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ORIGINAL ARTICLE

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The role of surgery and the effect of cisplatinum and cyclophosphamide (C+P) regimen in epithelial ovarian cancers

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OBJECTIVE(S): To study the role of surgery and effect of cisplatinum and cyclophosphamide (C+P) regimen in epithelial ovarian malignancy, both as neoadjuvant and in post-operative setting.

METHOD(S): This is a prospective analysis of 50 patients having epithelial ovarian malignancy studied over a period of 2 years (1st February, 2000 to 31st January, 2002). Twenty-eight patients underwent primary surgery and then received C+P chemotherapy post-operatively. Twenty-two patients were given C+P as neoadjuvant chemotherapy followed by interval laparotomy.

RESULTS: Mean age was 42.6 years. Out of the 28 patients who had primary surgery, 13 (46.4%) had optimal debulking. Thirteen patients had interval surgery after neoadjuvant chemotherapy of whom 10 (76.9%) had optimal debulking. Thirty-two percent of the patients has FIGO Stage-III disease. Seventy-eight percent of the patients has serous type tumors. Commonest toxicity was nausea and vomiting. Disease status was evaluable in only 41 patients since 9 were lost to followup. 30.4% of the patients with optimal debulking surgery were disease-free while 17% with suboptimal surgery were disease-free.

CONCLUSION(S): Management of epithelial ovarian cancer requires optimal surgery and effective combination chemotherapy. Neoadjuvant chemotherapy, improves resectibility rates without compromising on survival.

Key words : surgery, cisplatinum, cyclophosphamide.

Introduction

Epithelial ovarian carcinoma is a disease least diagnosed at an early stage, and the most common cause of death from gynecological malignancy. Ovarian cancer accounts for 4% of all female cancers and 5% of all female cancer deaths. In India it ranks third among all malignancies in women after cancer breast and cancer cervix. It is the commonest gynecological malignancy in western industrialized countries.

Epithelial ovarian tumors account for 70-80% of all ovarian malignancies. These tumors can be benign, borderline (low malignant potential), and malignant. Serous and mucinous tumors are the most common ovarian neoplasms. The combined 5 year survival rate for all patients with ovarian cancer approximates 40%. Those patients whose disease is confined to the ovary have a cure rate greater than 90% [1]. Seventy-five percent have advanced disease (Stage III and Stage IV). If patient is untreated, median survival is less than 9 months. In advanced (Stage III and IV) ovarian cancer, improving the present survival of only 10-15% remains a major challenge .

The role of surgery in ovarian cancer is to establish a diagnosis, determine the stage of the disease, and remove as much tumor as possible. Ovarian cancer patients should receive maximal surgical removal of the disease so as to reduce the residual disease to optimal. This will give a better chance for a complete response to chemotherapy. After surgery, most of the patients will require additional treatment, usually chemotherapy. According to DeVita et al [2], if ovarian

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carcinoma is treated with chemotherapy, life expectancy can be prolonged.

Till very recently, cisplatin was the drug of choice for chemotherapy of epithelial ovarian cancer. Cisplatin based chemotherapy, mainly cisplatin and cyclophosphamide (C+P) regime, is most popular and is effective. It is still the commonest drug used in countries such as ours because it not only gives response rates of 82-96% but is also very economical. However, today the gold standard for treatment of epithelial ovarian cancer is a combination of paclitaxel and carboplatin [2]. This is the standard regime used in developed nations and as this has become cheaper, we have started using it in our country.

