Assessment of prognostic significance of unique tumor regression scoring system in advanced epithelial ovarian cancer patients treated with neoadjuvant chemotherapy followed by interval debulking surgery -Single tertiary care center experience

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Abstract

Aim and Objective: To assess the prognostic significance of pathological factors and the use of unique tumour regression scoring system over survival in advanced epithelial ovarian cancer patients treated with neoadjuvant chemotherapy (NAC) and Interval debulking surgery.

Materials and Methods: We retrospectively investigated 135 patients from January 2011 to December 2017 received minimum of 3 cycles of NAC followed by interval debulking surgery (IDS) and their resected specimens were divided into 3 groups based on pathological tumour regression: Group 1: minimal response (residual disease with necrosis and fibrosis < 50%), Group 2: Partial response (residual disease with necrosis and fibrosis > 50%) and Group 3: complete response (No residual disease). The clinico-pathological parameters and their prognostic influence over survival outcomes were assessed using Statistical Package for the Social Sciences (SPSS 21.0) software and a p value of <0.05 was significant. Survival analysis was estimated by Kaplan Meier analysis.

Results: Histopathological tumour regression groups 1, 2 and 3 were significantly associated with histological grade, presence of residual disease in ovary with involvement of lymph node, omentum. DFS and overall survival were 42.0±8.0 and 47.1 ± 5.4 months respectively. The overall median survival in FIGO stage III patients was better than FIGO IV stage.

Conclusion: This proposed 3 simple criterions of histopathological tumour regression has prognostic significance in association with clinical stage and amount of residual disease in resected specimen. This simplified unique tumour regression system may serve in the future as highly valuable prognostic tool, which needs further validation.

Keywords: Advanced ovarian malignancy, Neoadjuvant chemotherapy, Interval debulking surgery, Tumour regression system.

Introduction

Malignant epithelial ovarian tumours are the fifth and seventh most common cause of cancer related mortality among western and Asian population respectively.[1] More than 70% of ovarian tumours patients are diagnosed at advanced stage (Stage III and IV) with poor long term (10 Years) survival rate of about 15-30% in contrast with >90% in early stage disease at presentation.[2-5]

Traditionally, optimal primary debulking surgery followed by adjuvant chemotherapy is considered to be the cornerstone therapy for ovarian malignancies.[6] Because of its advanced stage of presentation at diagnosis, it is often technically not feasible to achieve optimal cytoreduction. Hence, based on results of two randomized controlled phase III trials.[7,8] Interval debulking surgery (IDS) after three to four cycles of neoadjuvant chemotherapy (NACT) has been accepted as an alternative strategy with equivalent progression-free survival (PFS), overall survival (OS) and reduced postoperative morbidity than primary optimal debulking surgery. A number of common prognostic indicators have been identified including age, disease stage, tumour grade, histology, and residual disease status after debulking surgery.[9] One of the important questions in patients undergoing IDS is whether the result of the histological analysis of the operative specimen removed at IDS after NACT has a prognostic value. Although histopathologic assessment of response to neoadjuvant therapy is used in clinical practice for many solid tumours (eg, breast, rectum, oesophagus), so far there is no accepted system for epithelial ovarian malignant tumours. Multiple research studies have attempted to quantify residual tumour and/or chemotherapy-induced regressive changes and correlate them with patient outcome.[10-13] Although Histopathologic grade,[14] total or optimal debulking (<1 cm of residual disease)[15] were considered as best prognosticators, each study used different criteria (Fig. 5.) and none have been independently validated and widely adopted in routine clinical practice.

The aim of this study was to develop and validate a simple, prognostically significant and reproducible system for histopathological response to NACT in advanced epithelial ovarian malignancies on the basis of examination of IDS specimens, so that it can be applied universally in routine histopathology reporting. Furthermore, we investigated the survival outcomes in stage IIIc and stage IV patients in study population based on histopathological response as subtype analysis.

Materials and Methods

It is a retrospective study of 135 patients diagnosed with advanced EOC in a single institution with the clinical, radiological, treatment, postoperative histopathology reports and follow up details of the patients, collected from the Medical Records Department (MRD) from January 2011 to December 2017 and analyzed. A total of one hundred and thirty-five patients satisfying any of the following criteria's:

1. FIGO stage IIIc and IV, 2. Intrahepatic (multiple) metastases or extra abdominal metastases (excluding resectable inguinal or supraclavicular lymph nodes) 3. Poor performance status (ECOG score > 2) making optimal cytoreduction impossible 4. Treated with minimum three cycles of carboplatin (4-6 AUC /cycle) and paclitaxel (175 mg/cycle) intravenously for every 3 weeks, who were free of residual disease at the end of interval cytoreduction and followed by adjuvant chemotherapy 5. Patients with acute contraindications for surgery were included for the study. The surgeries performed included the conventional procedure of peritoneal washing, total abdominal hysterectomy, bilateral salpingo-oophorectomy, total omentectomy, bilateral pelvic and para-aortic lymph nodal dissection and peritoneal biopsies. The postoperative Histopathology slides were collected and graded the slides based on the presence of percentage of necrosis and fibrosis. All the patients (n=135) were categorized into three groups based on the histopathological regression after NACT. Group 1: No or minimal tumour response. Mainly viable tumour with no or minimal regression-associated fibroinflammatory changes (fibrosis <50%, necrosis-<50%) Group 2: Tumour is regularly distributed, ranging from multifocal or diffuse regression-associated fibroinflammatory changes with viable tumour in sheets, streaks, or nodules to extensive regression-associated fibroinflammatory changes (fibrosis >50% and necrosis >50%) with multifocal residual tumour. Group 3: Complete or response with no residual tumour, Mainly regression-associated fibroinflammatory changes. The clinico-pathological parameters of all groups 1,2 and 3 patients and their prognostic influence over disease free survival and overall survival were assessed using Statistical Package for the Social Sciences (SPSS 21.0) software for statistics and a p value of<0.05 was considered significant using Breslow test. An overall survival was estimated by Kaplan Meier analysis.

