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The interval between the primary cytoreductive surgery and adjuvant chemotherapy in patients with advanced ovarian cancer

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ABSTRACT

Aim of the study was to establish the effect of the time interval between the initial optimal cytoreductive surgery and the initiation of adjuvant chemotherapeutic treatment (ACT) on the overall survival (OS) of patients with advanced ovarian adenocarcinoma.

Materials and methods. Clinical cases of 60 patients with advanced ovarian adenocarcinoma (FIGO IIIC-IV), with the average age of 61 years, who underwent primary cytoreductive surgery (PDS) with the completeness of cytoreduction (CC) — 0 score according to Shugarbaker and adjuvant chemotherapeutic treatment according to the standard first-line regimen were examined. Patients were categorized depending on the time between surgery and chemotherapeutic treatment into two groups: I — delay of chemotherapy for no more than one month (30 patients), II — from two to six months (30 patients). The OS data of the patients obtained from the national cancer registry were analyzed.

Results. The results demonstrate an increase in OS of patients who underwent CC-0 PDS at the early initiation of ACT.

Conclusions. Delaying the onset of ACT is an independent predictor of the worse OS after performing PDS. According to the data obtained, patients should start ACT within 1 month after the surgery. However, the findings are proved if CC-0 is achieved during the operation.

Key words: primary cytoreductive surgery, adjuvant chemotherapeutic treatment, ovarian adenocarcinoma

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Introduction

According to the National Cancer Registry of Ukraine 2017–2018, ovarian cancer ranks seventh in the structure of the incidence of malignant neoplasms and fifth in the structure of mortality from them among women. Stage III in FIGO had 43.4%, IV — 15.5% among first identified patients. Nearly 25% of them did not live for one year. This survival is associated with a predominantly asymptomatic course of the disease in the early stages. Therefore the process is constantly diagnosed in the later stages. Ovarian cancer is classified according to its cellular origin. Most ovarian cancers come from superficial (epithelial) ovarian cells and are called epithelial tumors, although some cancers can also arise from ovarian stroma, from mesenchyme of embryonic gonads, sex stroma, etc. The development of peritoneal carcinomatosis is typical for the most common variant of ovarian cancer (epithelial) due to cellular and molecular processes which are specific to such tumors. It leads to rapid exfoliation of malignant cells into the abdominal cavity. The main methods for the special treatment of epithelial ovarian cancer are surgical and chemotherapeutic. In recent decades the paradigm shift in the treatment of advanced ovarian cancer has been observed. It is accompanied by the introduction of new active methods of combined treatment. According to their pathophysiological properties, these tumors respond relatively well to cytoreductive (surgical and chemotherapeutic) treatment. Any decrease in the total tumor mass has a definite effect on the overall survival (OS) of patients. However, the oncological results of special treatment directly depend on the surgical radicality [1] and the intensity of chemotherapeutic treatment [2]. The size of the residual tumor mass after cytoreductive surgery is an important prognostic factor for the OS of such

patients. The concept of the cytoreductive intervention was proposed by Paul H. Sugarbaker. It is based on the principle of maximum removal of macroscopically visible implantation metastases from the abdominal cavity in order to achieve the minimum microscopic level of the residual intraperitoneal pool of tumor cells. An increase in surgical radicalness in patients with advanced ovarian cancer is associated with an increase in overall and relapse-free survival. Although, it may lead to prolongation of postoperative recovery and delay the initiation of adjuvant chemotherapy treatment (ACT). The relationship between the interval from surgery and the onset of ACT with overall and relapse-free survival is being investigated. Nevertheless, the optimal interval has not yet been determined. Most studies allow an interval of 6–8 weeks. Until now there remains the issue of the order of combined treatment [3, 4], the volume of resection in standard surgery [5, 6] and the total intensity of the combined treatment, i.e., the time interval between each of its stages. Also, the role of hyperthermic intraperitoneal chemoperfusion in the treatment of advanced ovarian cancer still remains without a final assessment [7, 8].

