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Original Article

Management of Ovarian Cancer: Experience of a single Institution

Elkhouly. E.[1], Abdelghany. A.[1], Rageh. T.[2] and Shehata. M.[1]

[1]Department of Clinical Oncology, [2]Departement of General Surgery, Faculty of Medicine, Menoufia University, Egypt.

Objectives: Retrospective review of total management and survival analysis of epithelial ovarian cancer patients in a single institution.
Background: Epithelial ovarian cancer comprises the majority of ovarian neoplasms (about 80%). Predisposing factors may be Genetic, personal history of breast or endometrial, nulliparity, endometriosis and postmenopausal estrogen. Symptoms are often vague and till now there are no effective screening programs. Typically, treatment depends on a combination of surgery and chemotherapy in most of the patients.
Methods: A retrospective review of medical files of all patients diagnosed and treated as epithelial ovarian cancer at clinical oncology department, Menoufia University from January 2006 till December 2011. The data collected included clinico-pathological characteristics, treatment modalities, response evaluation, progression free survival (PFS), and overall survival (OS).
Results: This study included 83 patients; the median age for patients was 55 years (18-72 years). 84.3% of the patients presented in advanced stages (Stages III and IV). Serous cystadenocarcinoma was the predominant pathologic subtypes in 68.7% of patients. Surgery was the initial treatment in 86.7% of the cases. All surgeries were done by Gyne-surgeons, Onco-surgeons, and General surgeons. Paclitaxel-carboplatin was the most commonly used regimen as first line chemo-therapy. Response rate to first line chemotherapy reached 80.2% (35% complete response). The median PFS and OS after first line chemotherapy were 17 and 45 months respectively. None of the patients was involved in clinical trials.
Conclusion: In our study, the age incidence of ovarian cancer was 55 years. 84.3% of the patients' typical presentation was advanced stage disease. The PFS was nearly the same as reported in the western literature. There was a significant correlation between response and stage and the same for OS and PFS with the type of debulking.

Key words: Ovarian cancer, Epithelial subtype, Survival outcome
Corresponding Author: Enas Abou Baker Elkhouly **E-mail:** enasaboubaker6@hotmail.com

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INTRODUCTION

Epithelial ovarian cancer comprises the majority of ovarian neoplasms (about 80%)[1]. Ovarian cancer is the seventh most common cancer in women under the age of 65 years. A woman's risk of developing ovarian cancer by age 65 years ranges from 0.36% in developing countries to 0.64% in developed countries[2]. In Europe, just over a third of women with ovarian cancer live five years after diagnosis, largely because most women with ovarian cancer are diagnosed when the cancer is already at an advanced stage[3].

Screening in post-menopausal women, show promise in identifying early-stage disease, although survival data are still pending[4]. Typically, treatment of epithelial ovarian cancer depends on a combination of surgery and chemotherapy in most of the patients, Improvement in surgical techniques and chemotherapy agents has resulted in a modest increase in the 5-years survival over the last three decades from 37% to 45%, although, even now, two thirds of women die from their disease[5].

In early-stage disease (Federation of International Gynecologists and Obstetricians (FIGO) stage I/II) radical surgery will cure most women, although a minority of women will benefit from adjuvant chemotherapy, especially those who are not adequately staged at primary surgery[6]. Unfortunately, around 75% of women present when the disease has spread outside the pelvis (FIGO stage III/IV), when surgery alone cannot be curative. The standard treatment at these advanced stages is staging laparotomy with primary debulking surgery (PDS) followed by platinum-based chemotherapy. The extent of tumor cytoreduction is considered the most important independent prognostic factor[7]. Surgery is recommended

to be performed by a specialist gynecologic oncologist surgeon in cases highly suspicious for malignancy[8].

This is a retrospective study to analyze clinic-pathological features, different treatment modalities (chemotherapy protocols, type of surgery), and treatment outcome of epithelial ovarian cancer patients.

