1	47	32%
-	2	25	17%
Adj. chemotherapy			
-	No	87	59.2%
-	Yes	60	40.8%

In table 1 patient's characters were present where mean age of patients was 59.21 ± 10.121years with range 35 – 76 years and mean BMI was 29.6998 ± 5.37555 and range 22 – 43.

44.2% of patients had comorbidities as diabetes, hypertension and others some patients may had more than one disease. Patients were ranged from 0 to two ECOG performance; most of patients had zero performance (51%). 60(40.8%) patients had received adjuvant chemotherapy.

Tumor characteristics were presented in table 2; where the most common histology was serous carcinoma (40.1%) and the most frequent tumor grade was grad 2 (40.8%). 81.6% of tumor was unilateral, ascites in 65(44.2%), cytology was positive in (21.1%), most of patients had CA 125 less than 50Iu/ml, mean number of dissected lymph nodes was 14.3333 ± 16.82722 with range of 0 – 58 L.Ns and total number of patents had positive lymph nodes was 48(32.65%).

In table 3 we discussed operative details and operative and perioperative complications. Mean operative time was 163.71 ± 45.1219 mints with range of 90 – 270 mints mean blood loss was 368.98 ± 154.9358 ml and range of 150 – 800 ml and mean hospital stay was 5.0748 ± 3.8322, range between zero day and 24 days. The most common complication was Ileus presented in 23(15.6%) patients followed by lymphorrhea and wound dehiscence 10.9% for each of them. Perioperative mortality was 3(2%) patients one for each group. In our study overall survival and DFS was 74% and 68.7% respectively while mean time of survival and recurrence was 65.9456 ± 21.9450 with

range of 36 – 120 months and 56.76 ± 23.927 with range of 10 – 120 months respectively. The most common site of recurrence was peritoneal (10.2%) followed by pelvic (9.5%) then distant (7.5%), retroperitoneal (6.8%) and multiple sites (6.8%) table 4.

Table 2: Tumor characters

	Number	Percent
Histology		
- serous	59	40.1%
- endometroid	17	11.6%
- transitional	11	7.5%
- clear	15	10.2%
- mucous	31	21.1%
- adenocarcinoma	9	6.1%
- undiff	3	2.0%
- unclassified	2	1.4%
Grade		
- grade 1	52	35.4%
- grade 2	60	40.8%
- grade 3	35	23.8%
CA 125		
- <50	55	37.4%
- 50 - 300	40	27.2%
- >300	27	18.4%
- not done	25	17.0%
Laterality		
- unilateral	120	81.6%
- bilateral	27	18.4%
Ascites		
- + ve	65	44.2%
- - ve	82	55.8%
Cytology		
- + cytology	31	21.1%
- - cytology	83	56.5%
- unknown	33	22.4%
No. of dissected L.Ns		
- Mean ± SD	14.3333 ± 16.82722	
- Range	0 - 58	
No. of + ve L.Ns		
- Mean ± SD	10.5238±1.34919	
- Range	0 - 48	
Patients with + ve nodes		
+ ve PLN	34	23.13%
+ ve PAN	5	3.4%
+ ve PLN&PAN	9	6.12%
Total	48	32.65%

Table 3: Operative details

	Number	Percent
L.N dissection		
- non	74	50.3%
- pelvic	48	32.7%
- pelvic+para	25	17.0%
Op. time		
- Mean ± SD	163.71 ± 45.1219	
- Range	90 – 270 mints	
Bl. loss		
- Mean ± SD	368.98 ± 154.9358	
- Range	150 – 800 ml	
Hosp. stay		
- Mean ± SD	5.0748 ± 3.83225	
- Range	0 -24 days	
Complications		
- vascular.Ing	9	6.1%
- DVT	10	6.8%
- Ileus	23	15.6%
- Lymphorrhea	16	10.9%
- Lymphedema	10	6.8%
- Wound dehiscence	16	10.9%
Perioperative deaths	3	2%

