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Research Paper

Response Rate to the First Line Chemotherapy and Progression Free Survival in Iraqi Women with Advanced Epithelial Ovarian Cancer

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ABSTRACT:

BACKGROUND:

Ovarian cancer is the most lethal malignancy of female genital tract. Epithelial ovarian cancer comprises the majority of malignant ovarian neoplasms, response rate to platinum, taxan and bevacizumab is excellent in advance stages of disease, despite that recurrence can occur. Surgical intervention is correlated with progression free survival.

OBJECTIVE:

To estimated response rate to first line chemotherapy (platinum and taxane with bevacizumab) and progression free survival (PFS) in patients with advanced epithelial ovarian cancer (OC).

PATIENTS AND METHODS:

A total of 50 patients with OC were enrolled in this cross-sectional study whom received chemotherapy protocols (carboplatin ,paclitaxel and antiangiogenesis {bevacizumab} /Carboplatin was given at a dose of AUC 5 with paclitaxel (Taxol) 175 mg/m^2 and bevacizumab 7.5 - 15 mg/kg) each cycle repeated every 3 weeks. CA125 levels before and after treatment were determined. The responses of the patients were estimated according to response evaluation criteria in solid tumors guidelines. Also comparison between primary debulking surgery (PDS) and interval debulking surgery (IDS) in progression free survival (PFS) was measured.

RESULTS:

The median baseline level of CA125 was 695 U/ml (range= 9.2-5000 U/ml) compared with 54.6 (range= 5.0-27 U/ml) after treatment with a highly significant difference { p value < 0.001} The mean ovarian mass before treatment was 6.9±2.62 cm which reduced to 2.5±2.61 cm after treatment with a highly significant difference{ p value 0.001}. Similarly, the frequency of lymphadenopathy and ascites decreased from 72% and 68%, respectively before treatment to 22% and 18%, respectively after treatment with highly significant differences. One woman (2%) showed disease progression, 3 patients (6%) were stable, 42 patients (84%) had partial response and 4 patients (8%) had complete remission. Mean PFS time for IDS was 19.5±2.82 months, 95%CI= 13.97-25.03 compared with 8.5±2.82 months in PDS, 95%CI= 4.54-12.46 (p value 0.008).

CONCLUSION:

Platinum and taxan based with bevacizumab showed effective treatment regime for management of advanced OC and serum level of CA125 could be effectively used in monitoring the disease progression and response. Interval debulking surgery was more effective compared to primary debulking surgery and PFS was better in patient who is done IDS than in patient in PDS .

KEY WORDS: progression free Survival, response rate, advance ovarian cancer, Iraqi Women

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INTRODUCTION:

Ovarian cancer is one of the most prevalent gynecologic cancers worldwide. Early detection of this malignancy is challenging. Signs and symptoms of ovarian cancer are nonspecific and vague including abdominal bloating, abdominal pain, urinary frequency, early satiety or feeling full, or changes in bowel habits.[1] For this reason, patients may not seek medicare, resulting in a late diagnosis. In fact, most patients recall having these symptoms prior to their diagnosis, and even some who presented with such symptoms were treated without their health care providers looking further into the cause of their symptoms.[2]

A significant number of phase III clinical trials assessing first-line treatment for ovarian cancer have been published. Many include data pertaining to PFS and OS as primary or secondary trial endpoints, which allows for a direct comparison and assessment of the correlation between those outcomes. In the setting of adjuvant treatment for patients with early-stage ovarian cancer, the combined analysis of icon1 (International Collaborative Ovarian Neoplasm 1) and action (Adjuvant Chemotherapy in Ovarian Neoplasm) observed a statistically significant advantage in recurrence-free survival and os for patients receiving platinum-based adjuvant chemotherapy.[3] Two studies examined the addition of bevacizumab, with or without a maintenance phase, to front-line chemotherapy. Preliminary results from both studies showed a clear PFS advantage favouring arms in which bevacizumab was administered both concurrently with chemotherapy and as maintenance therapy afterward.[4] Despite the benefits accompanying the use of CA125, many challenges exist that render it not as effective in early screening. One of the primary challenges is its decline in sensitivity in early-stage ovarian cancer.[5]

AIMS:

To estimated response rate to first line chemotherapy (platinum and taxane with bevacizumab) and progression free survival (PFS) in patients with advanced epithelial ovarian cancer (OC).

