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Ovarian cancer stage III/IV: poor prognostic factors

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Ovarian cancer accounts for 32% of all gynecologic malignancies but causes 55% of all gynecologic cancer deaths, because some two-thirds of cases are detected in advanced stage. Between 1993 and 1995 we operated 63 patients with ovarian cancer, FIGO stages III /IV, in the Institute of Oncology Sremska Kamenica, Novi Sad. On the basis of several diagnostic methods such as ultrasonography, CT and operative findings we performed radical surgery in 24 (38%) patients, palliative surgery in 25 (40%) and exploratory laparotomy in 15 (22%) patients. Forty-five (71%) patients were treated with the first line chemotherapy according to the protocol CP (carboplatin or cisplatil and cyclophosphamide). Twenty (32%) patients were treated with second look operation after VI series of chemotherapy. Pathohistological examination of biopsies and cytologies were negative only in three (15%) patients. From 1993 to 1995, 85% of all patients with ovarian cancer treated in our Institute, were patients with advanced disease stage III/IV. Eighty-four percent of patients had residual of tumor more than 1-2 cm. Pathohistological types, such as cystadenocarcinoma serosum, carcinoma anaplasticum and clear cell carcinoma were detected in 86% of patients. These types of tumors also have poor prognosis. In our study, a three-year survival rate in the group of patients with advanced disease was 27%. The main problems that affect final results of ovarian cancer treatment, are the lack of early detection, histological type of tumor, stage of disease, and residual tumor volume.

KEYWORDS: *Ovarian Neoplasms; Neoplasm Staging; Prognosis*

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INTRODUCTION

Carcinoma of the ovary accounts for 32% of all gynecologic malignancies but causes 55% of all gynecologic cancer deaths (1). On stage-for-stage basis, survival rates for ovarian cancer are similar to those for other solid tumors. Approximately 75% of all cases have spread beyond the ovary at the time of diagnosis, which directly account for the high mortality rate associated with this tumor (2).

Pelvic pain and palpable adnexal mass during routine pelvic examination are first signals in early detection of ovarian cancer. However, most of adnexal masses are benign, especially in premenopausal women, and routine pelvic examination appears to be unsuited to mass screening for ovarian cancer (3). Unfortunately, the vast majority of women with ovarian cancer are diagnosed in advanced stages.

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In our experience, almost 85% of all examined patients were with advanced disease stage III and IV (FIGO classification) and clinical symptoms.

Factors that prolong survival include younger age, early stage, low tumor grade, low residual tumor volume, and rapid rate of tumor response. Other prognostic factors include initial tumor volume and para-aortic lymph node involvement. A serum CA 125 level obtained four weeks after surgical debulking appears to be helpful; however, it cannot be an independent prognostic factor.

Histological type of tumor is also one of important prognostic factors. As already stated, cystadenocarcinoma serosum, carcinoma anaplasticum or clear cell carcinoma are tumors with poor survival rate.

Adequate and complete surgery is mandatory primary therapy for ovarian cancer, permitting precise staging, accurate diagnosis, and optimal cytoreduction. A qualified gynecologic oncologist should conduct the surgery when there is high probability of ovarian cancer. When the mass is most probably benign, a qualified gynecologic surgeon can perform the operation.

Systemic chemotherapy following the surgery is the cornerstone of first-line treatment of advanced epithelial ovarian malignancy. Chemotherapy is most effective in patients who have undergone

maximal cytoreductive surgery or who manifest a low volume of disease.

MATERIALS AND METHODS

Between 1993 and 1995, 63 patients with ovarian carcinoma, FIGO stages III /IV, were operated in the Institute of Oncology Sremska Kamenica, Yugoslavia. We decided to proceed with radical, palliative or exploratory laparotomy, according to ultrasonography, CT and operative findings. Forty-five patients were treated with first line of chemotherapy after surgery according to protocol CP: carboplatin 200-300 mg/m2 or cisplatil 100 mg/m2 and cyclophosphamide 600 mg/m2 every three weeks, VI series. Side effects of chemotherapy on hematopoietic organs, function of liver and kidney were checked before each chemotherapy cycle. Twenty patients were treated with second look operation to see the effects of cytoreduction of tumor after VI series of chemotherapy. The survival rate was followed during three years.