Table 4: Survival and Recurrence

	Number	Percent
Overall survival		
- Dead	38	25.9%
- Living	109	74.1%
Disease free survival		
- Recurrent	60	40.82%
- Free	87	59.18%
Time of survival		
- Mean ± SD	65.9456 ± 21.94507	
- Range	36 – 120 months	
Time of DFS		
- Mean ± SD	56.76 ± 23.927	
- Range	10 – 120 months	
Site of recurrence		
- Pelvic	14	9.5%
- Peritoneal	15	10.2%
- Retroperitoneal	10	6.8%
- Distant	11	7.5%
- Multiple	10	6.8%

Table 4: Survival and Recurrence

Table 5: Comparison between groups of lymphatic dissections

	Group A 74 (50.3%)	Group B 48 (32.7%)	Group C 25 (17.0%)	Chi-square P value
Age	60.91 ± 10.043	56.23 ± 9.718	59.92 ± 10.210	0.087
BMI	30.1199 ± 5.69315	29.2083 ± 5.47318	29.4000 ± 4.17333	0.552
Associated condition				
- Healthy	40(54.1%)	30(62.5%)	12(48.00%)	
- D.M	7(9.5%)	5(10.4%)	1(4.00%)	
- Hypertension	13(17.6%)	5(10.4%)	6(24.00%)	0.650
- Cardiac	4(5.4%)	2(4.2%)	3(12.00%)	
- Hepatic	3(4.1%)	1(2.1%)	1(4.00%)	
- Renal	3(4.1%)	0(0.00%)	0(0.00%)	
- Multiple	4(5.4%)	5(10.4%)	2(8.00%)	
Performance				
- 0	36(48.6%)	26(54.2%)	13(52.00%)	0.722
- 1	26(35.1%)	12(25.00%)	9(36.00%)	
- 2	12(16.2%)	10(20.8%)	3(12.00%)	
Adj. chemotherapy				
- No	57(77.00%)	25(52.1%)	5(20.00%)	0.000
- Yes	17(47.9%)	23(47.9%)	20(80.00%)	
Histology				
- serous	29(39.2%)	19(39.6%)	11(44.00%)	
- endometroid	10(13.5%)	5(10.4%)	2(8.00%)	
- transitional	6(8.1%)	5(10.4%)	0(0.00%)	
- clear	4(5.4%)	7(14.6%)	4(16.00%)	0.201
- mucous	21(28.4%)	6(12.5%)	4(16.00%)	
- adenocarcinoma	1(1.4%)	5(10.4%)	3(12.00%)	
- undiff	2(2.7%)	0(0.00%)	1(4.00%)	
- unclassified	1(1.4%)	1(2.1%)	0(0.00%)	
Grade				
- grade 1	28(37.8%)	16(33.3%)	8(32.00%)	0.895
- grade 2	28(37.8%)	22(45.8%)	10(40.00%)	
- grade 3	18(24.3%)	10(20.8%)	7(28.00%)	
CA 125				
- 50<	24(32.4%)	21(43.8%)	10(40.00%)	
- 50 - 300	23(31.1%)	12(25.0%)	5(20.00%)	0.841
- >300	15(20.3%)	7(14.6%)	5(20.00%)	
- not done	12(16.2%)	8(16.7%)	5(20.00%)	
Laterality				
- unilateral	61(82.4%)	40(83.3%)	19(76.00)	0.721
- bilateral	13(17.6%)	8(16.7%)	6(24.00%)	
Ascites				
- + ve	37(50.00%)	17(35.42%)	11(44.00%)	0.285
- - ve	37(50.00%)	31(64.58%)	14(56.00%)	
Cytology				
- + cytology	7(9.46%)	14(29.17%)	10(47.9%)	
- - cytology	49(66.22%)	22(45.83%)	12(48.00%)	0.006
- unknown	18(24.32%)	12(25.00%)	3(12.00%)	
No. of dissected L.Ns	0.9865± 2.2964	18.7708± 5.7027	45.3200± 7.34688	0.000
No. of + ve L.Ns	0.7162± 1.81712	12.2708± 5.75285	36.1600± 6.78651	0.000
Patients with + ve nodes				
-ve L.N	61(82.43%)	29(60.42%)	8(32.00%)	
+ve PLN	13(17.57%)	19(39.58%)	3(12.00%)	0.000
+ve PAN	0(0.00%)	0(0.00%)	5(20.00%)	
+ ve PLN&PAN	0(0.00%)	0(0.00%)	9(36.00%)	
Op. time	130.20 ± 21.2525	175.83 ± 21.7171	239.60 ± 18.2529	0.000
Bl. loss	271.08 ± 80.7086	431.25 ± 110.466	539.20 ± 186.635	0.000
Hosp. stay	3.4324 ± 1.72873	5.5208 ± 2.71316	9.0800 ± 6.35689	0.000
Complications				
- Vascular. Ing	1(1.35%)	4(8.33%)	4(16.00%)	0.023
- DVT	2(2.70%)	4(8.33%)	4(16.00%)	0.065
- Ileus	9(12.16%)	9(18.75%)	5(20.00%)	0.499
- Lymphorrhea	5(6.75%)	4(8.33%)	7(28.00%)	0.010
- Lymphedema	1(1.35%)	3(6.25%)	6(24.00%)	0.001
- Wound dehiscence	6(8.11%)	4(8.33%)	6(24.00%)	0.069
Perioperative deaths	1(1.35%)	1(2.1%)	1(4.00%)	ND
Site of recurrence				
- Free	33(44.60%)	35(72.92%)	19(76.00%)	
- Pelvic	12(16.22%)	1(2.10%)	1(4.00%)	
- Peritoneal	11(14.86%)	2(4.20%)	2(8.00%)	0.041
- Retroperitoneal	7(9.46%)	3(6.25%)	0(0.00%)	
- Distant	5(6.76%)	4(8.33%)	2(8.00%)	
- Multiple	6(8.12%)	3(6.25%)	1(4.00%)	
Overall survival				
- Dead	19(25.68%)	13(27.10%)	6(24.00%)	0.959
- Living	55(74.32%)	35(72.90%)	19(76.00%)	
Disease free survival				
- Recurrent	41(55.40%)	13(27.18%)	6(24.00%)	
- Free	33(44.60%)	35(72.92%)	19(76.00%)	0.007
Time of survival	64.3108 ± 20.76808	65.8125 ± 21.50572	71.0400 ± 26.01359	0.946
Time of DFS	51.57 ± 22.045	59.81 ± 24.016	66.28 ± 26.058	0.015