Aim of the study was to establish the effect of the time interval between the initial optimal cytoreductive surgery and the initiation of ACT on the OS of patients with advanced ovarian adenocarcinoma.

Materials and methods

Clinical cases of 60 patients with advanced ovarian adenocarcinoma (FIGO IIIC-IV), with the average age of 61 years (interval from 37 to 71 years), who underwent primary cytoreductive surgery (PDS) with the completeness of cytoreduction (CC) — 0 score according to Shugarbaker and adjuvant chemotherapeutic treatment according to the standard first-line regimen (three-week regimen of carboplatin administration (area under the concentration-time curve 5–6) and paclitaxel 175 mg/m2) were examined. Patients were categorized depending on the time between surgery and chemotherapeutic treatment into two groups: I — delay of chemotherapy for no more than one month (30 patients), II — from two to six months (30 patients). The OS data of the patients obtained from the National Cancer Registry of Ukraine were analyzed. The study was conducted as a part of the scientific work of the Surgery Department No. 4 with a course of oncology at Odessa National Medical University. Compliance with the WMA Code of Ethics of the World Medical Association WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects 2013 (protocol of the meeting of the bioethics commission of the Odessa National Medical University No. 176a of 11/14/2019) was determined. All study participants were informed and agreed to the processing of their clinical data and participation in the research process.

Statistical analysis of the data was carried out using the GNU PSPP program version 1.2.0. Kaplan-Meier survival curves were constructed; the Log Rank test and a special case of the Peto & Peto modification of the Gehan-Wilcoxon test were used for statistical comparison.

Results

In the analysis of the first group of patients (the time interval before the start of ACT to 1 month), we obtained a variable series of periods (in months) between the start of special treatment and the establishment of death from the underlying disease and / or its complications: 10, 10, 12, 14, 15, 15, 16, 17, 18, 18, 19, 19, 20, 21, 22, 25, 26, 33, 35, 39, 43, 43, 43, 51, 53, 56, 63, 85, 101, 126. Variation indices: weighted average — 36, mode — 43, median — 26, standard deviation — 27.513.

In the analysis of the second group of patients (the time interval before the start of ACT from 2 to 6 months), we obtained a variable series of periods (in months) between the start of special treatment and the establishment of death from the underlying disease and / or its complications: 5, 5, 5, 5, 6 , 6, 12, 12, 12, 12, 14, 14, 18, 18, 19, 19, 19, 19, 19, 19, 19, 19, 19, 19, 27, 27, 35, 35, 40, 40. Variation indices: weighted average — 18, mode — 19, median — 19, standard deviation — 9.76.

Survival functions and confidence intervals are calculated using the obtained variational series, a table of the lifetime is constructed (Tab. 1.1, 1.2, 2). Kaplan-Meier plots were constructed for a graphical interpretation of the results (Fig. 1). Log Rank criterion was used to test the hypothesis of various survival rates in groups: xi-square 10.485957, $p = 0.001203$ ($p < 0.05$), and a special case of the Peto & Peto modification of the Gehan-Wilcoxon test: xi-square 8.493086, $p = 0.003565$ ($p < 0.05$)

Discussion of the results

The results demonstrate an increase in OS of patients who underwent CC-0 PDS with early ACT initiation. Intraoperative seeding by tumor cells is one of the reasons for the growth of residual micrometastases in the interval between surgical resection of the tumor and chemotherapeutic treatment. Such micrometastases are most sensitive to chemotherapeutic treatment. An important factor in the growth of residual tumor mass may be immune suppression in the early postoperative period and the production of pro-inflammatory cytokines. A mechanical effect on the tumor mass causes changes in the cell

Table 1.1. Group I (< 1 month interval)