RESULTS

Forty-six (73%) of all treated patients were between 51 - 70 years old, (median age 61) (Figure 1).

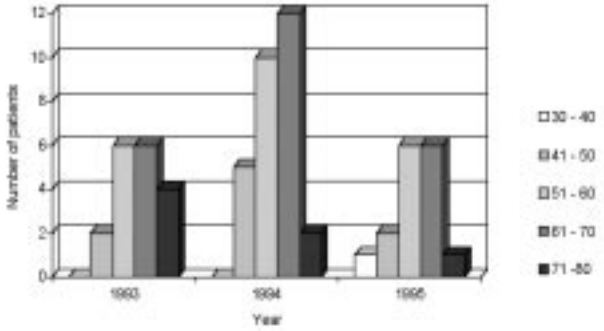

Figure 1. Age of patients with ovarian cancer treated in the Institute of Oncology Sremska Kamenica from 1993 to 1995

The Karnofsky score of our patients before operation is shown in Table 1. Eighty-three percent of them had Karnofsky score 70-100, in addition to poor clinical findings.

Table 1. KARNOFSKY SCORE during the clinical examination

Karnofsky score	1993	1994	1995	Total	%
100 - 70	15	25	12	52	83
50 – 60	2	3	2	7	11
< 50	1	1	2	4	6
Total	18	29	16	63	100

During the initial examination we found ascites in forty-five (71%) of patients. Forty-four (70%) patients were in stage III C and thirteen (21 %) in stage IV. Almost 91% of all treated patients were in terminal stages of disease (IIIC/IV) that affected the treatment prognosis and survival rate (Figure 2).

Expansion of disease dictated the type of surgical procedure: twenty-four (38%) patients had radical operation, twenty-five (40%) palliative and, unfortunately, there were 15 (22%) exploratory laparotomy (Figure 3).

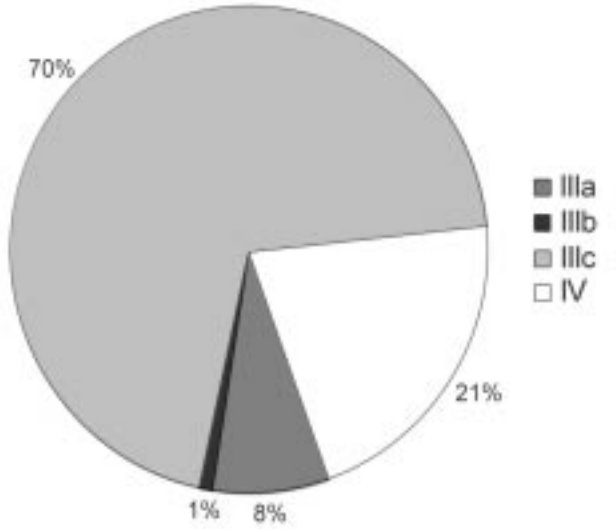

Figure 2. FIGO classification of ovarian cancer in treated patients

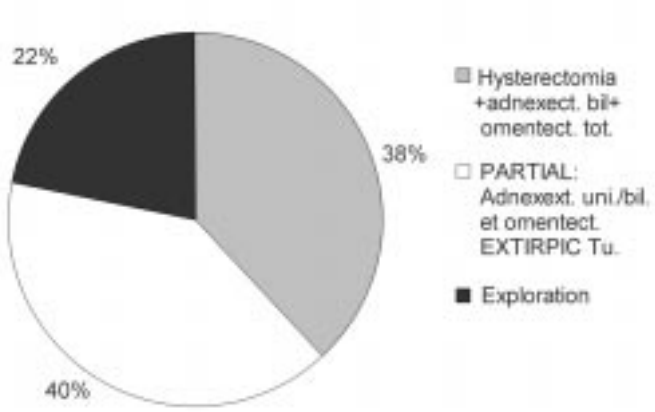

Figure 3. Type of operation

During the surgery we found adnexal mass presented as solid tumors in case of 24 (38%) patients, as cystic in 8 (13%) and as solid-cystic in case of 31 (49%) patients.