Methods

A prospective study of 50 cases of epithelial ovarian cancer was undertaken from 1st February, 2000 to 31st January, 2002 to evaluate the response to C+P regimen of chemotherapy in epithelial ovarian cancer. Age, symptoms, and clinical findings were evaluated. Investigations such as hemogram, renal and liver function tests, x-ray chest and ultrasongraphy (USG) were carried out. Ascitic fluid cytology or USG guided biopsy (FNAC/FNAB) were done in patients in whom neoadjuvant chemotherapy was planned. Pleural fluid tapping and cytology were done in patients having pleural effusion. These patients were also given neoadjuvant chemotherapy. CT scan was carried out if indicated. Special investigations like tumor marker CA-125 were done for diagnostic purpose and also to know the baseline value for follow-up of the patients later on. Proper treatment plan was decided according to the disease status. Staging laparotomy was performed in most of the patients, unless the tumor seemed to be technically unresectable. Staging laparotomy included meticulous exploration of the whole abdomen, four-quadrant cytology, total abdominal hysterectomy with bilateral salpingo-oophorectomy, infracolic omentectomy, and lymph node sampling. Site and size of residual disease were recorded carefully. In patients having technically unresectable tumors, two to four courses of neoadjuvant chemotherapy were given before surgery (interval laparotomy). Patients operated elsewhere and referred for further management, were considered unstaged. In such cases, slides and blocks were submitted to histopathological review and operative details were requested. Tumor markers and other investigations were done. Planned chemotherapy was given.

Most commonly used chemotherapy for epithelial ovarian cancer in our set up is C+P. The dose was calculated according to body surface area. Inj.cisplatin 70 mg/m [2] and inj.cyclophosphamide 700 mg/m [2] were given every three weeks for six cycles. The calculated dose of cisplatin in normal saline was given slowly intravenously along with proper hydration. This was followed by diuresis with 350 mL of 20% mannitol to flush out cisplatin from the kidneys to prevent nephrotoxicity. The calculated dose of cyclophosphamide was given intravenously followed by flushing of the vein with 10 mL of normal saline. To minimize gastro-intestinal toxicity, 12 mg ondansetron was given intravenously in 500 mL of normal saline over half an hour.

This cycle was repeated every three weeks. Before each cycle of chemotherapy, routine investigations like hemogram, blood urea nitrogen, serum creatinine, serum bilirubin and SGPT levels were carried out. During the course of the treatment, if the patient had a hemoglobin level of < 9/dL blood transfusion was given along with chemotherapy. In patients having hematological toxicity like thrombocytopenia and neutropenia, chemotherapy was delayed until the counts became normal. Patients were examined clinically and sonographically to evaluate the response after every two cycles of chemotherapy. Patients receiving neoadjuvant chemotherapy were re-evaluated for surgery. After completion of chemotherapy, each patient was evaluated every 3 months for 2 years and thereafter every 6 months for 3 years. Radiological assessment and CA-125 levels were done as and when required.

Results

Age - As seen in Figure 1, 60% of the patients were between the age group of 41 to 50 years. The mean age was 42.6 years.

FIGO Staging - As shown in Figure 2, 32% of the patients were in FIGO stage III. Sixteen percent presented in an earlier stage (I and II). Fifty percent or 25 patients were unstaged. Out of these 25, 21 were given neoadjuvant chemotherapy, after clinical and radiological examination as they seemed to be technically unresectable. The remaining four patients were operated elsewhere and staging laparotomy was not performed. So they were considered as unstaged.