Time period (months)	At risk	Died	Survival probability estimate	0.95 Confidence interval lower limit	0.95 Confidence interval upper limit	Time period (months)	At risk	Died	Survival probability estimate	0.95 Confidence interval lower limit	0.95 Confidence interval upper limit
1	30	0	1	0.85868	1	33	13	1	0.4	0.232234	0.592497
2	30	0	1	0.85868	1	34	12	0	0.4	0.232234	0.592497
3	30	0	1	0.85868	1	35	12	1	0.366667	0.205428	0.560919
4	30	0	1	0.85868	1	36	11	0	0.366667	0.205428	0.560919
5	30	0	1	0.85868	1	37	11	0	0.366667	0.205428	0.560919
6	30	0	1	0.85868	1	38	11	0	0.366667	0.205428	0.560919
7	30	0	1	0.85868	1	39	11	1	0.333333	0.179376	0.528626
8	30	0	1	0.85868	1	40	10	0	0.333333	0.179376	0.528626
9	30	0	1	0.85868	1	41	10	0	0.333333	0.179376	0.528626
10	30	2	0.933333	0.764928	0.988368	42	10	0	0.333333	0.179376	0.528626
11	28	0	0.933333	0.764928	0.988368	43	10	3	0.333333	0.179376	0.528626
12	28	1	0.9	0.723237	0.973812	44	10	0	0.233333	0.10635	0.427002
13	27	0	0.9	0.723237	0.973812	45	7	0	0.233333	0.10635	0.427002
14	27	1	0.866667	0.683577	0.956403	46	7	0	0.233333	0.10635	0.427002
15	26	2	0.8	0.608693	0.915952	47	7	0	0.233333	0.10635	0.427002
16	24	1	0.766667	0.572998	0.89365	48	7	0	0.233333	0.10635	0.427002
17	23	1	0.733333	0.538273	0.870245	49	7	0	0.233333	0.10635	0.427002
18	22	2	0.666667	0.471374	0.820624	50	7	0	0.233333	0.10635	0.427002
19	20	2	0.6	0.407503	0.767766	51	7	1	0.2	0.084048	0.391307
20	18	1	0.566667	0.376614	0.740245	52	6	0	0.2	0.084048	0.391307
21	17	1	0.533333	0.346399	0.712034	53	6	1	0.166667	0.063036	0.35451
22	16	1	0.5	0.31685	0.68315	54	5	0	0.166667	0.063036	0.35451
23	15	0	0.5	0.31685	0.68315	55	5	0	0.166667	0.063036	0.35451
24	15	0	0.5	0.31685	0.68315	56	5	1	0.133333	0.043597	0.316423
25	15	1	0.466667	0.287966	0.653601	57	4	0	0.133333	0.043597	0.316423
26	14	1	0.433333	0.259755	0.623386	58	4	0	0.133333	0.043597	0.316423
27	13	0	0.433333	0.259755	0.623386	59	4	0	0.133333	0.043597	0.316423
28	13	0	0.433333	0.259755	0.623386	60	4	0	0.133333	0.043597	0.316423
29	13	0	0.433333	0.259755	0.623386	61	4	0	0.133333	0.043597	0.316423
30	13	0	0.433333	0.259755	0.623386	62	4	0	0.133333	0.043597	0.316423
31	13	0	0.433333	0.259755	0.623386	63	4	1	0.1	0.026188	0.276763
32	13	0	0.433333	0.259755	0.623386	64	3	0	0.1	0.026188	0.276763

structure, in the microenvironment of tumor cells, as well as changes in their participation in the cell division cycle and the metastatic process. An increase in the amount of mitotically active cells makes them more sensitive to chemotherapeutic drugs that affect the cell division cycle (for example, taxanes). Another factor affecting the increase in the growth rate of residual tumor cells is an increase in the production of angiogenesis factors.