MATERIALS AND METHODS

This is a retrospective study included 83 patients diagnosed as epithelial ovarian cancer presented to Menoufia University, clinical oncology department from January 2006 till December 2011 and followed up till June 2013. Data was collected from the available files of patients regarding: patients' characteristics (age and median age group), disease characteristics including pathology, grade, staging was based on TNM staging according to the American Joint Committee on Cancer (AJCC 2010). Treatment modalities offered to the patients including surgery and chemotherapy. Data collected regarding surgery includes: Type of surgeon, debulking surgery (optimal versus suboptimal), Time of debulking (initial, interval or delayed debulking). Regarding chemotherapy, in this study we focused on first line platinum based chemotherapy either single agent carboplatin or combination platinum based chemotherapy. Response to treatment was assessed according to RECIST version 1.1.

Statistical Analysis:

Data analysis using SPSS program for windows version 16 (SPSS ICN, Chicago II, USA). Tests used in analysis were Pearson Chi. Square test and fisher's exact test. They were used to determine the significance of associations between categorical variables and response. PFS was analyzed using the Kaplan. Meier curves. It was calculated from the date of diagnosis to the date of progression or the date of death (all causes), whichever occur first, patients who weren't progressed at last follow up were censored. Differences between groups were assessed by means of the log-rank test. Two-sided *P*-value <0.05 was considered statistically significant.

RESULTS

Clinico-pathologic criteria for the studied patients represented in table 1. Median age for all patients in the study was 55 years (18-72 years), patients are classified into two groups according to this median age, first group was ≥ 55 years which were slightly more than half of the patients (54.2%) while the other group was < 55 years which were (45.8%). Serous cystadenocarcinoma was the prominent histological type (68.7%), followed by endometrioid type (18.1%) and lastly mucinous type (13.3%). Most of patients had high grade tumors (74.7%), 19.3% are grade I, and grade II represented 6% of the patients. Advanced disease (stage III and IV) presented in 84.3% of the patients, while 15.7% of patients were stage I and II.

Analysis of treatment is shown Table 2. Seventy two patients (86.7%) underwent debulking surgery and eleven patients (13.3%) didn't. Early debulking was done for 59% of cases. Fifty three percent of patients underwent optimal debulking while 47% had suboptimal debulking. Oncosurgeon performed 38.9% of surgery, gynecologist did 34.7%, and general surgeon did 26.4%. All patients received chemotherapy. 77 patients completed six cycles while 6 patients died before treatment was completed. Combination platinum based chemotherapy was received by 86.7% of patients, while only 13.3% received single agent carboplatin (Table 2).

Forty patients were eligible for assessment of response. After first line platinum based chemotherapy, 35% of patients had complete response (CR), while 55% had partial response (PR), 2.5% had stable disease (SD), and 7.5% had disease progression (DP) (Table 3). Correlation between response and stage is shown in Table 4.

Median follow up was 31 months with 67.5% of patients progressed during follow up while 27 patients (32.5%) remained progression free. Fifty one patients were alive while 32 cases died during the follow up period (table 5).

Median PFS was 17 month while the median OS was 45months. Kaplan Meier curve shows a statistically significant correlation between PFS and stage (*P*. value= 0.001) (Figure1). There is a statistically significant correlation between PFS in months and type of debulking surgery (*P*. value= 0.036) (Figure 2). Correlation between OS in months and debulking surgery was statistically significant (*P*. value= 0.003) (Figure 3). Kaplan Meier curve shows a statistically significant correlation between OS in months and chemotherapy regimen (*P*. value= 0.007) (Figure 4).

PFS univariate analysis, stage and type of debulking were statistically significant, but after multivariate analysis by Cox regression, stage was independent prognostic factor with significance of $P = 0.008$, hazard ratio= 4.228, 95% confidence interval (CI) =1.448-12.341, while type of debulking lost significance.