Results

In this total study of 135 patients diagnosed with advanced EOC, the mean age of the total study population was found to be 49.7± 10.8 years and ranged from 18 to 80 yrs. The mean follow-up period was 30.8 ± 25.1 months. The patient's clinic-pathologic characteristics are represented in Table 1.

Table 1: Patients' clinic-pathological characteristics and treatment outcome details

		Histopathology response groups				
S.No	**Parameter**	**Study Cohorts**	**Group 1**	**Group 2 n (%)**	**Group 3 n (%)**	**"p " value**
1	**Number of patients**	135	60	55	20	0.196
2	**Age (Mean +/- SD ran(range)**		49.7 +/-10.8 years (18-80 years)			
3	**WHO-PS (WHO)**					0.515
	PS ≤2	39 (28.9%)	19 (31.7%)	13 (23.6%)	7(35.0%)	
	PS >2	96 (71.1%)	41(68.3%)	42 (76.4%)	13(65.0%)	
4	**FIGO stage**					0.194
	Stage IIIc	96 (71.1%)	38(63.3%)	42(76.4%)	16(80.0%)	
	Stage IV	39 (28.9%)	22(36.7%)	13(23.6%)	4(20%)	
5	**Histological type**					0.487
	Clear cell	6(4.4%)	4(6.8%)	2(3.6%)	0(0%)	
	Endometroid type	9 (6.7%)	5(8.3%)	4(7.3%)	0(0%)	
	Mucinous cystadeno carcinoma	16 (11.9%)	9(15.0%)	7(12.7%)	0(0%)	
	Serous papillary cystadeno Carcinoma	104(77.0%)	42(70.0%)	42(76.4%)	20(100%)	
6	**Histological grade**					<0.001*
	Low grade	33 (24.4%)	9(15%)	24(43.6%)	0(0%)	
	Moderate grade	47 (34.8%)	30(50%)	17(30.9%)	0(0%)	
	High grade	55 (40.7%)	21 (35%)	14(25%)	20(100%)	
7	**Residual disease**					<0.001*
	Present	115(85.2%)	60(100%)	55(100%)	0(0%)	
	Absent	20 (14.8%)	0(0%)	0(0%)	20(100%)	
8	**Lymph node involvement**					<0.001*
	Reactive	91 (67.9%)	25(41.7%)	47(85%)	19(95.0)	

	Metastatic	44 (32.6%)	35(58.3)	8(14.5%)	1(5.0%)	
9	**Peritoneal disease**					<0.001*
	Present	67 (49.6%)	44(73.3%)	19(34.5%)	4(20%)	
	Absent	68 (50.4%)	16(26.7%)	36(65.5%)	16(80%)	
10	**Menstrual status**					P<0.05*
	Pre-menopausal		17(28.3%)	27(49.1%)	10 (50%)	
	Post-menopausal		43(71.7%)	28(50.9%)	10(50%)	
11	Recurrence (months)		16.7±15.7	23.4 ±19.5	19.2±11.2	0.413
12	Event free survival (months)		18.7±16.9	27.8±24.9	30.4±20.1	0.027*
13	Survival (months)		39.3±4.0	32.3±4.1	46.2±6.5	0.006*

Table 2: Univariate analysis of clinico-pathological parameters as predictor of Disease-free survival in Advanced Epithelial Ovarian Cancer patients treated with Neo adjuvant chemotherapy and Interval Debulking surgery

S. No.	Prognostic variable	Survival status alive		p-value (chi-square)
		With disease	*Without disease*	
1	**WHO Performance Status**			
	PS <=2	16(41.0%)	6(15.4%)	0.718 (0.663)
	PS >2	34(35.4%)	20(20.8%)	
2.	**FIGO Stage**			
	Stage IIIc	43 (44.8%)	16(16.7%)	0.014 (8.581)
	Stage IV	7(17.9%)	10(25.6%)	
3	**Histological subtype**			
	Clear cell	5(84.5%)	0(0%)	
	Endometroid	4(44.4%)	1(11.1%)	0.281 (12.068)
	Mucinous cystadenocarcinoma	2(12.5%)	6(37.5%)	
	Serous cystadenocarcinoma	39(37.5%)	19(18.3%)	
4.	**Histological Grade**			
	Low Grade	15(45.5%)	9(27.3%)	
	Moderate Grade	16(34.0%)	6(12.8%)	0.197 (6.027)
	High Grade	19(34.5%)	11(20.0%)	
5	**Residual disease**		12(20%)	
	Group 1	7(11.7%)	30(54.5%)	
	Group 2	17(30.9%)	2(10%)	0.0033 (6.786)
	Group 3	8 (40%)		
6	**Lymph node involvement**			
	Reactive	36(39.6%)	18(19.8%)	0.574 (1.111)
	Metastatic	14(31.8%)	8(18.2%)	
7	**Involvement of omentum**			
	Present	24(35.8%)	15(22.4%)	0.657
	Absent	26(38.2%)	11(16.2%)	(0.841)