In a study by Tewari K.S. et al. from the materials of phase III of a randomized, double-blind, placebo-controlled trial, the Gynecological Oncology Group protocol 218 obtained similar data on the increase in OS of patients with advanced ovarian cancer with ACT initiation up to 25 days from PDS [9]. Timmermans M. et al. proved that delayed ACT initiation is an independent predictor of OS reduction after cytoreductive surgery,

Table 1.2. Group I (< 1 month interval)

Time period (months)	At risk	Died	Survival probability estimate	0.95 Confidence interval lower limit	0.95 Confidence interval upper limit	Time period (months)	At risk	Died	Survival probability estimate	0.95 Confidence interval lower limit	0.95 Confidence interval upper limit
65	3	0	0.1	0.026188	0.276763	96	2	0	0.066667	0.011632	0.235072
66	3	0	0.1	0.026188	0.276763	97	2	0	0.066667	0.011632	0.235072
67	3	0	0.1	0.026188	0.276763	98	2	0	0.066667	0.011632	0.235072
68	3	0	0.1	0.026188	0.276763	99	2	0	0.066667	0.011632	0.235072
69	3	0	0.1	0.026188	0.276763	100	2	0	0.066667	0.011632	0.235072
70	3	0	0.1	0.026188	0.276763	101	2	1	0.033333	0.001742	0.19053
71	3	0	0.1	0.026188	0.276763	102	1	0	0.033333	0.001742	0.19053
72	3	0	0.1	0.026188	0.276763	103	1	0	0.033333	0.001742	0.19053
73	3	0	0.1	0.026188	0.276763	104	1	0	0.033333	0.001742	0.19053
74	3	0	0.1	0.026188	0.276763	105	1	0	0.033333	0.001742	0.19053
75	3	0	0.1	0.026188	0.276763	106	1	0	0.033333	0.001742	0.19053
76	3	0	0.1	0.026188	0.276763	107	1	0	0.033333	0.001742	0.19053
77	3	0	0.1	0.026188	0.276763	108	1	0	0.033333	0.001742	0.19053
78	3	0	0.1	0.026188	0.276763	109	1	0	0.033333	0.001742	0.19053
79	3	0	0.1	0.026188	0.276763	110	1	0	0.033333	0.001742	0.19053
80	3	0	0.1	0.026188	0.276763	111	1	0	0.033333	0.001742	0.19053
81	3	0	0.1	0.026188	0.276763	112	1	0	0.033333	0.001742	0.19053
82	3	0	0.1	0.026188	0.276763	113	1	0	0.033333	0.001742	0.19053
83	3	0	0.1	0.026188	0.276763	114	1	0	0.033333	0.001742	0.19053
84	3	0	0.1	0.026188	0.276763	115	1	0	0.033333	0.001742	0.19053
85	3	1	0.066667	0.011632	0.235072	116	1	0	0.033333	0.001742	0.19053
86	2	0	0.066667	0.011632	0.235072	117	1	0	0.033333	0.001742	0.19053
87	2	0	0.066667	0.011632	0.235072	118	1	0	0.033333	0.001742	0.19053
88	2	0	0.066667	0.011632	0.235072	119	1	0	0.033333	0.001742	0.19053
89	2	0	0.066667	0.011632	0.235072	120	1	0	0.033333	0.001742	0.19053
90	2	0	0.066667	0.011632	0.235072	121	1	0	0.033333	0.001742	0.19053
91	2	0	0.066667	0.011632	0.235072	122	1	0	0.033333	0.001742	0.19053
92	2	0	0.066667	0.011632	0.235072	123	1	0	0.033333	0.001742	0.19053
93	2	0	0.066667	0.011632	0.235072	124	1	0	0.033333	0.001742	0.19053
94	2	0	0.066667	0.011632	0.235072	125	1	0	0.033333	0.001742	0.19053
95	2	0	0.066667	0.011632	0.235072	126	1	1	0	0	0.14132

Table 2. Group II (2–6 months interval)