Univariate analysis of OS, type of debulking and chemotherapy regimen were statistically significant, after multivariate analysis by Cox regression, type of debulking was independent prognostic factor with significance of $P = 0.003$, hazard ratio (HR) = 2.977, 95%

CI=1.435- 6.173, and similarly chemotherapy regimen was independent prognostic factor with significance of *P*= 0.005, HR= 0.296, 95% CI= 0.125 - 0 .699

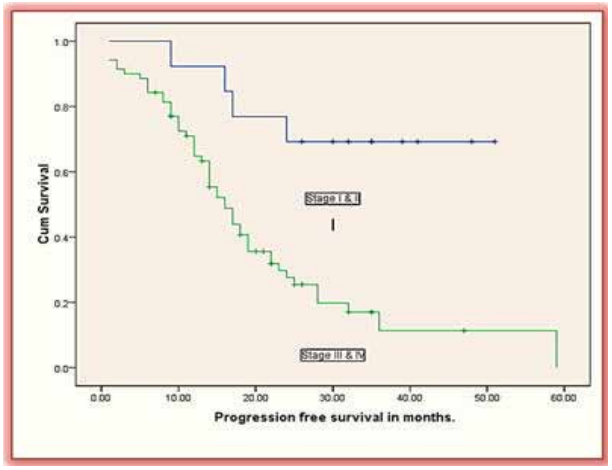

Figure 1: Kaplan Meier curve shows association of PFS and stage (*P* = 0.001).

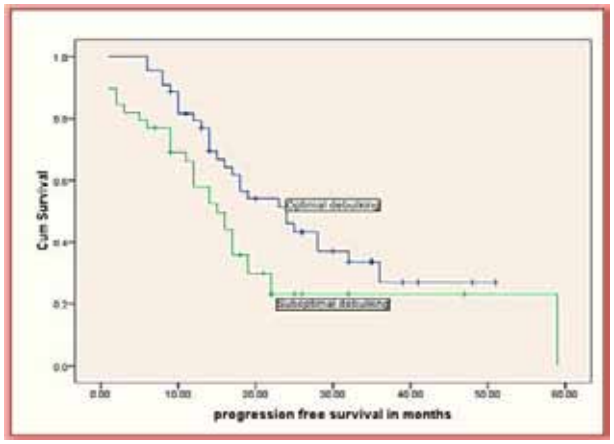

Figure 2: Kaplan Meier curve shows association of PFS and type of debulking (*P* = 0.036).

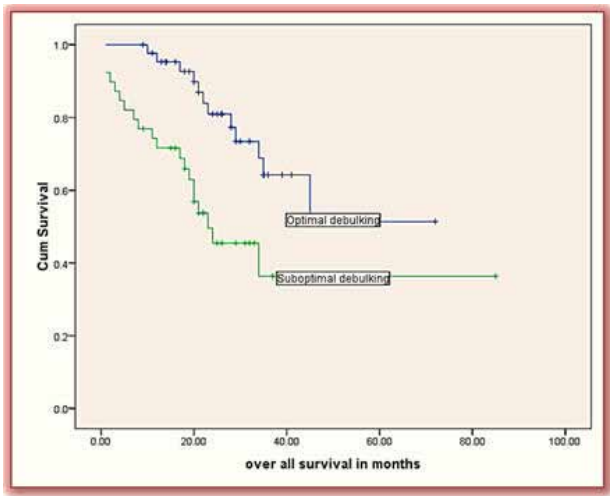

Figure 3: Kaplan Meier curve shows association of OS and type of debulking (*P* = 0.003).

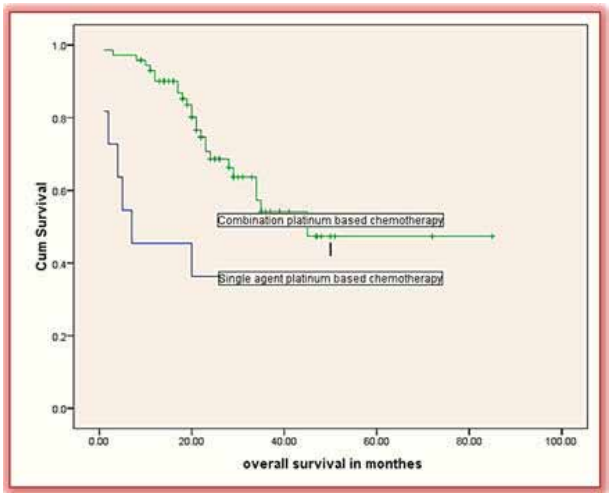

Figure 4: Kaplan Meier curve shows association of OS and chemotherapy regimen (*P* = 0.007).

Table 1: Patients clinico-pathological characteristics.