In table 5 we compare between groups according to parameters of the study; mean age was 60.91 ± 10.043 for group A, 56.23 ± 9.718 for group B and 59.92 ± 10.210 for group C without significant difference (P=0.087). Mean BMI was 30.1199 ± 5.69315, 29.2083 ± 5.47318 and 29.4000 ± 4.17333 for group A, B and C respectively without significant difference (P=0.552). There were no significant difference between groups in comorbidities (P=0.650); the most common disease in group A was hypertension (17.6%), D.M (9.5%) followed by cardiac (5.4%) and multiple (5.4%), the most common disease in group B hypertension (10.4%), D.M (10.4%) followed by multiple (10.4%) and cardiac (4.2%) while in group C hypertension came first (24%) followed by cardiac (12%) then multiple (8%) and D.M (4%), performance (P=0.722), histology (P=0.201); serous subtype came first for all groups (39.2%), (39.6%) and (44%) respectively. Mucous subtype came second in group A (28.4%) followed by endometroid (13.5%) then transitional (8.1%). In group B the second common subtype was clear cell type (14.6%) followed by mucinous type (12.5%) then endometroid, transitional and adenocarcinoma (10.4%). While in group C; clear and mucinous subtype (16.00%) came second then adenocarcinoma (12.00%) followed by endometroid type (8.00%), other histological types as undifferentiated and unclassified are present but in small numbers and not in all groups. Also there were no statistical difference between groups in grade (P=0895), CA 125 level (P=0.841), laterality (P=0.721), ascites (P=0.285), overall survival (P=0.959), mean time of survival (p= 0.946). There was significant difference between groups in number of patients taking adjuvant chemotherapy (P= 0.000) where group c (80%) first followed by group B (47.9%) then group A (47.9%). There was significant difference in number of patient having positive cytology (p=0.006) where group C had highest incidence (47.9%) then group B (29.17%) followed by group A (9.46%). Mean number of dissected lymph nodes, number of patients with positive lymph nodes, operative time, blood loss and hospital stay were significantly high in group C (P=0.000). Mean number of positive L.NS in group A, B and C was (0.7162±1.81712), (12.2708±5.75285) and (36.1600±6.78651) respectively, (P= 0.000). Group C had significantly high incidence of vascular injury (P=0.023), lymphorrhea (P=0.010) and lymphedema (P=0.001) than other groups but in other complications no significant difference. When comparing groups for recurrence; group A had significantly (P=0.041) high incidence of recurrence (55.4%) than group B (27.18%) and group C (24%) where pelvic recurrence came first (16.22%) then peritoneal (14.86%), retroperitoneal (9.46%), (8.12%) later distant (6.76%). Mean time of recurrence is significantly high (P=0.015) in group C (66.28 ± 26.058) than group A (51.57 ± 22.045) or group B (59.81 ± 24.016).