Time period (months)	At risk	Died	Survival probability estimate	0.95 Confidence interval lower limit	0.95 Confidence interval upper limit
1	30	0	1	0.85868	1
2	30	0	1	0.85868	1
3	30	0	1	0.85868	1
4	30	0	1	0.85868	1
5	30	4	0.866667	0.683577	0.956403
6	26	2	0.8	0.608693	0.915952
7	24	0	0.8	0.608693	0.915952
8	24	0	0.8	0.608693	0.915952
9	24	0	0.8	0.608693	0.915952
10	24	0	0.8	0.608693	0.915952
11	24	0	0.8	0.608693	0.915952
12	24	4	0.666667	0.471374	0.820624
13	20	0	0.666667	0.471374	0.820624
14	20	2	0.6	0.407503	0.767766
15	18	0	0.6	0.407503	0.767766
16	18	0	0.6	0.407503	0.767766
17	18	0	0.6	0.407503	0.767766
18	18	2	0.533333	0.346399	0.712034
19	16	10	0.2	0.084048	0.391307
20	6	0	0.2	0.084048	0.391307
21	6	0	0.2	0.084048	0.391307
22	6	0	0.2	0.084048	0.391307
23	6	0	0.2	0.084048	0.391307
24	6	0	0.2	0.084048	0.391307
25	6	0	0.2	0.084048	0.391307
26	6	0	0.2	0.084048	0.391307
27	6	2	0.133333	0.043597	0.316423
28	4	0	0.133333	0.043597	0.316423
29	4	0	0.133333	0.043597	0.316423
30	4	0	0.133333	0.043597	0.316423
31	4	0	0.133333	0.043597	0.316423
32	4	0	0.133333	0.043597	0.316423
33	4	0	0.133333	0.043597	0.316423
34	4	0	0.133333	0.043597	0.316423
35	4	2	0.066667	0.011632	0.235072
36	2	0	0.066667	0.011632	0.235072
37	2	0	0.066667	0.011632	0.235072
38	2	0	0.066667	0.011632	0.235072
39	2	0	0.066667	0.011632	0.235072
40	2	2	0	0	0.14132
41	0	0	0	0	0

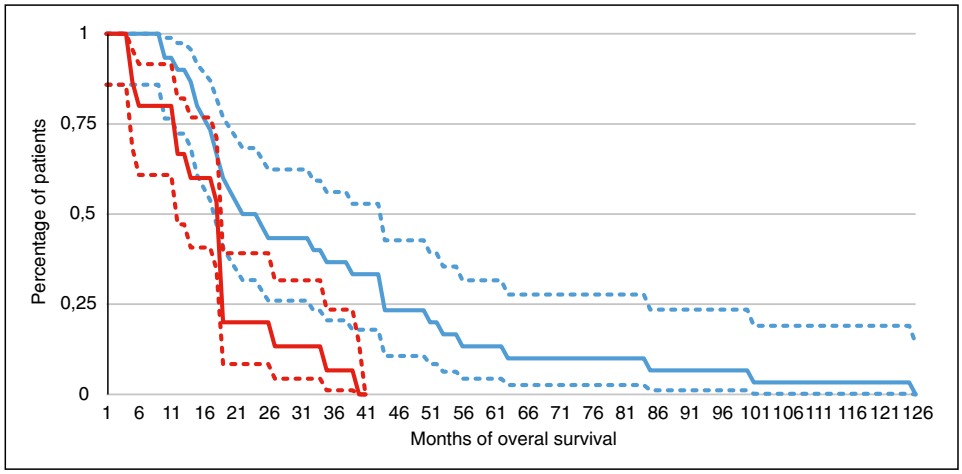

Figure 1. The distribution graphs of the survival of patients I — blue graph (the time interval before the start of ACT to 1 month) and II — red graph (the time interval before the start of ACT from 2 to 6 months) of the Kaplan-Mayer groups with the 0.95 confidence interval shown by dotted lines