Characteristics		No of patients	%
Age	<55	38	45.8
	≥55	45	54.2
Type of biopsy	Histology	54	65.1
	Cytology	6	7.2
	Cytology and postchemotherapy histology	10	12
	Histology and postchemotherapy histology	13	15.7
Grade	Grade I	16	19.3
	Grade II	5	6
	Grade III	62	74.7
Pathology	Serous	57	68.7
	Mucinous	11	13.3
	Endometrioid	15	18.1
Stage	Stage I	11	13.3
	Stage II	2	2.4
	Stage III	49	59
	Stage IV	21	25.3

Table 2: Analysis of the treatment received by the patients

Treatment analysis	No of patients	Percent	No of patients	%
surgery	Timing of surgery	Early debulking	49	59%
		Interval debulking	14	16.9%
		Delayed debulking	9	10.8%
		Only Biopsy	11	13.3%
	Type of debulking	Optimal	44	53%
		Suboptimal	39	47%
	Type of surgeon	General surgeon	19	26.4%
		Oncosurgeon	28	38.9%
		Gynecologist	25	34.7%
chemotherapy	Timing of chemotherapy	Neoadjuvant	30	36.1%
		Adjuvant	53	63.9%
	Chemotherapy regimen	Single agent carboplatin	11	13.3%
		Combination carboplatin based	72	86.7%
	Platinum sensativety	Platinum sensative	62	74.7%
		Platinum resistant	15	18.1%
		Not assessed	6	7.2%

Table 3: Treatment response of the patients

Response	No of patients	percent
Complete response	14	35%
Partial response	22	55%
Stable disease	1	2.5%
Disease progression	3	7.5%
Total	40	100%

Table 4: Relation between treatment response and stage.

Complete response	Stage			*P.* value
	Stage III	Stage IV	total	
Yes	12	2	14	
	52.2%	11.8%	35%	
No	11	15	26	
	47.8%	88.2%	65%	
Total	23	17	40	
	100%	100%	100%	0.009

Table 5: Analysis of disease progression and living status at June 2013 (median follow up 31 months).

Status		No of patients	percent
Progression status	Progression free	27	32.5%
	Progressed	56	67.5%
Living status	Living	51	61.4%
	Dead	32	38.6%

DISCUSSION

Ovarian cancer incidence is strongly related to age, with the highest incidence rates being in older women. In our study we find that the mean age was 53.4 years with a range of 18-72 years and median age was 55 years. In the Gharbia population based cancer registry, the mean age at diagnosis was 47.2 years and the median age was 49 years[9].

In UK between 2008 and 2010, an average of 53% of cases diagnosed in women aged 65 years[10]. In USA, the median age at the time of diagnosis is 63 years[10]. So, the Age of ovarian cancer incidence in our study is 10 years younger than seen in UK & USA. This is could be explained by difference in sample size, age at menarche, or other reasons that worth further confirmation studies.

Among our patients, 68.7% were serous carcinomas, 13.3% were mucinous carcinomas and 18.1% were endometrioid. In the Middle East consortium study, serous carcinomas predominated with percentage ranging between 27.2% and 49.9%, followed by adenocarcinomas. The proportion of mucinous carcinomas among Egyptians in this study was 16.1% and among Jordanians was 11.7% whereas in Israeli and Cyprious registries the percentage was lower ranging from 6% to 8.7%[11].

Paes, *et al.*[10], found that 30% of the epithelial tumors were serous while 13.7% were mucinous. So, the incidence of serous among all ovarian cancer cases in our study is higher than those reported by others, while mucinous is nearly the same. This difference could be

explained by a relative a relative small sample size of the present study or predominance of molecular phenotype and genotype expressing more serous histology.

The majority of patients presented in late stages III and IV (84.3% of the cases). Our results were the highest among most of other studies. In Pakistan, Pak[12] found that 78% of the cases were in stages III and IV at presentation. Paes, *et al.*[10] in their study found that stages III and IV accounted for only 56.2% of his cases. This can be explained by low social class of patients in Menoufia.

In the present study 86.7% of patients were treated initially with surgery. In a study evaluating ovarian cancer in oriental women from Singapore found that surgery was the primary treatment modality in 97% of the cases[13]. In a university hospital in Berlin that reviewed 372 consecutive patients with advanced ovarian cancer found that 89% of the cases underwent surgery[14].