The 3 year and 5 year survival for group (A) was 74.32% and 50% and 72.9% and 47.92% for group (B) while that for group (C) was 76% and 56% without significant difference.

Table 6: Correlation between clinicopathological factors with overall survival and DFS

	Overall survival		Chi-square p value	DFS		Chi-square p value
	Dead (38)	Living (109)		Recurrent (61)	Free (86)	
Age Mean ± SD	64.34± 10.846	57.42± 9.256	0.028	59.25± 10.175	59.19± 10.142	0.674
BMI Mean ± SD	32.31± 5.9485	28.78± 4.8682	0.311	29.68± 4.9541	29.71± 5.68405	0.601
Associated condition						
• Healthy	4(10.52%)	78(71.56%)	0.000	36(59.01%)	46(53.49%)	0.764
• D.M	8(21.05%)	5(4.60%)		3(4.92%)	10(11.63%)	
• Hypertension	5(13.16%)	19(17.42%)		11(18.03%)	13(15.12%)	
• Cardiac	4(10.52%)	5(4.60%)		3(4.92%)	6(6.98%)	
• Hepatic	4(10.52%)	1(0.91%)		2(3.28%)	3(3.49%)	
• Renal	2(5.26%)	1(0.91%)		2(3.28%)	1(1.16%)	
• Multiple	11(28.95%)	0(0.00%)		4(6.56%)	7(8.14%)	
Performance						
• 0	6(15.79%)	69(63.30%)	0.000	35(57.38%)	40(46.51%)	0.263
• 1	14(36.84%)	33(30.28%)		15(24.60%)	32(37.21%)	
• 2	18(47.37%)	7(6.42%)		11(18.03%)	14(16.28%)	
Adj. chemotherapy						
• No	23(60.53%)	64(58.72%)	0.845	39(63.93%)	48(55.81%)	0.324
• Yes	15(39.47%)	45(41.28%)		22(36.07%)	38(44.19%)	
Histology						
• serous	16(42.11%)	43(39.45%)	0.311	23(37.70%)	36(41.86%)	0.985
• endometroid	5(13.16%)	12(11.01%)		7(11.47%)	10(11.63%)	
• transitional	1(2.63%)	10(9.17%)		4(6.56%)	7(8.14%)	
• clear	5(13.16%)	10(9.17%)		7(11.47%)	8(9.30%)	
• mucous	9(23.68%)	22(20.18%)		15(24.60%)	16(18.60%)	
• adenocarcinoma	1(2.63%)	8(7.34%)		3(4.92%)	6(6.98%)	
• undiff	0(0.00%)	3(2.75%)		1(1.64%)	2(2.33%)	
• unclassified	1(2.63%)	1(0.92%)		1(1.64%)	1(1.16%)	
Grade						
• - grade 1	14(36.84%)	38(34.86%)	0.898	12(19.67%)	40(46.51%)	0.000
• - grade 2	16(42.11%)	44(40.37%)		25(40.98%)	35(40.70%)	
• - grade 3	8(21.05%)	27(24.77%)		24(39.34%)	11(12.79%)	
CA 125						
• <50	10(26.32%)	45(41.28%)	0.190	20(32.79%)	35(40.70%)	0.605
• 50 - 300	15(39.47%)	25(22.94%)		19(31.15%)	21(24.42%)	
• >300	6(15.79%)	21(19.27%)		10(16.39%)	17(19.77%)	
• not done	7(18.42%)	18(16.51%)		12(19.67%)	13(15.12%)	
Laterality						
• unilateral	32(84.21%)	88(80.73%)	0.634	50(81.97%)	70(81.40%)	0.930
• bilateral	6(15.79%)	21(19.27%)		11(18.03%)	16(18.60%)	
Ascites						
• + ve	15(39.47%)	50(45.87%)	0.494	28(45.90%)	37(43.02%)	0.729
• - ve	23(60.53%)	59(54.13%)		33(54.10%)	49(56.98%)	
Cytology						
• + cytology	8(21.05%)	23(21.10%)	0.771	10(16.39%)	21(24.42%)	0.292
• - cytology	23(60.53%)	60(55.05%)		34(55.74%)	49(56.98%)	
• unknown	7(18.42%)	26(23.85%)		17(27.87%)	16(18.60%)	
No. of dissected L.Ns Mean ± SD	13.6579± 16.3480	14.5688± 17.0589	0.366	10.0328± 15.0210	17.3837± 17.44718	0.261
Patients with + ve nodes						
-ve L.N	27(71.05%)	72(66.06%)	0.950	43(70.50%)	56(65.12%)	0.717
+ve PLN	8(21.05%)	26(23.85%)		14(22.95%)	20(23.25%)	
+ve PAN	1(2.63%)	4(3.67%)		1(1.63%)	4(4.65%)	
+ ve PLN&PAN	2(5.26%)	7(6.42%)		3(4.92%)	6(6.98%)	
Number of + ve nodes Mean ± SD	9.6842± 12.5161	10.8073± 13.8660	0.710	7.2131± 11.7176	12.8605± 14.2334	0.747