and determined the optimal interval of 5–6 weeks [10]. Seagle B.L. et al. performed a retrospective cohort study in patients who underwent special treatment according to the National Comprehensive Cancer Network guideline for 1998-2011 and determined an improvement in survival after ACT initiation within 21–35 days from PDS [11]. In a study by Joseph N. et al., patients with advanced ovarian cancer in the age group of 65 years were considered. Such patients quite often need to reduce the doses of ACT, as well as to delay its initiation. The postponement of ACT is determined by an independent factor associated with a decrease in OS [12]. Similar results were also obtained by Liu Y. et al. in a meta-analysis of 14 studies with 59.569 patients with ovarian cancer. A decrease in OS with a prolonged interval prior to initiation of ACT was found, especially among patients with advanced ovarian cancer [13]. Lee Y. Y. et al. also noted a negative effect on OS with an increase in the intervals between the stages of special treatment of advanced epithelial ovarian cancer [14].

A similar effect is also exerted by a decrease in time between ACT cycles, which was reviewed by Starbuck K.D. et al. In their results, even short delays in the passage of all cycles lead to a progressive decrease in OS [15].

According to Olawaiye A.B. et al. another factor is dose modification in ACT regimens with carboplatin and paclitaxel. Dose reduction and delayed admission increases the risk of disease progression and reduces the OS of patients with advanced ovarian cancer [16].

The results of the Garcia-Soto A.E. et al. study are contradictory. There was demonstrated the lack of effect of time before initiation of adjuvant intraperitoneal chemotherapy on relapse-free survival and OS [17].

Lee Y.J. et al. noted the effect on OS of the time interval from completion of neoadjuvant chemotherapeutic treatment to initiation of ACT in patients with ovarian cancer [18].

In a study, Chen M. et al. demonstrated a decrease in relapse-free survival over a time interval from completion of neoadjuvant chemotherapeutic treatment to cytoreductive surgery for more than 4 weeks, and the absence of the effect of this interval on OS [19].

Jeong S.J et al. noted the absence of a decrease in OS with delayed ACT after secondary cytoreductive surgery due to the progression of ovarian cancer disease [20].

Important prognostic factors for delaying the initiation of chemotherapeutic treatment in patients were postoperative complications, which were often caused by the most aggressive surgical approach to achieve CC-0. It resulted in long periods of stay in a surgical hospital. The treatment opportunities of the oncology center have a great influence on the possibilities of early initiation of ACT because they determine the period of postoperative recovery of the patient and the increase in options for further special treatment of residual disease.

Study Limitations

This study was a single center, retrospective and nonrandomized. The histological subtypes of ovarian adenocarcinoma of each patient, the degree of differentiation of the tumors, and the Ki67 proliferation index, which probably had a slight effect on the homogeneity of the patient samples, were not taken into account when the groups were formed.

Prospects for further research

The study of the effect of the interval between neoadjuvant chemotherapeutic treatment and cytoreductive

surgery is also promising. Comparison of the effectiveness of neoadjuvant chemotherapeutic treatment and further cytoreductive surgery with PDS and adjuvant chemotherapeutic treatment at different intervals between the stages of each of the combined treatment regimens, assessing the quality of life of patients with different options and different treatment intensities is also relevant.

Conclusions

The results demonstrate a statistically significant difference in the overall survival of patients with advanced ovarian adenocarcinoma (FIGO IIIC–IV) who underwent optimal PDS and ACT according to the standard regimen in a time interval of up to one month compared to the group of patients with a delay of the second stage of treatment by 2–6 months. Thus, delaying the onset of ACT is an independent predictor of the worse OS after performing PDS. The results of our study highlight the importance of minimizing delays before starting adjuvant chemotherapy. According to the data obtained, patients should start ACT within 1 month after surgery, which is predictive in achieving CC-0 in PDS.

Conflict of interest: *The authors declare that there is no conflict of interest regarding the publication of this article.*

Abbreviations:

ACT — adjuvant chemotherapeutic treatment
OS — overall survival
PDS — primary cytoreductive surgery
CC — completeness of cytoreduction

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