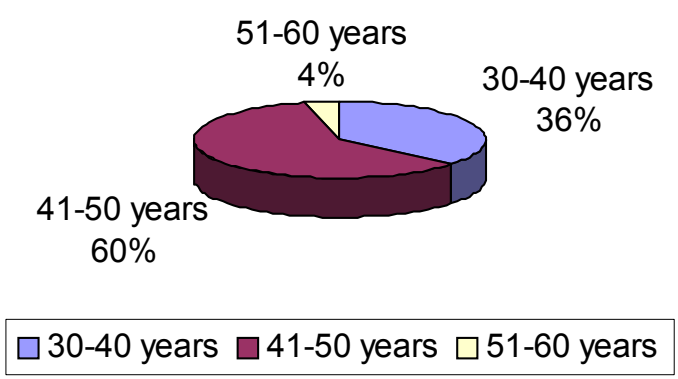


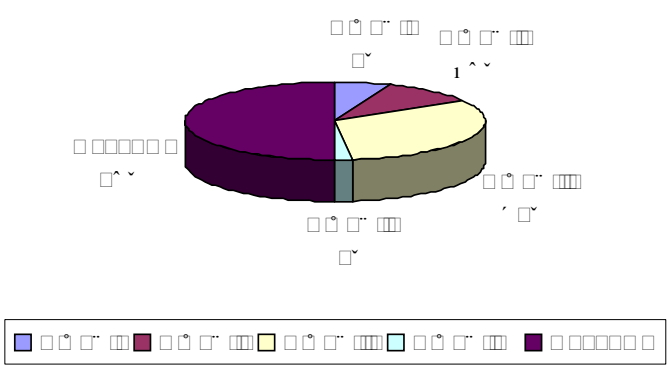
Figure 1. Age

Figure 2. FIGO stage.

Histopathology - Seventy-eight percent of the patients had serous type, while 17.1% had mucinous type and 4.8% had endometroid type of epithelial ovarian cancer.

Table 1 – Type of Surgery (n=41).

Type of surgery	Optimal debulking	Sub-optimal debulking	Inoperable	No. of patients
Primary	13	13	2	28
Interval	10	3	-	13



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Interval surgery after neoadjuvant chemotherapy

Twenty-two patients were given neoadjuvant chemotherapy because after clinical and radiological examination, they were judged to be technically unresectable. After every two courses of chemotherapy the patients underwent clinical and sonographic examination (with or without CA-125) to judge the response.

Nine patients were lost to follow up after 2-3 courses of chemotherapy. In the remaining 13 patients, interval surgery was done after 3-4 courses of chemotherapy. Ten patients had optimal debulking and three had suboptimal debulking.

Toxicity to chemotherapy

All the patients in our study were treated with cisplatin 70mg/m² and cyclophosphamide 700mg/m². Median number of courses given was five. The most common toxicity was nausea and vomiting (Group I and II) seen in 44 (88%) patients. It was tolerable and treated with antiemetics and intravenous fluids. Nineteen patients developed grade II-III hematological toxicity (lukopenia in 17 and thrombocytopenia in 2). These patients were treated expectantly and chemotherapy was delayed for 1 to 2 weeks until counts returned to normal. Three patients developed anemia (hemoglobin < 9 g/dL) during the course of chemotherapy and were given blood transfusion during chemotherapy.

Two patients developed neurological toxicity (tingling and numbness) and two developed renal toxicity as seen by renal function tests after 6 courses of chemotherapy, so further chemotherapy was omitted. There was no death due to toxicity (Table 2).

Table 2. Toxicity of chemotherapy (n=50).

Toxicity	No. of patients
Nausea/Vomiting	44 (88%)
Alopecia	7
Anemia	13
Lucopenia	17
Thrombocytopenia	2
Renal	2
Neurological	2

Clinical response to chemotherapy

Only in 16 patients who had measurable disease, the response could be evaluated. Out of these 16 patients, five had complete response, ten had partial response and one had stable disease (Table 3).

Table 3 – Clinical response (n=16).

Response	No. of patients
Complete response	5
Partial response	10
Stable disease	1

Status after treatment

Status of all the 23 patients who had optimal debulking at primary or interval (post-chemotherapy) laparotomy was evaluated. Seven of these 23 (30.4%) were disease free. Fourteen (60.9%) were living with disease and two (8.7%) died of the disease (Table 4).

Table 4 – Status 2 years after optimal debulking (n=23).

Status	Primary surgery	Interval surgery	Total no. of patients	Percentage
Free of disease	2	5	7	30.4%
Living with disease	9	5	14	60.9%
Died of disease	2	-	2	8.7%

Eighteen patients had sub-optimal debulking surgery either primarily or at interval laparotomy after chemotherapy. Out of these 18 patients, 12 were staged (nine primarily and three at interval laparotomy after CT) and had > 2cm residual disease, and two had inoperable disease. Three patients (17%) were disease free and 14 patients (78%) were living with the disease. One patient died of the disease (Table 5).

Table 5 – Status 2 years after suboptimal debulking (n=18).