The total number of patients (p=<0.196), FIGO stages (p=<0.194) and Histological types (p=<0.487) distributed among three groups were statistically insignificant. However, the histological grades (p=<0.001), residual disease in resected specimen status (p=<0.001), lymph nodes (p=<0.001), peritoneal involvement (p=<0.001) and Menstrual status were found to be significantly associated with the response to NAC groups.

The oncological outcomes such as disease-free survival and overall survival status were analyzed against the clinico-pathological characteristic features as described in Table 2 and 3 respectively.

Performance status of the patients, histological types, histological grades, residual disease in resected specimen status, involvement of lymph node and peritoneum were found to be statistically not associated with disease free survival and overall survival of the patients. These data proved that the above parameters do not influence the disease recurrence and survival status in the study population. FIGO stage of the disease (p=0.014) and response to NACT (p=0.033) were independently associated with disease free survival of the patients. FIGO stage has borderline significant association with overall survival (p=0.058) but response to NACT has significant impact on overall survival (p=<0.001). Among Stage IIIc (n=96) population studied, out of 59 alive patients, 44.8% were living with recurrent disease and 16% were disease free at the time of this analysis.

Table 3: Univariate analysis of clinico-pathological parameters as predictor of overall survival in advanced ovarian cancer patients treated with neoadjuvant chemotherapy and interval debulking surgery

S.No.	Prognostic variable	Survival status		p-value (chi-square)
		Alive	Dead	
1	**WHO Performance Status**		17(43.6%)	
	PS <=2	22 (56.4%)	42(43.8%)	0.986
	PS >2	54 (56.3%)		(0.0001)
2.	**FIGO Stage**		37(38.5%)	
	Stage IIIc	59 (61.5%)	22(56.4%)	0.058
	Stage IV	17 (43.6%)		(3.599)
3	**Histological subtype**		1(16.5%)	
	Clear cell	5 (84.5%)	4(44.4%)	
	Endometroid	5(55.6%)	8(50.0%)	0.793
	Mucinous cystadenocarcinoma	8(50.0%)	46(44.2%)	(2.393)
	Serous cystadenocarcinoma	58(55.8%)		
4.	**Histological Grade**			
	Low Grade	24 (72.7%)	9(27.3%)	0.067
	Moderate Grade	22(46.8%)	25(53.2%)	(5.409)
	High Grade	30(54.5%)	25(45.5%)	
5	**Residual disease**			
	Group 1	19(32.2%)	41(67.8%)	
	Group 2	47(85.7%)	8(53.2%)	0.0001
	Group 3	10 (50.0%)	10(50.0%)	(34.121)
6	**Lymph node involvement**			
	Reactive	54(59.3%)	37(40.7%)	0.305
	Metastatic	22(50.0%)	22(50.0%)	(1.052)
7	**Involvement of omentum**			
	Present	39(58.2%)	28(41.8%)	0.657
	Absent	37 (54.4%)	31(45.6%)	(0.198)