In the Medicare population evaluating patients with advanced ovarian epithelial carcinoma found that surgery was performed initially in 58.8% of the women which is much lower than our study, German and the Singapore trials[15].

Of those who underwent surgery 53% had optimum cytoreduction surgery (no residual or residual less than 2 cm). In the study evaluating surgery in 115 patients with stages III and IV ovarian cancer in the south west of the Netherlands, the investigators found that optimal surgery was done in only 45% of the cases[16]. Survey study among gynecologist performing surgery for ovarian carcinoma in Australia and New Zealand, they found that about 65% of the surgeons perform optimal cytoreductive surgery[17]. It is obvious from the comparison that in our series, optimal cytoreductive surgery is performed in the median range between two previously mentioned trials and this can be explained by; the experience of our surgeons and their awareness of their surgical fields as 73.6% of optimal debulking done by gynecologists or oncosurgeons.

In the present study, all patients received platinum based chemotherapy, 77 patients completed six cycles chemotherapy and 6 patients received only one or two cycles and died. Thirty six percent of the cases started neoadjuvant chemotherapy. As regard the type of chemotherapy regimen, Paclitaxel-carboplatin was the most frequently used regimen as first line in 86.7% of the cases and single agent carboplatin was used in 13.3% of the cases (two cases indicated for only single agent carboplatin and others used it alone for fragile patients with moderate performance status or when there is shortage in paclitaxel because of the limited resources).

All of our cases were sub-optimally debulked stage III or stage IV either with initial, interval or delayed debulking. The response rate to the first line chemotherapy after six cycles of chemotherapy was seen in 90% of the cases (CR 35%), if we add cases with stable disease after three cycles chemotherapy, the overall response will increase to 92.5%. Only 7.5% of the cases progressed after six cycles of first line chemotherapy. There are different percentages of complete responses[18]. In the GOG study protocol 47, they found that the complete response rate for the cisplatin containing arm reached 51%. The response rate to paclitaxel followed by either cisplatin or carboplatin in the exploratory phase III study ranged between (64–74%)[19], while the pathological complete response in another Phase III trial comparing paclitaxel plus cisplatin versus paclitaxel plus carboplatin, was nearly similar among both groups (46 vs. 53%)[20].

The possible explanation of the difference in clinical complete response between our study and the different international studies could be explained by: first, the number of the patients in our study was relatively small in comparison to those studies. Second, no standard chemotherapy protocol was given among all patients in our study (most of patients received single agent carboplatin were indicated for combination paclitaxel and carboplatin), and third: the high frequency of chemotherapy under-dosage and frequent interruption of the treatment were due to limited resources and unavailability of the drugs specially paclitaxel (i.e. lower compliance).

In the present study, PFS after first line chemotherapy was 17 months which is largely similar to the results of international studies[18-22].

Poorer results were associated with advanced clinical stage (III & IV), suboptimal surgery or no surgery at all. Differences were statistically significant. These results agree with reported series by other investigators.

Higher tumor grade had lower PFS compared to low grade tumor, 20.5 versus 34.5 months. The difference was statistically significant ($P = 0.002$).

There was a statistically significant correlation between OS and age (*P*. value = 0.039). The median OS for patients of age group (<55 years) was 60 months while for older patients (≥ 55 years) was 37.7 months. This is could be explained by poor tolerance of elderly especially who presented by advanced disease to standard combination chemotherapy, associated co-morbidities which made the patient inoperable, and patient had bulky disease also increases the risk of death from other causes.

CONCLUSION

The age incidence of ovarian cancer in our study is fifty five years which is eight years higher than that

of other parts of Egypt. For all patients in this study, typical presentation was late. The response rate to first line chemotherapy was high and the PFS was nearly the same as reported in the western literature. The response was significantly correlated to stage. There was significant correlation for PFS with the grade, stage, and debulking surgery. Also OS significantly correlated to median age group, type of debulking, and chemotherapy regimen. The main limitation of the study is the small sample size, low compliance to treatment, suboptimal treatment, and short follow up.

Disclosure

The authors declare no conflict of interest

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