When evaluating correlation between clinico-pathological factors with overall survival and DFS(table 6), in using Chi-Squar test we found that only age, comorbidities and performance independatly had significant relation with survival(p= 0.028, 0.000 and 0.000, respectively) but other factors as BMI, histolog, grade, adjuvant chemotherapy, CA 125, laterality, ascitis, cytology, number of dissected L.Ns, number of patients with + ve L.Ns and Number of + ve nodes had non-significant correlation with overall survival (P= 0.311, 0.311, 0.898, 0.845, 0.190, 0.634, 0.494, 0.771, 0.366, 0.950 and 0.710, respectively). Although, in multivariate analysis age had no significant correlation with overall survival (P= 0.825) but BMI had this significance (P= 0.020) and other factor s had the same relation in Chi-Square test (table 7).

While Chi-Square test for Disease Free Survival represent that only grade had significant relation (P= 0.000), other factors as age, BMI, comorbidities, performance, histolog, adjuvant chemotherapy, CA 125, laterality, ascitis, cytology, number of dissected L.Ns, number of patients with + ve L.Ns and Number of + ve nodes had non-significant correlation (P= 0.674, 0.601, 0.764, 0.263, 0.985, 0.324, 0.605, 0.930, 0.729, 0.292, 0.261, 0.717 and 0.747, respectively). But in multivariate analysis, in addition to grade; histolog and cytology had significant correlation with DFS (P= 0.033 and 0.018, respectively). Other factors had the same relations (table 7).

Table 7: Multivariate analysis of clinicopathological factors Correlation with overall survival and DFS

Clinicopathological factors	Overall survival & DFS	P-value
Age	survival	0.825
	Disease free survival	0.405
BMI	survival	0.020
	Disease free survival	0.940
Associated condition	survival	0.000
	Disease free survival	0.488
CA125	survival	0.708
	Disease free survival	0.982
Chemotherapy	survival	0.933
	Disease free survival	0.539
Grade	survival	0.896
	Disease free survival	0.004
Histology	survival	0.999
	Disease free survival	0.033
Performance	survival	0.102
	Disease free survival	0.717
Cytology	survival	0.754
	Disease free survival	0.018
Ascitis	survival	0.797
	Disease free survival	0.951
No of dissected nodes	survival	0.919
	Disease free survival	0.721
Laterality	survival	0.899
	Disease free survival	0.977
No of positive L.Ns	survival	0.690
	Disease free survival	0.491

Discussion:

Ovarian cancer especially epithelial type is the most common gynecological tumor and one of the most lethal tumors in females if not diagnosed and treated early and effectively. The most important factor affecting survival in patients with epithelial ovarian cancer is the maximization of surgical resection and postoperative residue; from this point of view many studies discuss role of lymphatic dissection on overall survival and disease free survival.[7-15] Due to its prognostic importance; In 1988, FIGO incorporating pelvic and para-aortic lymph node lymphadenectomy or sampling in surgical staging scheme for ovarian cancer. Although it has diagnostic value and is necessary for accurate staging; Systematic lymphadenectomy may increase surgical morbidity. [16] A meta-analysis done by Hee Seung et al.[17] studying effect of systemic lymphadenectomy on overall survival in 9 studies of ovarian cancer, 2 randomized controlled studies [9,10] and 7 observational studies[7,8,11-15]. A total of 21,919 patients included in these 9 studies, 5 studies and 1 sub-analysis of them had demonstrated the role of SL in FIGO stage III-IV EOC.[7,10-14] whereas 3 studies had shown it in FIGO stage I-II EOC[7,8,15]. This meta-analysis showed that SL may has limited efficacy for OS in early-stage EOC, whereas SL may be efficient to increase OS in advanced-stage EOC (FIGO stage III-IV). Previous studies had shown that about 30% of patients who were presumed to have early-stage ovarian cancers are upstaged after lymphadenectomy.[18-20] Consequently, studies that found improvement on OS and DFS on systemic lymphadenectomy arm and encouraging it emphasis that an adequate staging may help the physician to provide the most appropriate adjuvant treatment. Furthermore, a thorough lymphadenectomy removing micro-metastatic disease within the node which may improve patient's survival.[21] These findings suggest that micro-metastatic tumor cells can potentially develop into macro-metastatic nodal disease that initially would have been considered negative on pathological examination. In addition, survival improvement found in patients who underwent lymphadenectomy may attributed to the removal of regions with poor blood supply and resistant clones of cells rather than a dramatic reduction in tumor volume. A study was done by Chan et al on 6,686females (median age 54 years) with stage I invasive ovarian cancer between 1988 and 2001. He found that on multivariable analysis, the extent of lymphadenectomy was a significantly associated with improved survival, independently of other factors such as age, histology, grade and stage of disease. Lymphadenectomy had improved 5-year disease-specific survival of all patients from 87.0% to 92.6% (P<.001). More specifically, lymphadenectomy improved the survival in those with non– clear cell epithelial ovarian cancer (85.9% to 93.3%, P<.001) but not in those with clear cell carcinoma, sarcomas, sex cord stromal tumors and germ cell tumors. Also number of retrieved lymph nodes (0 nodes, less than 10 nodes, and 10 or more nodes) improved survival rates from 87.0% to 91.9% to 93.8%, respectively (P<.001). [22] Another randomized study done by Maggioni and co-workers published in 2006; comparing systematic aortic and pelvic lymphadenectomy (SL) in comparison with sampling of bulky pelvic lymph node in ovarian cancer. 268 patients (130 lymph node sampling (control) and 138 to systematic lymphadenectomy).median age of patients was 52 (44–59) for control group and 51 (43–60) for SL group, nodal involvement was correlated with tumor histology (in SL arm, 33% of patients with serous or undifferentiated tumor had metastatic nodes *vs* 10% of patients with other cell types; *P*=0.005) while tumor grade (in SL arm, 11% of patients with grade I/II tumor had metastatic nodes *vs* 31% of patients with grade III tumor; *P*=0.004). Patients with positive nodes were distributed as follows, 21% had pelvic, 54% aortic and 25% pelvic plus aortic involvement. Systematic lymphadenectomy had a significant impact on surgical parameters such as, blood loss, patients undergoing blood transfusions and operative time. Median hospital stay was one day longer in SL group than non-lymphadenectomy group but it is statistical significant (*P*=0.003). Intraoperative and perioperative/late complications were not statistically different between the two groups (4 cases *vs* 8 and 16 cases *vs* 8 in lymphadenectomy arm and the control, respectively). Lymphocysts and lymphedema occurred in eight cases of the lymphadenectomy group *while* no cases in the control arm. Two patients of lymphadenectomy group suffering from Adhesive intestinal obstruction vs one patient in lymph nodes sampling group. There was no operative mortality. (61%) of patients received adjuvant chemotherapy (56% and 66 for SL and control, respectively with no significant difference; *P*=0.11). 30% of patients of the control arm had recurrences while 22% of patients in systematic lymphadenectomy group and the most common sites of recurrences was pelvic and multiple .5-year overall survival was 81.3 for the control group and 84.2% for the SL group (*p*=0.56) while Five-year progression-free survival was 71.3 and 78.3% respectively (*p*=0.56), these differences had no statistical significance.[9] 13 918 of female patients with stage III–IV epithelial ovarian cancer were evaluated for the effect of systemic lymphadenectomy on survival, the median age was 62.7 years. 4260 patients underwent lymphadenectomy, median number of removed nodes was 6 (range: 1–90), while median number of positive nodes was two (range: 1–54). According to histology, serous subtype represented (66.8%), endometrioid (9.2%) followed by mucinous(5.6%) then clear cell(2.8%). 4.2% of patients had grade 1and 17.6% grade 2 disease but the larger proportion of patients had grade 3 disease (60%). The median follow-up time was 22 months (range: 0–167 months). The 5-year disease-specific survival for was 37.1 and 24.4% for patients ⩽64 years and >64 years respectively (*P*<0.001). Incidence of survival in grade 1tumors was (56.9%), (33.4%) for grade 2 and (29.2%) for grade 3 tumors (P<0.001). The estimates of survival based on histology were endometrioid 43.6%, mucinous 33.3%, serous 30.6%, and clear cell 25.5% (*P*<0.001).