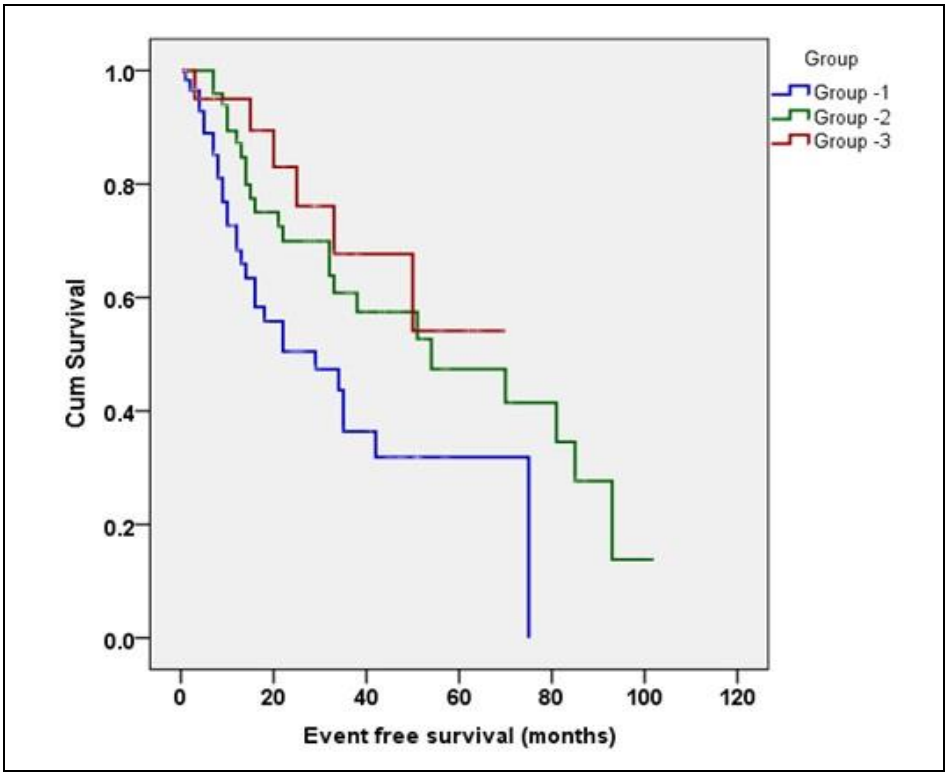

Fig. 1: Event free survival estimate of histopathologic tumour regression groups to Neoadjuvant chemotherapy in advanced epithelial ovarian malignancy

Among stage IV patients (n=39), out of 17 live patients, 17.9% were living with recurrent disease and 25.6% were living without recurrence. It shows maximum number of patients with FIGO stage IV (56.4%) were expired and FIGO IIIc survived (61.5%), even though marginally statistically associated (p=0.058). This proved the fact that the survival status of patients with FIGO stage IV was poor than stage IIIc. In similar, recurrence rate was also found to be increased (51.3%) in patients with FIGO stage IV than FIGO IIIc patients (39.6%) rate but statistical significance was not observed (p=0.213). maximum percentage of dead patients had moderate (53.2%) to higher (45.5%) grade histology outcome but was not statistically different from survival (p=0.067). Tumor grade does not have any prognostic significance.

The mean follow-up interval of 30.8 ±25.1 (ranged from 2 to 106 months). Kaplan Meier survival analysis results showed that the median DFS was maximum in group 2 (54.0 months, 95% CI: 17.4 – 90.6) than group 3 (51.0 months) (95% CI: 39.7 – 63.2) and group 1 (29.0 months, 95% CI: 8.9 – 49.1) patients as shown in Fig. 1.

The overall DFS was 42.0±8.0 months and was found to be statistically different among the groups (P<0.05). Disease recurrence free survival was found to be excellent in Group 2 and group 3 than group 1. Table 4. The estimated median overall survival was found to be 47.1 ± 5.4 months (95% CI: 36.4-57.5) in the studied population. Among the groups, the overall median survival in group 3 was 62 ± 14 months (95% CI: 34.3-89.6) better than group1 [37 ± 7.7 months (95% CI: 21.8-52.1)] and group 2 [51± 4.9months (95% CI: 41.2-60.8)] and it was found to be borderline statistically significant (p=0.054) as shown in Fig. 2. Result showed that group 3 and group 2 had better overall survival than group 1. Hence, group 3 was found to have excellent survival rate.

Table 4: Impact of prognostic factors on event free and overall survival in advanced epithelial ovarian cancer patients treated with neoadjuvant chemotherapy followed by Interval debulking surgery

	Event free survival in months (C.I 95%)	P value (chi square)	Overall survival in months (C.I 95%)	P value (chi square)
Histological response				
Group 1	29.000 (8.9 – 49.1)		37.000 (21.8-52.1)	
Group 2	54.000 (17.4 -90.6)		51.000 (41.2-60.8)	
Group 3	51.000 (39.7 – 63.2)	0.008	62.000 (34.3 – 89.6)	0.054
overall	42.000 (26.2 -57.7)	(9.703)	47.000 (36.4 – 57.6)	(5.831)
FIGO stage				
Stage IIIc – group 1	16.000 (9.7 – 22.2)	0.001	51.000 (47.7 – 54.2)	0.008
group 2	81.000 (19.2 – 142.8)	(14.563)	28.000 (12.4 – 43.5)	(9.671)
group 3	57.000(44.9 – 70.1)		62.000 (21.7 – 102.2)	
overall	42.000 (2.6-81.4)		37.000 (27.8 – 46.2)	
Stage IV - group 1	52.000 (36.9-67.6)	.948	57.000 (38.8 – 75.1)	0.081
group 2	38.000 (17.1 – 58.9)	(.106)	69.000 (53.8 – 84.1)	(5.036)
group 3	33.000 (13.4 – 52.6)		82.000 (82.0 – 82.2)	
overall	38.000(20.2 – 55.8)		60.000 (48.2 – 71.7)	

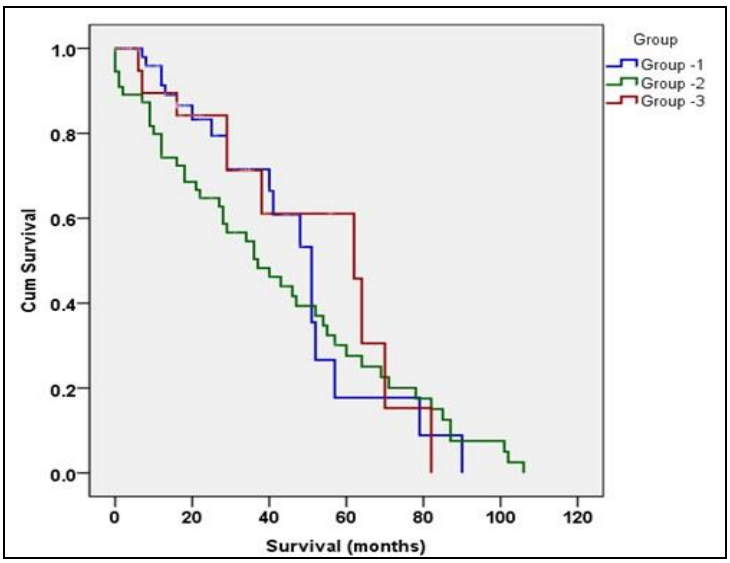

Fig. 2: Overall survival estimate of histopathologic Tumour Regression groups to Neoadjuvant chemotherapy in advanced epithelial ovarian malignancy