PATIENTS AND METHODS:

This is a cross-sectional study including a total of 50 patients with ovarian cancer who were attending Oncology Department, Baghdad Medical City, Oncology Teaching Hospital, during the period from 1st February 2021 to 31st October 2021. All patients were diagnosed with ovarian cancer underwent thorough physical examination, radiological studies (CT imaging), tumor markers and histopathological confirmation (peritoneal fluid cytology, laparoscopic biopsy,CT/USG guided biopsy and histopathological results of surgical specimen after PDS surgery) prior to surgery and chemotherapy . Chemotherapy gave to patient regarding to ECOG [Eastern Cooperative Oncology Group] performance status of patient

Inclusion criteria included patients who had all patients diagnosed with epithelial ovarian carcinoma stage III and IV , Patients with performance status of ECOG Zero 1 or 2 and patient who can give consent and above 18 yrs.

Exclusion criteria included patients who had poor performance status ECOG 3 and 4, Patient with non-epithelial ovarian malignancy like germ cell tumors ,sex cord tumor and borderline epithelial tumor ,Patients less than 18 years and who cannot give informed consent and patient with known allergy to chemotherapy drugs.

Platinum and Taxan based chemotherapy with antiangiogenesis (bevacizumab) was administered as primary treatment. Carboplatin was given at a dose of AUC 5 with paclitaxel (Taxol) 175 mg/m^2 Chemotherapy with antiangiogenesis agent (bevacizumab) 7.5-15 mg/kg was repeated every 3 weeks{bevacizumab stopped 6 weeks before surgery and returned 4-6 weeks after surgery}. Primary debulking surgery was performed in patients showing operable tumor. Interval debulking surgery was performed after neoadjuvant chemotherapy (twenty two of patients received neoadjuvent six cycles chemotherapy before IDS and eleven patients received three cycles before and three after IDS). During surgery intraoperative tumor size was observed and also presence of non- target lesions were documented, the surgical specimen was sent for histopathological examination.

CA125 levels before and after treatment was determined by COBAS E 411 test (Germany) according to the manufacturer's instructions. The kit was designed to measure human CA125 levels in serum. The measurement range of device 0.6- 5000 U/ml. (normal range of ca125 0-35U/ml).

Complete response (CR) was defined as the vanishing of all related lesions; partial response (PR), a reduction of at least 30% in the summation of the lengthiest diameters of related lesion; progressive disease (PD), an increase of at least 20% in the summation of the lengthiest diameters of related lesions or the presence of one or more new lesion; and stable disease (SD) also defined, neither adequate shrinkage to qualify for PR nor adequate increase to qualify for PD. Data entry was performed using SPSS software (version 25). Quantitative variables are presented as the mean ± standard deviation (SD), and the categorical data are expressed as a number (percentage). Evaluation of the statistical significance differences in the categorical data were performed using the Chi-square (χ^2) test. Comparison of quantitative variable was performed by the Student t-test. Progression-free survival (PFS) was measured.The Kaplan–Meier curve was employed to determine medians and 95% confidence interval (CI) of the time-related parameters. A p-value of < 0.05 was considered significant.

RESULTS:

This study included 50 patients with ovarian cancer. The mean age of the patients was 58.14±11.37 years (range 30-77 years). The mean weight, height and BMI of the patients were 73.22±13.57 kg, 157.56±5.67 cm and 29.52±5.29 kg/m^2, respectively.

The vast majority of included patients (94%) were married, while the majority of patients (88%) were never smokers. Most patients (62%) had multiparity. In about two-third of the patients (72%) the ECOG was one (Table 1)

Table 1: Demographic characteristics of the patients (n=50).

