Factors influencing period of time between negative second-look laparotomy and ovarian carcinoma recurrence. Multicenter study in Poland

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Summary

Objective: The aim of our study was to evaluate factors such as primary clinical stage, presence of ascites, serum CA 125 antigen level, histological type of ovarian cancer, cell differentiation and number of chemotherapy cycles influencing the time of recurrence after negative second-look operations.

Material and Methods: Having observed complete clinical remission in 356 patients with ovarian cancer, second-look laparotomy was performed. In 180 patients complete pathologic remission was detected and in 73 recurrence was observed. Correlation analysis between time of recurrence and the above-mentioned prognostic factors was carried out by means of the Mann-Whitney and Kruskal-Wallis tests.

Results: The time from the second-look operation till diagnosis of relapse ranged from 7 to 36 months (average 21 months). The statistical analysis showed a correlation between the presence of ascites, increased serum CA 125 antigen level, the administration of six chemotherapy courses and the time of recurrence. In all those cases relapse occurred earlier than in patients without ascites, with normal CA 125 antigen levels and after ten courses of chemotherapy.

Conclusion: Our findings suggest that the stage of clinical advancement and histologic grading do not influence the time of recurrence. The presence of ascites, increased serum CA 125 antigen level and the administration of fewer chemotherapy courses (6 versus 10) after primary surgery affects the earlier relapse of disease.

Key words: Ovarian cancer; Second-look operation; Recurrence.

Introduction

The value of second-look operations in ovarian cancer management is still controversial [3, 10, 11], especially because of the ineffectiveness of the second line therapy and recurrence of neoplasms after the negative operation [6-9, 13, 19]. So far, however, conformation of ovarian cancer remission is possible exclusively on the basis of a negative result of the second-look operation [4, 8]. Clinical, biochemical and radiological tests can not yield this conclusion. According to ACOG, second-look laparotomy is not considered as a routine or mandatory procedure, and its application should be personalized [2]. It can be used both as a therapy completion or the foundation of consolidating therapy. It has not been decided yet, which procedure gives better results: second-look laparotomy or laparoscopy. The advantage of laparoscopy over laparotomy is that, in the course of treatment with laparoscopy, one can observe smaller blood loss, shorter operation time, fewer intra- and postoperative complications, shorter hospitalization time and reduced expenses. Both procedures detect recurrences equally well [1]. On the other hand, during laparotomy it is possible to palpate the residual disease (for example in retroperitoneal lymph nodes) and promptly remove the changes during the same procedure. Also, the laparotomy may give a more accurate diagnosis when, for example, extensive adhesions after previous operations are present.

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The aim of the study

The aim of our study was to evaluate the following factors influencing the time of recurrence after negative second-look operations:

a) primary clinical stage
b) presence of ascites
c) CA 125 level in the course of disease
d) histological type of cancer
e) cell differentiation
f) number of chemotherapy cycles.

Material and Methods

Three hundred and fifty-six women with ovarian cancer, whose treatment between the years 1987 and 1998 resulted in complete clinical remission, were included in our study. The investigations were carried out in the Department of Oncology, University of Medical Sciences, Poznan, in the I and II Gynecological Clinics of the Medical Academy in Wroclaw and in the Gynecological and Obstetrics Clinic of the Medical Academy in Gdansk.

All patients underwent surgery which was followed by chemotherapy. Chemotherapy was based on Cisplatin and Cyclophosphamide cycles or Cisplatin, Cyclophosphamide and Farmorubicin cycles. All the patients in the I and II clinical stage and 27 out of 50 patients (54%) in the III clinical stage received six chemotherapy cycles. In the remaining cases the first-line treatment included ten chemotherapy cycles.

During treatment and remission periods patients were monitored by evaluation of CA 125 antigen levels in blood serum. CA 125 antigen was evaluated prior to the treatment, after the first surgery, after every chemotherapy course, before the second-look operation and on every ambulatory follow-up visit. The Abbott test for radioimmunologic essay was used to evaluate the level of CA 125 antigen. The level of CA 125 below 35 mU/mL was assumed to represent the normal value.

All 386 women underwent second-look laparotomy. It was considered negative if neither residual disease on physical examination nor cancer cells in tissue (biopsy, adhesions), washings and smears could be found. It is interesting to note that in six cases with pathologic remission, washings and smears from the peritoneal cavity contained stimulated mesothelial cells, which were detected on histologic examination. We found pathologic remission in 180 cases (50.6%), and in the remaining 176 patients (49.4%) persistent neoplastic disease was revealed. Seventy-three patients who had negative results of the second-look operation developed recurrence of the disease. The age of this group of patients ranged between 21 and 72 years, and they were followed-up from 7 to 104 months after diagnosis of recurrence.