The median DFS in FIGO IIIc and IV was found to be 42.0 ± 20.1 months (95% CI: 2.6 - 81.4) and 38.0 ± 9.1 months (95% CI: 20.2-55.8) respectively. Among patients with FIGO stage IIIc, group 2 (81 months, 95% CI: 19.2 – 142.8) and group 3 (57 months, 95% CI: 44.9-70.1) had better disease-free survival than group 1 (16 months, 95% CI: 9.8-22.2) patients. Among patients with FIGO stage IV disease, event free survival was found to be better in group 1[52±7.9 months (95% CI: 36.9-67.9)] than group 2 [38±10.7 months, (95% CI: 17.1-58.9)] and group 3 (33 ±10months, 95%CI: 13.4-52.6) as shown in Fig. 3 and Fig. 4 ($p<0.05$). Patients with FIGO IIIc have better survival than patients at FIGO stage IV. Group 2 population had a longer time for disease recurrence followed by group 3 than group 1 (statistically non-significant). The event free survival was good in group 3 population followed by group 2 than group 1. Among the groups, the overall survival was good in group 2 followed by group 3 than group 1.

Discussion

The median age at diagnosis is 63 years[16] but in our study it is about 49.7+/-10.8 years. Currently, based on histopathology, immunohistochemistry, and molecular genetic analysis, EOC are classified as: Serous

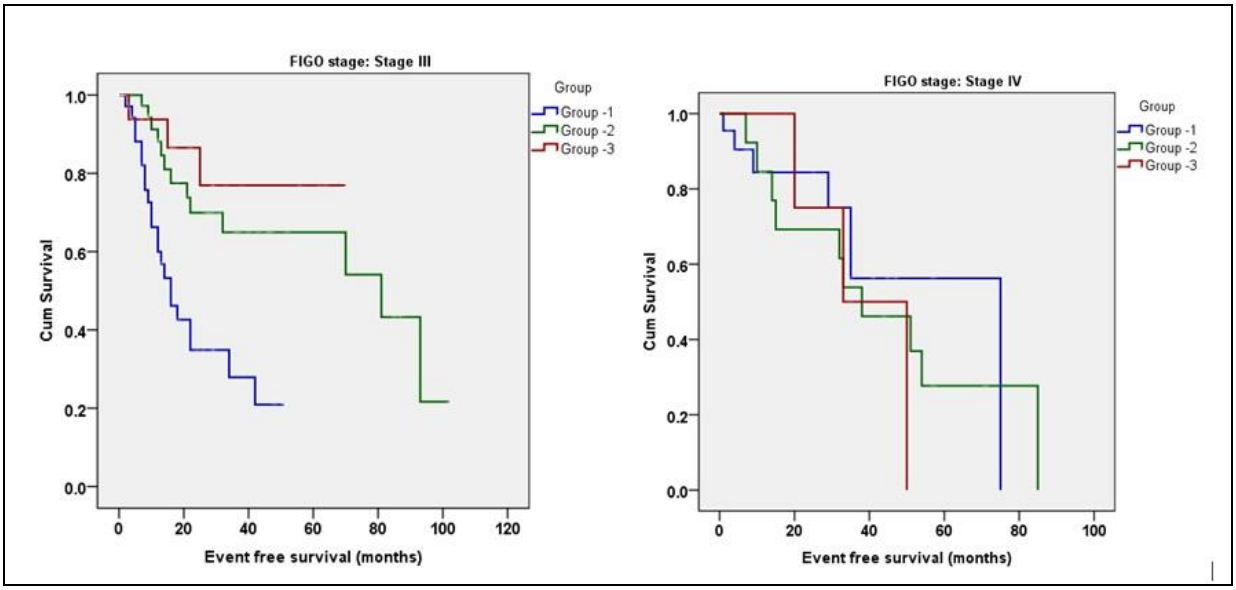

Fig. 3: Comparison of Event free survival curves among stage IIIc and stage IV ovarian cancer patients based on histopathologic regression to neoadjuvant chemotherapy