Variables	Values
Age, years	
Mean±SD	58.14±11.37
Range	30-77
Weight, kg	
Mean±SD	73.22±13.57
Range	55-114
Height, cm	
Mean±SD	157.56±5.67
Range	145-168
BMI, kg/m^2	
Mean±SD	29.52±5.29
Range	21.48-42.91
Marital status	
Married	47(94%)
Unmarried	3(6%)
Parity	
Nulliparity	10(20%)
One child	9(18%)
Multiparity	31(62%)
Smoking, pack/year	
Never	44(88%)
Ex/current smokers	6(12%)
ECOG	
Zero	7(14%)
One	36(72%)
Two	7(14%)

Exactly half of the patients had no comorbidity, while diabetes and hypertension were encountered in 36% and 32% of the patients, respectively. Family history of cancer was reported in 15 of the patients, of whom 8 were first degree relatives, and 5 were second degree relatives, mostly affected with breast cancer. Serous cystadenocarcioma was the most common histopathological ovarian cancer accounted for 58% of the patients, followed by clear cell carcinoma (26%) and endometrioid (16%). More than half of the included patients (54%) had abdominal distension at presentation. Abdominal pain was the second most common presentation found in 26% followed by bloating (18%)vaginal bleeding (16%) and constipation (14%). Less common presentation included epigastric pain (10%) and headache (8%). Fourteen patients (28%) were using contraceptive, of whom 6 patients with less than one-year duration, 7 patients with 1-3 years' duration, and only one patient with five years' duration. History of recurrence was reported in 19 patients (38%), three patients of whom were treated with 2nd line topotecan + bevacizumab, 3 patients treated with liposomal-doxorubicin+ bevacizumab, and 13 patients managed with rechallenge platinum base CT + bevacizumab (Table 2).

Table 2: Therapeutic and clinical characteristics of the patients (n=50).

Variables	Number	Percentage
Comorbidities		
No comorbidity	25	50%
Diabetes mellitus	18	36%
Hypertension	16	32%
Family history		
No	35	70%
Yes	15	30%
First degree relative	8	16%
Second degree relative	5	10%
Third degree relative	2	4%
Histopathological type		
Serous cystadenocarcinoma{high grade serous}	29	58%
Clear cell carcinoma	13	26%
Endometrioid	8	16%
Tumor stage		
IIIA1	5	10%
IIIA2	9	18%
IIIB	12	24%
IIIC	15	30%
IV	9	18%
Presentation		
Abdominal distension	27	54%
Abdominal pain	13	26%
Bloating	9	18
Vaginal bleeding	8	16%
Constipation	7	14%
Epigastric pain	5	10%
Headache	4	8%
Others	9	18%
Contraceptive		
No	36	72%
Yes	14	28%
<1 year duration	6	12%
1-3 years	7	14%
5 years duration	1	2%
History of recurrence		
No	31	62%
Yes	19	38%
2nd line topotecan + bevacizumab	3	6%
Liposomal doxorubicin+ bevacizumab	3	6%
Rechallenge platinum base CT + bevacizumab	13	26%

Other clinical presentation included 3 cases of amenorrhea, 2 cases of nausea 2 cases of seizure, and one case of each of cough and dysuria. The median baseline level of CA125 was 695 U/ml (range= 9.2-5000 U/ml) compared with 54.6 (range= 5-27 U/ml) after treatment with a highly significant difference { p value < 0.001}. The mean ovarian mass before treatment was 6.9±2.62 cm which reduced to 2.5±2.61 cm after treatment with a highly significant difference [p value 0.001]. Similarly, the frequency of LAP and ascites decrease from 72% and 68%, respectively before treatment to 22% and 18%, respectively after treatment with highly significant differences[p value for both 0.001] other radiological findings such as omental and mesenteric deposit , liver lesions and lung lesion response to treatment was significant with [p value e 0.022] (Table 3-3).

Table 3: Association of radiological findings with treatment.

Variables	Before treatment	After treatment	p-value
Ovarian mass (SLD), cm Mean±SD Range	 6.9±2.62 2.0-11.2	 2.5±2.61 0.0-13.0	 <0.001
Lymphadenopathy Present Absent	 36(72%) 14(28%)	 11(22%) 39(78%)	 <0.001
Ascites Present Absent	 34(68%) 16(32%)	 9(18%) 41(82%)	 <0.001
Other radiological findings Present Absent	 14(28%) 36(72%)	 5(10%) 45(90%)	 0.022

About two-third of the patients (66%) had IDS, while 8 patients (16%) received PDS. However, 9 patients (18%) had no surgery at all. Patients were complaining with treatment with no drugs discontinuation otherwise four cases interrupted in treatment due to thrombocytopenia, one case stopped bevacizumab due to fistula complications and six patients were complaining from non-significant peripheral neuropathy Slightly less than half of the patients (44%) received Neoadjuvant therapy, while perioperative and adjuvant therapies were used for 22% and 16% of the patients respectively. On the other hand, the treatment in 9 patients (18%) restricted on palliative therapy. Out of 50 women included in the study, only one woman (2%) showed disease progression, 3 patients (6%) were stable, 42 patients (84%) had partial response and 4 patients (8%) had complete remission (Figure 1).