The diagnosis of relapse was based on histologic examination of tissue and fluids obtained during laparotomy, cytologic smears from the peritoneal cavity and abdominal organs or tumor bioptic material. The decision about laparotomy, which was performed in 69 cases, was made in two situations. First, when on gynecological or ultrasound examination of the pelvis minor relapse of the disease was found. And second, when, without any clinical evidence of the disease, the CA 125 level was elevated over 35 mU/mL on two occasions, separated in time by 1-2 months. In the remaining four patients biopsy of tumor through the vagina was performed, and on histological examinations cancer cells were found.

Statistical analysis was performed in the Department of Statistics of the University of Medical Sciences in Poznan. Correlation analysis was carried out by means of the Mann-Whitney and Kruskal-Wallis tests.

Results

We examined the group of 73 patients with relapse of ovarian cancer after negative second-look laparotomy. The average time that elapsed from primary surgery till diagnosis of relapse ranged from 7 to 36 months (average 20.1 months). In ten cases, clincally detectable signs of ovarian cancer relapse were preceded by elevation of CA 125 levels in blood serum over 35 mU/mL. The elevation of CA 125 level was observed from 1 to 32 months (average 3 months) before clinical relapse. In the remaining 63 patients elevation of CA 125 levels occurred simultaneously with clinically evident relapse.

We tested whether there is a connection between clinical stage of advancement of ovarian cancer and the time of recurrence. Among 73 patients, I stage of clinical advancement was diagnosed in 10, II in 6, III in 50, and IV in 7 patients. At the same time in 27 cases (36.9%) ascites was observed. There was no statistical difference between successive times of relapse in respective clinical stages of advancement. The statistical analysis showed a correlation between the presence of ascites on primary diagnosis and the time of recurrence. Relapse occurred earlier in patients with ascites than in patients without. The average time of recurrence in the first group was equal to 14.1 months and in the second one 18.1 months. The results are shown in Tables 1 and 2.

We also analyzed whether there was a statistical difference between CA 125 antigen level in successive clinical stages of ovarian cancer advancement. The analysis was carried out for assays obtained before the treatment (assay number 1) and for assays taken in patients with suspected relapse (assay number 2). The results are shown in Table 3.

Table 1. — *Time of ovarian cancer recurrence in respective stages of clinical advancement.*

		FIGO stage			
		I	II	III	IV
Number of patients	n	10	6	50	7
Time	x	16.9	25.3	13.8	26.3
of recurrence	Me	14.0	18.0	18.0	19.2
in months	SD	16.5	24.2	11.1	23.3

Test Kruskal-Wallis, $p<0.05$.
x=mean value, Me=median value, SD=standard deviation.

Table 2. — *Time of ovarian cancer recurrence in patients with and without ascites.*

		Preferences of ascites	
		Yes	No
Number of patients	n	27	46
Time	x	14.1	18.1
of recurrence	Me	13.2	18.0
in months	SD	11.3	16.8

Test Kruskal-Wallis, $p<0.05$.
x=mean value, Me=median value, SD=standard deviation.

Table 3. — *Serum CA 125 level in patients before treatment (assay no. 1) and in case of suspected relapse (assay no. 2).*

FIGO Stage	Serum CA 125 level					
	assay 1			assay 2		
	X	Me	SD	X	Me	SD
I	49.3	48.0	31.0	57.5	59.6	38.8
II	670.9	137.0	1115.0	103.1	53.2	98.1
III	454.2	342.0	583.2	199.4	73.2	98.1
IV	694.8	600.0	475.2	180.3	162.9	198.5

Test Mann-Whitney, $p<0.07$ test Kruskal-Wallis, $p<0.05$
x=mean value, Me=median value, SD=standard deviation.

The statistical analysis performed by means of the Mann-Whitney test revealed that serum CA 125 level measured at the time of ovarian cancer diagnosis in patients with I stage of clinical advancement (assay no 1) was significantly lower (average 49.3 mU/mL) than in the II (670.9 mU/mL), III (454.2 mU/mL) and IV (694.8 mU/mL) stage of clinical advancement. There was no significant statistical difference between serum CA 125 levels in patients with suspected relapse (assay no 2) in respective stages of clinical advancement.

We also investigated whether correlations exist between time of relapse occurence and a) cancer cell differentiation, b) histologic type of the cancer. In 73 patients well-differentiated neoplasm G1 was diagnosed in 23 cases (31.5%), moderately-differentiated G2 in 26 cases (35.6%) and poorly-differentiated in 24 cases (32.9%). Based on histologic examination the following types of cancer were recognized: serous in 53 patients (72.6%), endometrioid in 8 patients (11.0%), undifferentiated in 6 patients (8.2%), mucinous in 4 patients (5.5%) and mesonephroid in 2 patients (2.7%).