On multivariate analysis, after adjusting for age, grade and stage of disease; the extent of lymphadenectomy and number of positive nodes were significant independent prognostic factors. The extent of lymph node dissection is associated with increased disease-specific survival of patients with advanced epithelial ovarian cancer.[23] on a study of 127 patients with early clear cell carcinoma of the ovary, Their median age was 53 years. Four patients (3%) had enlarged lymph nodes radiological examination and 112 (88%) patients had pT1 disease. 36 (28%) patients did not undergo lymph node dissection; twelve patients (10%) underwent only pelvic lymph node dissection (PLND); and seventy nine patients (62%) underwent both PLND and PAND. Patients with enlarged lymph nodes underwent both pelvic and para-aortic lymph node dissection. 12% (11 patients) of the 91 patients with lymphadenectomy had lymph node metastasis. The pT1a and pT1c/pT2 groups had no significant difference in lymph node metastasis (2/23 (9%) vs 9/68 (13%), p=0.720). 2 patients with pT1a and pN1 had enlarged lymph nodes. The median number of dissected lymph node was 55 in Patients who underwent lymphadenectomy as all(91 patients) while median number of dissected lymph node from the 12 patients who underwent PLND only was 22. In patients with both PLND and PAND (n=79), median number of harvested lymph nodes was 41 pelvic lymph nodes and 18 para-aortic lymph nodes. Only one patient of the 127 patients had postoperative macroscopically residual disease. 93 (73%) patients received systemic chemotherapy (CT) as a primary treatment. Only 38.2% of patients with pT1a disease received adjuvant chemotherapy while 86.0% of patients with pT1c/pT2 disease were given adjuvant CT (p<0.001). Adjuvant chemotherapy was administered to all patients with pN1. Platinum-taxane was the most frequently used combination of CT (n=37) then irinotecan-mitomycin combination (n=26) followed by platinum-irinotecan combination (n=19). There was no significant difference in the 2 groups in age, histology, stage, peritoneal involvement, capsule rupture, radiologically enlarged lymph nodes, or chemotherapy. $PAND^{-}$ group had higher rate of positive peritoneal cytology 11.8% than the $PAND^{+}$ group but without statistical significance (p=0.140). There was significant difference in DFS between the PLND group and PLND+PAND group (p=0.011), but not between no lymphadenectomy group and PLND group (p=0.320). There was no significant difference between the PLND-only and no-lymphadenectomy groups in DSS (p=0.39) but the significant difference was between the PLND-only and PLND+PAND groups (p=0.035) . On multivariate analysis confirmed that older age, positive peritoneal, cytology and lymph node metastasis were significant independent factors related to poor outcomes, but systemic lymphadenectomy (PLND+PAND) as independent factor was significantly related to improved outcomes. Lymphatic recurrence was significantly higher in the PLND-only/no lymphadenectomy group compared with the PLND+PAND group (25% (12/48) vs. 6% (5/79), p=0.003). There was no significant difference in peritoneal or hematologic recurrence between the 2 groups (25% (12/48) vs. 15% (12/79), p=0.170) and (4% (2/48) vs. 6% (5/79), p=0.600), respectively.[24]