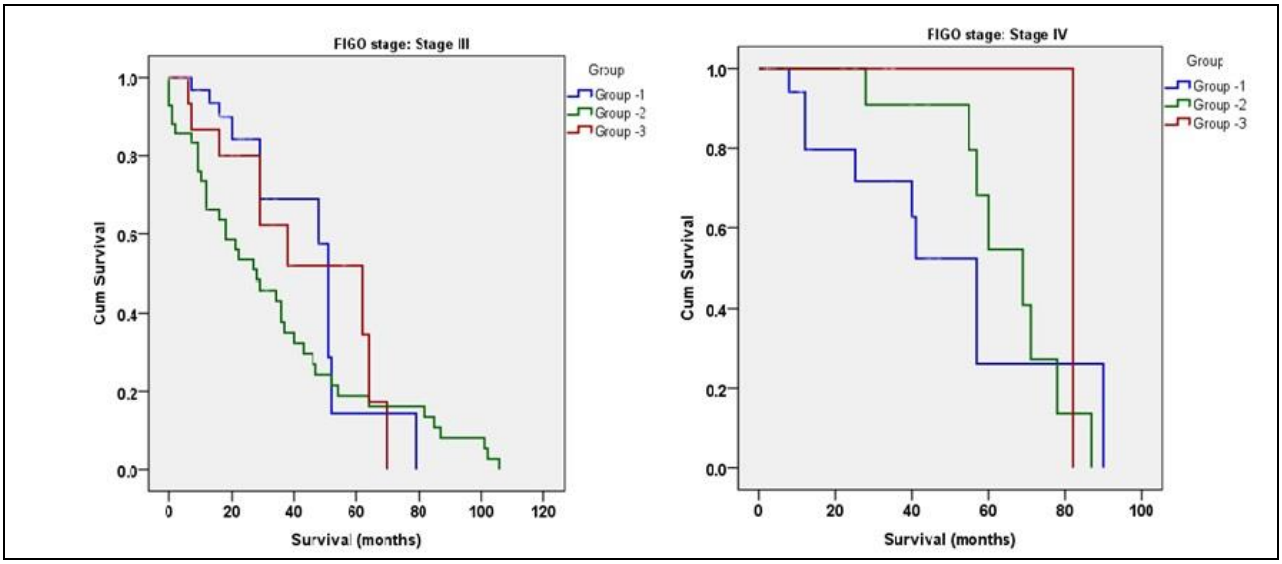

Fig. 4: Comparison of overall survival curves among stage IIIc and stage IV ovarian cancer patients based on histopathologic tumour regression to neoadjuvant chemotherapy

Papillary epithelial carcinomas (SCs; 75%), endometrioid carcinomas (EC; 10%), clear-cell carcinomas (CCC; 10%) and mucinous carcinomas (MC; 3%).[17] But in our study, it has been distributed as Serous papillary epithelial carcinomas (SCs; 77%), endometrioid carcinomas (EC; 6.7%), clear-cell carcinomas (CCC; 4.4%), mucinous carcinomas and (MC; 11.9%). Although no universal grading schema exists for ovarian serous carcinoma, a 2-tiered system (low-grade vs high-grade) has received increasing acceptance.[18,19]

A study on 101 EOC patients had showed that Pathological tumor response was only the predictor of time to disease linked death[11] and in specific, fibrosis and necrosis was related to patient's outcome with EOC.[20] A randomized trial of European Organization for Research and Treatment of Cancer (EORTC 5597) showed that OS between NACT and PDS was same. Another trial by CHORUS (Chemotherapy or upfront surgery) also confirmed the finding of EORTC 5597 and concluded that NACT was related to higher optimal debulking with less mortality and similar survival rate.[21] There is no recommended tumor regression grading system currently available for ovarian cancer treated with NACT. Hence, there is a need for a system to be formulated in order to evaluate the histopathological tumor response to NACT and its prognostic significance. The important research literatures are compared with our study design are illustrated in the Fig. 5.

Sassen S et al[10] concluded that the patients with absence of residual tumor, scattered solitary tumor cells, or residual tumor foci of 5 mm or less after neoadjuvant chemotherapy had possessed longer median overall survival of 45.6 versus 27.3 months in patients with larger tumors in concordance with our report in which group 3 population had higher survival of 62 ± 14 months than group 1 (51 ± 4.9 months) and group 2 (37± 7.7 months).