There was no significant statistical correlation between time of ovarian cancer relapse and a) degree of cell differentiation, b) histological type of cancer.

However, in the case of endometrioid cancer the remission lasted longer than in the cases with the other types of cancer. The results of the analysis are shown in Table 4.

The treatment consisted of surgery which was followed by chemotherapy: 37 patients out of 72 (50.7%) received the first line treatment consisting of 6 chemotherapy cycles. This treatment was administered to patients with I and II stage of clinical advancement and to some patients with III stage of clinical advancement. The remaining 36 patients received 10 cycles of chemotherapy. Cycles comprised Cisplatin (80-100 mg/m^2) and Cyclophosphamide (600-800 mg/m^2) or Cisplatin, Cyclophosphamide (the same doses as above) and Farmorubicin (60-90 mg/m^2).

We analyzed whether the number of chemotherapy cycles had any influence on the remission period. The results are illustrated in Figure 1.

We have observed that in patients who received six cycles of chemotherapy as a first line treatment which followed the primary surgery, ovarian carcinoma relapse occurred significantly earlier than in the group of patients who received 10 chemotherapy courses. The recurrence in the former group appeared on average after 14.6 months and in the latter after 19.2 months.

Table 4. — *Differentiation and histological type of ovarian cancer cells versus time of relapse.*

Grade of cell differentiation	Time of relapse		
	X	Me	SD
G1	11.7	9.0	9.3
G2	18.8	15.0	15.4
G3	18.5	12.0	19.1
Histological type	X	Me	SD
Serous	16.7	12.0	14.5
Endometrioid	26.9	15.5	24.5
Undifferentiated	11.0	11.0	5.6
Mucinous	11.0	10.0	7.9
Mesonephroid	14.0	14.0	16.9

Test Kruskal-Wallis, $p<0.05$

x=mean value, Me=median value, SD=standard deviation.

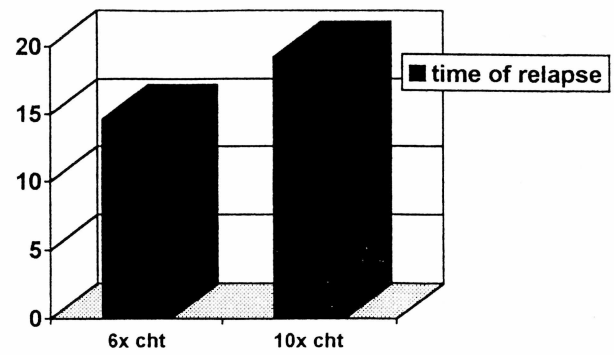

Figure 1. — Time of recurrence versus the number of chemotherapy cycles.

Conclusions

1. Relapse of ovarian cancer after negative second-look operation occurs earlier in patients with ascites.
2. The number of first line chemotherapy cycles affects the remission period.
3. In 13.7% cases elevation of the serum CA 125 level preceded clinically detectable relapse of the disease by 3 months.
4. The stage of clinical advancement and ovarian cancer maturity have no effect on the time of relapse.

Discussion

According to our study, relapse of ovarian cancer is diagnosed on average 20.1 months after negative second-look laparotomy. It is consistent with other investigations in which an average relapse time of 18-22 months was reported [9, 14]. Estimation of CA 125 level after negative second-look operation is valuable because we found that in 10 out of 73 patients (13.7%) the level of the marker was elevated before clinical evidence of relapse was detectable.

As a result of the marker level increase the patients were examined in order to detect the recurrence.

The existence of stimulated mesothelial cells in washings should be carefully noted because the relapse, notwithstanding the negative second-look operation, occurred in all six patients slightly earlier, after 17 months on average.

We have found no correlations between frequency of relapse occurrence and a) stage of clinical advancement, b) grade of cell maturity, c) histologic type. Some authors [5, 9] are of the opinion, that advanced ovarian cancer

and grading indicate earlier recurrence. In other papers, however, such a correlation is not reported [13].

We have observed that the presence of ascites proved to be significantly related to the recurrence after second-look laparotomy (median value 13.2 months, without ascites 18 months). According to some studies, there is no such correlation [5], but according to others [18], the presence of ascites is related to a worse prognosis.

The presence of stimulated mesothelial cells in washing samples constitutes another problem. In six cases where stimulated mesothelial cells where found, relapse in the abdominal cavity was observed. We could not find any reference to this finding.

We observed that the remission period following second-look laparotomy was longer after 10 chemotherapy cycles (19.2 months) than after 6 cycles (14.6 months). This contradicts the opinion that the dosage, not the number of chemotherapy cycles, influences treatment results [16].

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