According to the advanced stage of the disease and local findings of tumor dissemination beyond the pelvic region, 40 (63%) of our patients had residual tumor more than 2 cm/vol. after the operation. In thirteen patients (21%) the residual tumor was less than 2 cm/vol. and only ten patients (16%) were without tumor residual (Table 2).

Table 2. Residual tumor after primary operation of ovarian cancer

Residual tumor	1993	1994	1995	Total	%
> 2 cm	11	20	9	40	63
< 2 cm	4	3	6	13	21
Without	3	6	1	10	16
Total	18	29	16	63	100

Histological type of ovarian cancer is also one of the most impor-

tant prognostic factors. After pathohistological examinations, cystadenocarcinoma serosum was confirmed in 50 (79%) patients, cystadenocarcinoma mucinosum in 9 (14%) patients, anaplastic carcinoma in 1 (2%) and clear cell carcinoma in three patients (5%) (Figure 4).

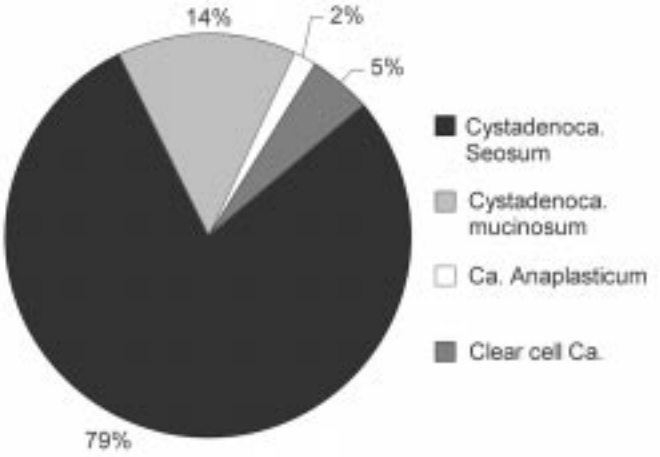

Figure 4. Histological type of ovarian cancer

Twenty (32%) patients were treated with second look operation after VI series of chemotherapy. Pathohistological examination of biopsies and cytologies were negative in three (15%) patients only (Table 3).

Table 3. Second look operation

	1993	1994	1995	Total	%
Second look operation	8	8	4	20	100
PH/citology Positive	6	7	4	17	85
PH/citology Negative	2	1	0	3	15

Total three-year survival rate of all treated patients was 27% (Figure 5).

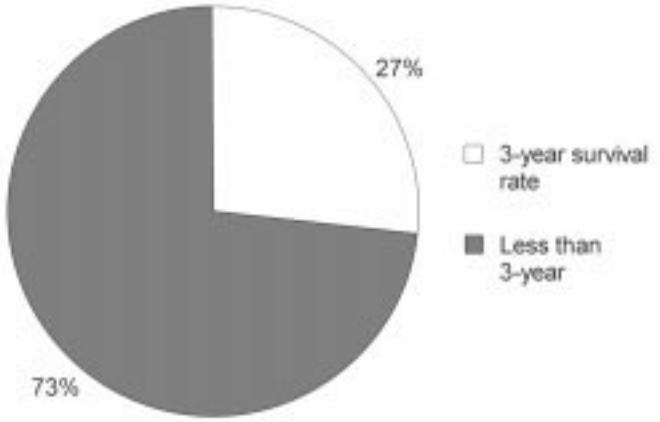

Figure 5. Total 3-year survival rate in patients with advanced disease

DISCUSSION

Ovarian carcinoma is one of the major problems in gynecologic oncology because early clinical symptoms are obscure. Although sometimes women with early ovarian cancer have symptoms such as vague gastrointestinal discomfort, pelvic pressure, and pain, more often they have no symptoms, or very mild and non-specific symptoms. By the time symptoms are present, women with ovarian cancer usually have advanced disease. Introduction of CA 125 serum tumor marker and improvements in pelvic ultrasound diagnostics, along with newer techniques of color Doppler imaging (CDI), have led some to advocate the use of these modalities in the attempt to detect early-stage ovarian cancer. Serum CA 125 determinations and transabdominal and/or transvaginal sonography have proved helpful in the evaluation of asymptomatic pelvic adnexal masses and have become standard techniques in studies aimed at testing the utility of ovarian cancer screening (4).