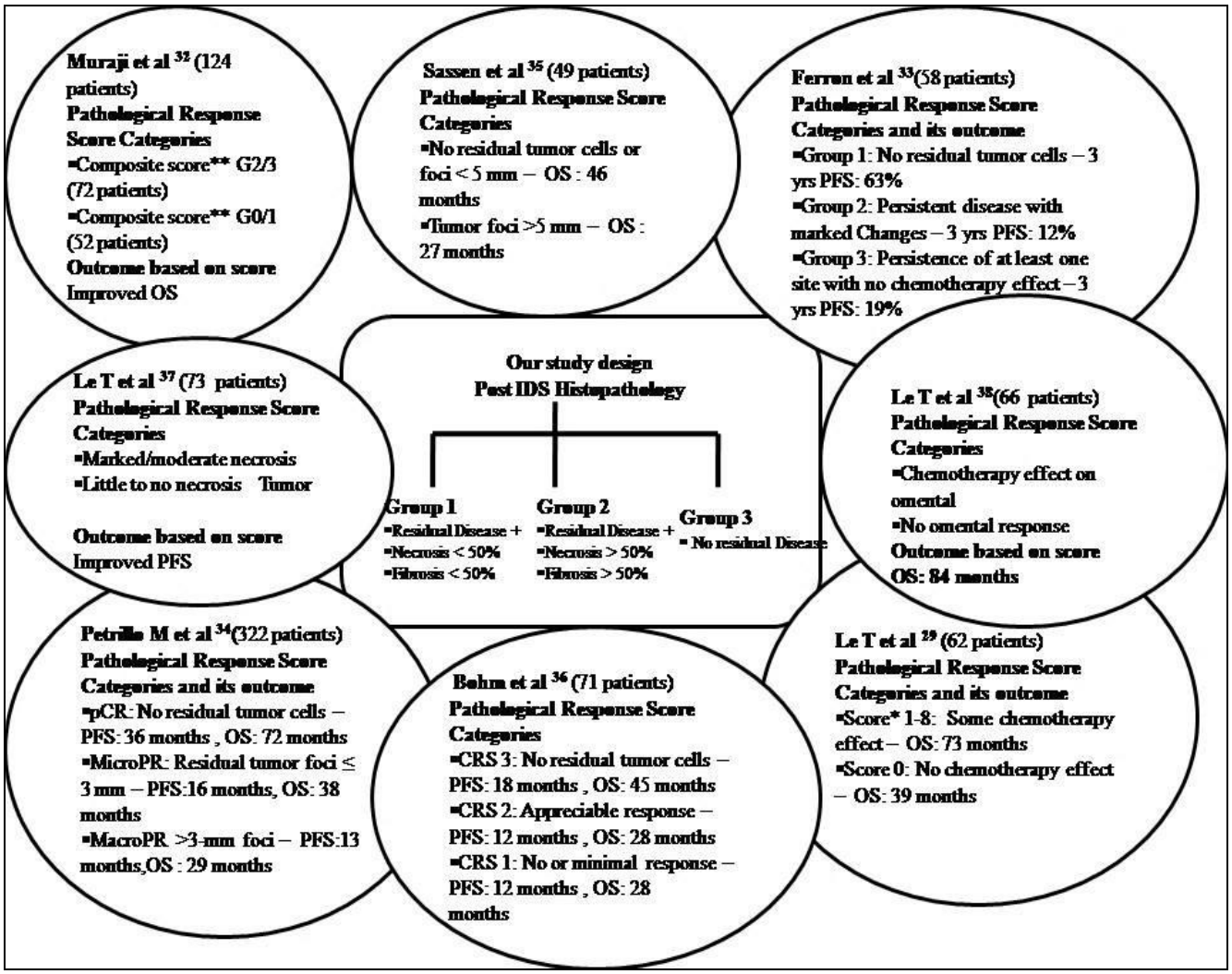

Fig. 5: Schematic representation of cluster of tumor regression studies and their outcomes

Le T Williams et al[11] conducted a study in 62 patients using tumor necrosis, fibrosis, tumor induced inflammation and composed a composite scoring system and concluded that younger age, optimal tumor residual status and higher response score were significant predictors for prolonged DFS as same as our report. In contrast, our study had showed the stage of disease might influence the OS as well as the DFS. The overall median follow-up duration was 29.2 months with an OS of 73.23 months in chemotherapy effectors population and 38.9 months in non-chemotherapy responders. Follow-up duration was shorter on comparison to our study and the overall survival was found to be similar with our study group populations.

Muraji M et al[12] studied the pathological response based on composite scoring system and grouped into 4 groups based on disappearance of tumour cells, necrosis, tumour induced inflammation and concluded that the residual disease of ≥1 cm at the end of surgery (sub optimal cytoreduction), advanced stage, and the presence of more viable disease in resected specimens are prognostic factors for survival. He had also observed improved OS. Ours study finding are in agreement with the disease advanced stage as the prognostic factor for survival.

A recent study by Petrillo M et al[13] in 2014 showed that the median overall survival was 72 months in cPR, 38 in micro PR, and 29 in macro PR (P=018) as analogous to our findings in which group 3 showed 62 ± 14 months higher than group 1 (51 ± 4.9 months) and group 2 (37± 7.7 months). They concluded that the proposed pathological response classification might be easily assessable and highly valuable prognostic tool in this clinical setting for future generations.

Ferron et al[22] followed up the patients for 41 months as similar to our study. Histological subtype, FIGO stages and involvement of peritoneal disease were significantly different among the study groups as comparable to our study except the histological sub type. Based on the histological response, the OS (88%) and DFS (63%) was found be excellent in group 1 than other groups as like our study in which overall median survival (62 months) and DFS (51.0months) was found to excellent in group 3 than other groups.

Bohm et al[23] designed a six-tier histopathological scoring system for estimating response to NACT in IDS of 62 patients at stage IIIc to IV cohorts and validated in three tier scoring system by applying in 71 patients. The study concluded that three-tier chemotherapy response score (CRS) is reproducible and demonstrated prognostic significance for high-grade serous carcinoma, which is relatively more complicated scoring system than ours.

In short, among our study groups, we observed that the histological grades, residual disease in resected specimen status, lymph nodes, and peritoneal involvement were found to be significantly distributed among the study groups. Histopathologic response to chemotherapy in terms of presence of no residual disease has significant positive predictive value in DFS and overall survival. Statistical significance was found to be better in FIGO stage IIIc patients than in stage IV patients.