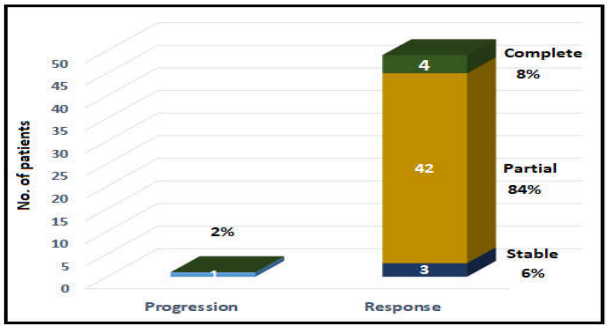

Figure 1: Responsive and non-responsive patients.

Demographic and clinical characteristics of patients had no significant association with patient's response. Although all patients with stable response (100%) had stage IV tumor compared with 25% of the patients with complete response and 11.91% of the patients with partial response, the difference was not significant (table 4.)

Table 4: Association of patient's profile with the response to treatment .

Variables	Complete response (n=4)	Partial response (n=42)	Stable (n=3)	p-value
Age, years	53.75±6.13	57.76±11.56	63.67±11.5	0.521
BMI, kg/m^2	25.22±2.6	30.04±5.19	30.15±7.7	0.215
Marital status UnMarried Married	 0(0%) 4(100%)	 3(7.14) 39(92.86%)	 0(0%) 3(100%)	0.760
Parity Nulliparity One child Multiparity	 0(0%) 0(0%) 4(100%)	 9(21.43%) 8(19.05%) 25(59.52%)	 1(33.33%) 1(33.33%) 1(33.33%)	0.466
Smoking, pack/year Never Ex/current smokers	 4(100%) 0(0%)	 36(85.71%) 6(14.29%)	 3(100%) 0(0%)	0.566
ECOG Zero One Two	 1(25%) 2(50%) 1(25%)	 6 (14.29%) 32(76.19%) 4(9.52)	 0(0%) 1(33.33%) 2(66.66%)	0.206
Comorbidities No comorbidity Diabetes mellitus Hypertension	 2(50%) 2(50%) 2(50%)	 20(47.62%) 15(35.71%) 14(3.33%)	 3(100%) 0(0%) 0(0%)	 0.215 0.363 0.366
Family history No Yes	 3(75%) 1(25%)	 30(69.047%) 12(28.57%)	 1(33.33%) 2(66.67%)	0.419
Histopathological type Serous cystadenoma Clear cell carcinoma Endometrioid	 3(75%) 0(0%) 1(25%)	 24(57.14%) 13(30.95%) 5(11.91%)	 2(66.67%) 0(0%) 1(33.33%)	0.835
Stage III IV	 3(75%) 1(25%)	 37(88.09%) 5(11.91%)	 0(0%) 3(100%)	0.060
Contraceptive No Yes	 3(35%) 1(25%)	 30(71.42%) 12(30.09%)	 2(66.67%) 1(33.33%)	0.867

Progression Free Survival

Mean PFS time for IDS was 19.5±2.82 months, 95%CI= 13.97-25.03 compared with 8.5±2.82 months in PDS, 95%CI= 4.54-12.46 with a highly significant difference (p= 0.008) (Figure 2).

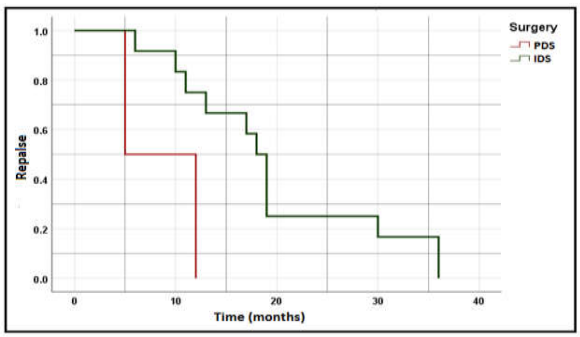

Figure 2: Kaplan Meier curve for PFS.