A meta-analysis done by Kim et al on nine studies (seven observational studies and tow randomized controlled trials) between 1995 and 2008, including 21,919 patients with epithelial ovarian cancer who underwent operative treatment some with systemic lymphadenectomy and others without. They concluded that systemic lymphadenectomy may improve Overall Survival in advanced stage EOC especially in cases underwent optimal debulking. But effect of SL on Overall Survival is unclear. So more randomized controlled trials are needed to this effect.[25]

Another meta-analysis done by Gu et al comparing between SL (1634 patients) and USL (1719) including 3 Randomized control trial (RCT) and 11 observational studies. They found that there was significant difference in 5-year overall survival rate (p=0.001) between SL and USL in all stages in favor with SL especially in observational group while in RCTs group, SL lacking this efficacy (P=0.90). So, They concluded that the effect of systemic lymphadenectomy on the survival of patients with EOC is still unclear and requires more relevant randomized controlled studies.[26]

Xu et al performed meta-analysis on 33,257 patients with advanced ovarian cancer comparing between SL and USL in PFS and OS. The study was including three RCTs and 12 observation studies. In RCTs, there was no significant difference between SL and USL in PFS and OS (p=0.16 and p=0.07 respectively). While in observational studies, SL showed increased PFS and OS (P=0.00001 and P=0.00001 respectively). They also recommended more randomized controlled studies.[27]

In our retrospective study which started in December 2014 and ended in January 2019, including 147 female patients with clinically FIGO stage I and II epithelial ovarian cancer. Overall mean age of patients in the study was 59.21 ± 10.121years with range 35 – 76 years and mean BMI was 29.6998 ± 5.37555 and range 22 – 43. Perioperative mortality was 3 (2%) patients one for each group without detectable difference. in our study overall survival and DFS was 74% and 68.7% respectively while mean time of survival and recurrence was 65.9456 ± 21.9450 with range of 36 – 120 months and 56.76 ± 23.927 with range of 10 – 120 months respectively. The 3 year and 5 year survival for group (A) was 74.32% and 50% and 72.9% and 47.92% for group (B) while that for group (C) was 76% and 56% without significant difference.

There was no significant difference between groups in comorbidities, performance, histological types, grade, CA125, laterality and presence or absence of ascites. Group C (PLN+PAN) differed significantly than other groups in number of patients with +cytology, mean of dissected L.Ns, mean number of + ve nodes, Patients with + ve nodes and number of patients taking adjuvant chemotherapy. Although, group C significantly high in Op. time, Bl. Loss, operative and post-operative Complications and Hospital stay; patients has

significant low rate of recurrence and increased time of disease free survival.

The 3 year and 5 year survival for group (A) was 74.32% and 50% and 72.9% and 47.92% for group (B) while that for group (C) was 76% and 56% without significant difference.

There was no significant difference in overall survival and time of survival between groups, p=0.959 and p=0.946 respectively.

In discussing correlation between clinico-pathological factors with overall survival and DFS, using Chi-Square test and multivariate analysis we found that age, BMI, comorbidities and performance independatly had significant relation with survival (p= 0.028, 0.020, 0.000 and 0.000, respectively). While the significant correlation was found between grade, histolog and cytology with DFS (P= 0.000, 0.033 and 0.018, respectively).

Conclusion:

In conclusion epithelia ovarian cancer may have better prognosis and survival if discovered and treated early. Systemic lymphadenectomy even if have significant effect on DFS but it has multiple operative and post-operative morbidities and no significant effect on overall survival. Other factors as age, BMI, comorbidities and performance have an effect on extent of surgery and survival. Tumor histology, grade and positive peritoneal cytology have significant effect on DFS. On our observation; when tumor recurs while patient still on chemotherapy, this is a sign of bad prognosis.

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