Conclusion

Pathological assessment of operative specimens in patients who undergo optimal interval debulking surgery is useful in predicting patients' survival. Hence, the proposed 3 simple criterion of histopathological tumor tissue response to NACT based on necrosis and fibrosis has prognostic significance and should be further studied on larger population for validation. Future studies should be directed to assess whether the proposed 3 criteria would help in change of chemotherapy regime or second line of treatment based on initial chemotherapy tissue response.

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References

1. Felay J, Shin H, Bray F, Forman D, Mathers C, Parkin D. GLOBOCAN 2008: cancer incidence and mortality worldwide: IARC Cancer Base No. 10. Lyon: IARC Press; 2010.
2. K. M. Jochumsen, Q. Tan, E. V. Høgdall. Gene expression profiles as prognositic markers in women with ovarian cancer. *Int J Gynecol Cancer* 2009;19(7):1205-13.
3. J. R. McLaughlin, B. Rosen, J. Moody. Long-term ovarian cancer survival associated with mutation in BRCA1 or BRCA2. *J Natl Cancer Inst* 2013;105:141-8.
4. J. Engel, R. Eckel, G. Schubert-Fritschle, Moderate progress for ovarian cancer in the last 20 years: prolongation of survival, but no improvement in the cure rate. *Eur J Cancer* 2002;38(18):2435–45.
5. Jemal, R. Siegel, E. Ward, T. Murray, J. Xu, and M. J. Thun. Cancer statistics, 2007," CA: A *Cancer J Clinicians* 2007;57(1):43–66.
6. Cannistra SA. Cancer of the ovary. *N Engl J Med* 2004;351:2519–29.
7. Vergote I, Tropé CG, Amant F. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med* 2010;363:943-53.
8. Kehoe S, Hook J, Nankivell M. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): An open-label, randomised, controlled, non-inferiority trial. Lancet [epub ahead of print on May 19, 2015]
9. Hoskins WJ, Perez CA, Young RC. Principles and practice of gynecologic oncology. Philadelphia, PA: Lippincott Williams & Wilkins; 2000.
10. Sassen S, Schmalfeldt B, Avril N. Histopathologic assessment of tumor regression after neoadjuvant chemotherapy in advanced-stage ovarian cancer. *Hum Pathol* 2007;38:926-34.
11. Le T, Williams K, Senterman M. Omental chemotherapy effects as a prognostic factor in ovarian cancer patients treated with neoadjuvant chemotherapy and delayed primary surgical debulking. *Ann Surg Oncol* 2007;14:2649-53.
12. Muraji M, Sudo T, Iwasaki S. Histopathology predicts clinical outcome in advanced epithelial ovarian cancer patients treated with neoadjuvant chemotherapy and debulking surgery. *Gynecol Oncol* 2013;131:531-34.

13. Petrillo M, Zannoni GF, Tortorella L. Prognostic role and predictors of complete pathologic response to neoadjuvant chemotherapy in primary unresectable ovarian cancer. *Am J Obstet Gynecol* 2014;211:632.e1-8.
14. Gershenson DM, Sun CC, Bodurka D Recurrent low-grade serous ovarian carcinoma is relatively chemoresistant. *Gynecol Oncol* 2009;114:48-52.
15. Bian C, Yao K, Li L, Yi T, Zhao X. Primary debulking surgery vs. neoadjuvant chemotherapy followed by interval debulking surgery for patients with advanced ovarian cancer. *Arch Gynecol Obstet* 2016;293:163.
16. Altekruse SF, Kosary CL, Krapcho M. eds. SEER Cancer Statistics Review, 1975– 2007. Bethesda, MD: National Cancer Institute; Year. Available at: http://seer. cancer.gov/csr/1975_2007/. Accessed April 5, 2011.
17. Samrao D, Wang D, Ough F, Lin YG, Liu S, Menesses T, et al. Histologic parameters predictive of disease outcome in women with advanced stage ovarian carcinoma treated with neoadjuvant chemotherapy. *Transl Oncol* 2012;5:469–74.
18. Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener HC, Lopes T, et al. Chemotherapy or upfront surgery for newly diagnosed advanced ovarian cancer: Results from the MRC CHORUS trial. *J Clin Oncol* 2013;3(15):5500.
19. Malpica A, Deavers MT, Lu K. Grading ovarian serous carcinoma using a two tier system. *Am J Surg Pathol* 2004;28:496-504.
20. Prat J. Ovarian carcinomas: five distinct diseases with different origins, genetic alterations, and clinicopathological features. *Virchows Arch* 2012;460:237-49.
21. Silverberg SG. Histopathologic grading of ovarian carcinoma: a review and proposal. *Int J Gynecol Pathol* 2000;19:7-15.
22. Ferron JG, Uzan C, Rey A, Gouy S, Pautier P, Lhomme´C, Duvillard P, Morice. Histological response is not a prognostic factor after neoadjuvant chemotherapy in advanced-stage ovarian cancer with no residual disease. *Eur J Obstet Gynecol Reprod Biol* 2009;147:101–105.
23. Steffen Böhm, Asma Faruqi Elly Brockbank, Arjun Jeyarajah. Chemotherapy Response Score: Development and Validation of a System to Quantify Histopathologic Response to Neoadjuvant Chemotherapy in Tubo-Ovarian High-Grade Serous Carcinoma. *J Clin Oncol* 33:2457-63.

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