Most demographic and clinical characteristics of the patients had no significant association with PFS. However, stage IV tumor was more common among patients with PFS<14 months than those with > 14 months (36.84% vs. 6.45%) with a highly significant difference {0.004} (Table3-5).

Table 5: Association of patient's profile with PFS.

Variables	>14 months (n=31)	≤14 months (n=19)	p-value
Age, years	58.74±12.25	57.16±10	0.637
BMI, kg/m^2	30.03±5.71	28.69±4.56	0.391
Marital status			
Unmarried	3(9.68%)	0(0.00%)	0.162
Married	28(90.32%)	19(100.00%)	
Parity			
Nulliparity	6(19.35%)	4(21.05%)	0.557
One child	7(22.58%)	2(10.53%)	
Multiparity	18(58.06%)	13(68.42%)	
Smoking, pack/year			
Never	26(83.87%)	18(94.74%)	0.251
Ex/current smokers	5(16.13%)	1(5.26%)	
ECOG			
Zero	5(16.12%)	2(10.52%)	
One	22(70.96%)	9(47.36%)	0.985
Two	4(12.90%)	8(42.11%)	
Comorbidities			
No comorbidity	13(41.94%)	12(63.16%)	0.145
Diabetes mellitus	13(41.94%)	5(26.32%)	0.264
Hypertension	10(32.26%)	6(31.58%)	0.960
Family history			
No	19(61.29%)	16(84.21%)	0.251
Yes	12(38.71%)	3(15.78%)	
Histopathological type			
Serous	16(51.61%)	13(68.42%)	0.604
cystadenoma	10(32.25%)	3(15.79%)	
Clear cell carcinoma	5(16.12%)	3(15.79%)	
Endometrioid			
Stage			
III	29(39.54%)	12(63.15%)	0.004
IV	2(6.45%)	7(36.84%)	
Contraceptive			
No	20(64.51%)	16(84.21%)	0.11
Yes	11(35.48%)	3(15.78%)	

DISCUSSION:

This study highlights the effectiveness of platinum, Taxan and bevacizumab for advanced ovarian cancer as a first line treatment. In this study, we confirmed that platinum, Taxan and anti-angiogenic therapy that target the VEGF pathway as well as aggressive surgery could effectively treat advanced OC. This result is in line with many previous studies which indicated the efficiency of bevacizumab and platinum with Taxan in the treatment of advanced OC. [6, 7] A prospective observational study that investigated first-line chemotherapy showed that paclitaxel-carboplatin combination chemotherapy with the addition of bevacizumab for OC was high effective in terms of PFS and response rate, suggesting that the addition of bevacizumab could play a key role in the optimization of treatment for OC[27]. In another study International Collaborative Ovarian Neoplasm Trial Randomized Trial of Adjuvant Chemotherapy in Women With Ovarian Cancer [ICON7], [8] the efficacy of bevacizumab in respect of both PFS and OS in patients with high risk was highly proved; however, more than 50% of patients in that study were diagnosed with early-stage ovarian cancer (stages I and II).

Our study showed significant decline in the tumor marker CA125 after treatment with a highly significant difference with p value <0.001} in accordance with results several studies worldwide. In a Japanese study, Matsuhashi et al. [9] appraised the relationship between post-NAC serum level of CA-125, surgical consequences, and clinical consequences in a total of 107 patients with FIGO stage III or IV epithelial OC. A significant drop in CA125 (from 346.5±295.2 U/mL to 48.1±27.6 U/ml) was reported. Furthermore, Rodriguez et al. evaluated the relationship between mean serum CA 125 levels and surgical outcomes in 103 patients with Stage IIIC/IV EOC who were treated with platinum-based NAC followed by IDS. In the complete/optimal surgery groups it dropped from 1566 U/ml to 92 U/ml compared with 2077 to 233 U/mL in patients having suboptimal surgery, so patients with a preoperative CA-125 of ≤100U/mL were very likely to be cytoreduced to no residual disease.[10] There is a close relationship between post-treatment serum CA125 levels and the size of residual lesions after cytoreductive surgery. As the residual size increases, the decrease serum CA-125 level will be slower or absent. Thus, when there is no rapid decrease in serum CA-125 level post CRS, it always implies large size of residual lesions, the worse prognosis, and the high possibility of relapsing. The speed by which serum CA-125 drops to normal level after treatment has a role in predicting relapse. Patients having high pre-treatment serum level of CA-125 associated with better prognosis if their serum CA-125 reduces to normal level rapidly after surgery. In contrast, patients with a low pre-treatment serum level of CA-125 associate with a worse prognosis if their serum CA-125 does not reach the normal level rapidly after surgery.[11]