Surgery remains a major therapeutic tool but its success rate still directly correlates with the spread of disease. Cytoreduction surgery is beneficial but tumor reduction of less than 1 cm/vol. is very hard in case of advanced disease.

Chemotherapy is not specific enough. The standard initial chemotherapy program for ovarian cancer includes a platinum agent (generally carboplatin) and paclitaxel. Despite high response rates to cytotoxic chemotherapy, most women with FIGO stages III/IV relapse and eventually become resistant to therapy. Further clinical research must therefore focus on (a) understanding the mechanisms of drug resistance, and (b) developing pharmacological techniques that circumvent, reverse, or prevent resistance.

Many studies have examined the first-line chemotherapy in ovarian cancer and evaluated the combination of carboplatin-paclitaxel versus standard therapy (5-8).

P. Hoskins described the experience of the National Institute of Canada with a regimen consisting of sequential couplets of cisplatin (50 mg/m2)/topotecan (0.75 mg/m2 day 1-5) every 21 days for 4 courses, followed by cisplatin (75 mg/m2)/paclitaxel (135 mg/m2 over 24 hours) every 21 days for 4 courses (9). This couplet strategy was employed because of difficulty in administering all three drugs in combination without producing excessive hematological toxicity. A high objective response rate was observed in this pilot study. However, a considerable grade 4 of hematological toxicity was also noted.

In 1996, the Gynecologic Oncology Group (GOG) published the results of a randomized Phase III trial that compared the at that time "standard chemotherapy" regimen of cisplatin (75 mg/m2) plus cyclophosphamide (75 mg/m2) to an experimental regimen of cisplatin (75 mg/m2) plus paclitaxel (135 mg/m2 delivered over 24 hours). This landmark study demonstrated that the paclitaxel-containing regimen resulted in a major improvement in both progression-free and overall survival in suboptimal residual advanced ovarian cancer. These results significantly changed the management of this difficult malignancy.

Topotecan is a semi-synthetic, water soluble topoisomerase I inhibitor which has recently been approved for the treatment of ovarian cancers after failure of first-line therapy (10,11).

In our study a three-year survival rate in group of the patients with advanced disease was 27%. During the period 1993-1995 of all treated patients with ovarian cancer in our Institute 85% were patients with advanced disease stage III / IV, which was one of poor prognostic factors. The age of patients was another poor prognostic factor: 84% percent of patients had residual tumor less and more than 2 cm. Pathohistological types, such as cystadenocarcinoma serosum, carcinoma anaplasticum and clear cell carcinoma were detected in 86% of all treated patients. These types of tumors are also with poor prognosis.

Patients were operated after six series of chemotherapy and in 85% results of biopsies and cytologies were positive.

All those were the main reasons for poor, but expected results of a three-year survival rate.

CONCLUSION

Sixty-three patients with ovarian carcinoma, FIGO stages III /IV, were operated in the Institute of Oncology Sremska Kamenica, Yugoslavia from 1993 to 1995. Spreading of the disease dictated the type of operation: 24 (38%) patients had radical operation, 25 (40%) had palliative and unfortunately, there were 15 exploratory laparotomies. Forty-five (71%) patients were treated with first line of chemotherapy. Twenty (32%) patients were treated with second look operation after VI series of chemotherapy. Pathohistological examination of biopsies and cytologies were negative in three (15%) patients only. Total three-year survival rate of all treated patients was 27%.

The main problems that affect final results of treatment of ovarian cancer are the lack of early detection, histological type of tumor, stage of disease, and residual tumor volume.

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