Status	Primary surgery	Interval surgery	Total no. of patients	Percentage
Free of disease	2	1	3	17%
Living with disease	12	2	14	78%
Died of disease	1	-	1	8.3%

Discussion

Epithelial ovarian cancer tends to be a disease of affluent societies where life spans are long. Death from this disease is the rule rather than the exception. About 80-90% ovarian tumors are epithelial. The cornerstone of any scheme of management for ovarian malignancy is necessarily surgery. It plays a primary role in establishing the diagnosis and determining the extent of the malignancy, which form the basis upon which adjunctive therapy can most accurately be planned. In the early stage, outcome will be more a consequence of adequate surgical staging and post-operative adjuvant therapy, but in advanced disease curability is dependent more upon the surgeon's ability to maximally reduce the tumor burden [3]. During 1950 to 1960, single agent chemotherapy was used effectively. Skipper introduced the concept of combination chemotherapy in 1950. It has been shown to be superior to single agent therapy in most patients with advanced epithelial ovarian cancer [3].

In our study, median age of the patients having ovarian cancer was 42.6 years. This is comparable with the findings of Gupta et al [4] and Conte et al [5]. Sixty-four percent patients in our series had FIGO stage III disease. This is also comparable with the findings of Conte et al [5] who had 65% patients with FIGO stage III disease. This suggests that epithelial ovarian carcinoma is least diagnosed at an early stage. Most of our patients (78%) had serous type tumors. Conte et al[5] and Neijt et al [6] also reported that most of their patients had serous type of epithelial ovarian tumor. This suggests that serous type of tumor is the most commonly encountered epithelial ovarian malignancy.

Surgery in epithelial ovarian tumors not only helps in diagnosis but also removes nondividing as well as poorly perfused area. This facilitates the effect of subsequent therapy. Patients are benefitted and survival improves if residual tumor is < 2cm (optimal debulking). But in advanced malignancy, optimal debulking may not be possible due to wide spread disease in the whole abdomen [7]. In such cases neoadjuvant chemotherapy helps to reduce the bulk of the tumor and hence facilitates surgery for optimal debulking. In our series with primary surgery, optimal debulking was possible in 46.4% of the patients while with interval laparotomy after neoadjuvant chemotherapy, optimal debulking surgery was possible in 76.9% of patients. Neijt et al [6] reported that 48.09% had optimal debulking at primary surgery and 63.5% had optimal debulking after neoadjuvant chemotherapy. This shows that neoadjuvant chemotherapy facilitates thorough debulking of the tumor.

The most common toxicity was nausea and vomiting seen in 88% of our patients. In the series of Neijt et al [6], the commonest toxicity was also nausea and vomiting seen in 75% of the patients.

The disease status was evaluated. Only 41 out of 50 patients were evaluable as nine patients on neoadjuvant chemotherapy were lost to follow-up after two or three courses of chemotherapy. These 41 patients were followed up for a period of 2 years. In patients with optimal debulking surgery (primarily or at interval laparotomy after chemotherapy), 30.4% were disease free at 2 years. While in patients with suboptimal debulking surgery (primarily or at interval laparotomy), only 17% were disease free at 2 years (Tables 4 and 5). Similarly 60.9% of the patients who had optimal debulking surgery were living with disease compared to 78% of those who had suboptimal surgery. This indicated that the optimal surgery plays a very important role in the survival and prognosis of the patients in epithelial ovarian tumors. In

our series, the survival with the combination of C + P chemotherapy in epithelial malignancy was 24.4% (10/41) with the follow-up period of 24 months. Conte et al [5] reported 20% survival with the follow-up period of 42 months with the same combination.

The combination of chemotherapy and surgery has not only revolutionized the management but has improved survival of the patients. Although paclitaxel with carboplatin remains the first line treatment in epithelial ovarian malignancy, it is very costly. In our country, C + P combination being effective and cheap remains the treatment of choice for majority of the patients. In our institution we are using cisplasin in the dose of 70mg/m ^{2}. Since the last 7 years we have found similar response rate but with lower neurotoxicity when compared with the higher dose of 100 mg/m ^{2}. This is also supported by Hoskins et al [8].

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