In the present study, all radiological findings (ovarian mass, LAP, ascites and other findings) were significantly reduced after treatment in patient who was treated with neoadjuvent chemotherapy. Most available studies regarding radiological finding after treatment in patients with advanced OC did not show a radical changes in radiological parameters. For examples, in a recent study, McNulty et al.[12] assessed if radiological response is associated with progression-free survival and investigated whether radiological response predicts the response to treatment in 71 Australian patients with EOC. Most patients showed moderate ascites and diffuse peritoneal nodularity before treatment. However, after 6 cycles of neoadjuvent chemotherapy, ascites has been drained even though the presence of the omental caking and peritoneal deposits was almost similar. Radiological response was not associated with progression-free survival or overall survival on univariate analysis [stable disease vs partial response].

There are numerous challenges in assessing tumor response in OC by CT modality. It may be problematic to precisely measure such a response in patients with spread and diffuse small-volume serosal disease. Furthermore, there is an interobserver variability in the evaluation of tumor bulk on imaging. One study appraised the inter-observer inconsistency that may exist in the evaluation of imaging in OC using RECIST guidelines and found considerable variability in tumor measurements, especially in peritoneal lesions.[13]

In the present study, one woman (2%) showed disease progression, 3 patients (6%) were stable, 42 patients (84%) had partial response and 4 patients (8%) had complete remission, with a recurrence rate of 38% (within a median of 14 months follow up).

In a similar study, Mazzeo et al. [14] evaluated the response rate in 45 Belgian patients with advanced OC receiving platinum-based neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy. The study revealed that 1 patient (2.2%) had achieved a clinical CR, 33 (73.4%) PR, and 8 (17.8%) had stable disease. Only 3 (6.6%) patients showed disease progression (PD), which was very close to our study. On the other hand, Batra et al.[15] recruited 50 Indian patients with advanced OC who were treated with neoadjuvent chemotherapy followed by surgery. Complete response occurred in 17 patients (34%), and 27 (54%) had PR, while stable disease was reported in 6 patients (12%). Also, none of included patients had progression. A prospective observational study that investigated first-line chemotherapy showed that paclitaxel-carboplatin combination chemotherapy with the addition of Bevacizumab for OC was associated with a response rate of 63.6%. [16] These variations among different studies can be attributed to several factors the most important of which are the tumor stage, histopathological subtype, number of cycle, and demographic characteristics of the patients.

Based on the results of the current study, interval debulking surgery had a better PFS than that of primary debulking surgery with a significant difference.This difference needs more number of patients to comparison and confirms that. This result does not agree with many studies worldwide. Accumulated evidence from two

large prospective randomized controlled trials indicated that neoadjuvent chemotherapy followed by IDS had at least equivalent overall survival, with fewer rates of morbidity and mortality, than patients treated by PDS.[17, 18] Petrillo[19] reported that a prolonged PFS and increased rate of patients remaining recurrence-free at 5 years following PDS compared with IDS. However, when patients received PDS there was a trend towards platinum-sensitive recurrences compared to patients undergoing IDS. This difference between our study and other studies can be attributed to pattern of PDS performed in Iraq which can be described as suboptimal surgery with many anatomical sites remains undisected. Such sites act as foci for cancer spread and recurrence. In the present study, most demographic and clinical characteristics of the patients had no significant association with patient's response or PFS. The only exception was that advanced tumor stage was significantly associated with reduced PFS.

CONCLUSION:

In summary, although limited number, the results of our study revealed that platinum and Taxan based with bevacizumab as first line chemotherapy is very effective treatment regime for management of advanced epithelial OC. Variation in serum level of CA125 could be effectively used in monitoring the disease progression and response to treatment and primary debulking surgery may be not the most proper choice for treatment of Iraqi patients with OC, the IDS is more effective and PFS was better in patient who is done IDS than in patient in PDS.

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