Neoadjuvant chemotherapy for advanced epithelial ovarian carcinoma: a retrospective case-control study

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Summary

Neoadjuvant chemotherapy has been proposed as an alternative approach to primary cytoreductive surgery as initial management of bulky ovarian cancer with the aim of improving surgical efficiency and quality of life. The data of a retrospective case-control study including 75 patients with advanced epithelial ovarian carcinoma Stages IIIC and IV are presented. In 20 patients, neoadjuvant chemotherapy (3-5 cycles of cytostatics) was applied before cytoreductive surgery which was followed by chemotherapy, six cycles in total. In 55 patients cytoreductive surgery was applied as the primary treatment followed by six cycles of chemotherapy. A comparison of both groups of patients showed no significant difference regarding patient age, tumor stage, grade and treatment modality (chemotherapy and surgery, without irradiation) applied cytostatics and total number of chemotherapeutic cycles. The data from our study confirmed a statistically significant difference in radicality of cytoreduction that was more extensive when applied in combination with neoadjuvant chemotherapy than when applied as primary cytoreductive surgery ($p = 0.009$). No statistically significant difference was found in the survival of the two groups ($p = 0.79$), the response to primary treatment ($p = 0.52$), relapse ($p = 0.88$) or disease-free survival ($p = 0.61$). From the findings of the study and literature review, we may conclude that neoadjuvant chemotherapy followed by interval debulking surgery in patients with advanced epithelial ovarian carcinoma does not have an unfavorable effect on the prognosis.

Key words: Neoadjuvant chemotherapy; Primary cytoreductive surgery; Advanced ovarian cancer.

Introduction

Epithelial ovarian carcinoma is one of the most common gynecological malignancies with half of all cases occurring in women over age 65. Epithelial ovarian carcinoma is often a rapidly fatal disease with yearly mortality approximately 65%. Today, we still do not have proven methods for screening or prevention.

In Slovenia, the incidence of ovarian cancer in 1998 was 17.3/100,000. Epithelial ovarian carcinoma is the first cause of death among gynecological malignancies and the fourth among all female malignancies [1].

In the 1970s it became apparent that the presence of residual disease after surgery is one of the most important adverse prognostic factors for survival [2]. It was accepted that patients with advanced ovarian cancer should undergo extensive tumor-debulking or cytoreductive surgery to remove all macroscopic tumor. There is considerable evidence that the volume of the residual tumor after the primary surgical procedure is related to patient survival [3]. However no prospective randomized controlled trials concerning the role of primary cytoreductive surgery in advanced ovarian carcinoma have been performed. Primary cytoreductive surgery should be performed in cancer centers with specific expertise. Cooperation between gynecological oncologists, abdominal surgeons and anesthesiologists is essential. The rate of optimal primary cytoreductive surgery in cancer centers with particular gyneco-oncological expertise is between 60-90%, compared with general results, which are between 20-30% [4].

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In the past 20 years the definition of optimal primary cytoreductive surgery has changed from the largest residual tumor of 2 cm to less than 0.5 cm [4-6]. Recently, it was proposed that the definition of optimal primary cytoreductive surgery should consider total residual tumor load. According to this new definition, total residual tumor load in optimal cytoreductive surgery should be 0-1 g, (i.e., less than 1 cm in diameter) [7].

Primary cytoreductive surgery followed by chemotherapy is the current treatment applied in patients suspected of having advanced ovarian cancer. Neoadjuvant chemotherapy has been proposed as an alternative approach to conventional surgery as the initial management of bulky ovarian cancer with the aim of improving surgical efficiency and quality of life [8-14]. According to the results of epidemiological studies, neoadjuvant chemotherapy may have a positive impact on the tumor resection rate and median survival time [15-18]. The fact is that patients with initial chemoresistance have a poor prognosis regardless of treatment modality. Neoadjuvant chemotherapy for primary unresectable ovarian carcinoma could lead to the selection of a subset of patients sensitive to chemotherapy in whom optimal cytoreduction can be achieved after chemotherapy by standard surgery in a high proportion of cases. Conversely, aggressive surgery can be avoided in patients with initial chemoresistance in whom the prognosis is known to be poorer regardless of treatment modality [17].

General acceptance of neoadjuvant chemotherapy as an alternative to primary surgery for a subset of patients remains limited because equal or better survival has not yet been demonstrated in prospective randomized trials

[7, 17]. A prospective randomized trial of neoadjuvant chemotherapy and primary cytoreductive surgery is currently going on. Until its completion, the results from retrospective studies could also be noteworthy.

In view of providing some additional information about neoadjuvant chemotherapy, data from a retrospective case-control study including patients with advanced epithelial ovarian carcinoma Stages IIIC and IV are presented.

Materials and Methods

The study included 298 patients treated for invasive epithelial ovarian carcinoma from January 1996 to December 1998 at two central Slovenian institutions specialized in ovarian cancer treatment, i.e., the Department of Gynecology and Obstetrics of the University Medical Center of Ljubljana and the Institute of Oncology of Ljubljana. The chemotherapeutic schedules were calculated by an oncologist from the Institute of Oncology and also applied under the oncologist's control.

Stage I disease was detected in 73/298 patients (24%), stage II in 38/298 (12%), stage III in 152/298 patients (51%), and stage IV in 35/298 patients (13%).

Of the total number of patients with invasive ovarian cancer, 75 patients were eligible for the study. Seventy-five patients had epithelial ovarian cancer of a considerably large tumor mass in advanced stage, i. e. in Stages IIIC and IV (cytologically confirmed distant metastases in addition to positive cytology of pleural effusion). None of the 75 patients had any medical contraindications for surgical treatment. In 20/75 patients (27%), neoadjuvant chemotherapy (3-5 cycles of cytostatics) was applied before cytoreductive surgery which was followed by chemotherapy, six cycles in total, whereas 55/75 patients (73%) had cytoreductive surgery as primary treatment followed by six cycles of chemotherapy. In order to make an unbiased comparison, only the patients who received exclusively platinum-based chemotherapy (without taxanes) in combination with other cytostatics were included in the study. In all patients who received neoadjuvant chemotherapy, the diagnosis was confirmed by laparoscopy or explorative laparotomy. Primary cytoreductive surgery was in all cases more or less radical. In all patients included in the study the pathohistological diagnosis of ovarian carcinoma was made by experts in pathology from the Institute of Oncology and from the Department of Gynecology and Obstetrics of the University Medical Center of Ljubljana.

Patients who received more than four cycles of neoadjuvant chemotherapy prior to cytoreductive surgery or some other treatment modality, e.g. altogether more than six cycles of chemotherapy, irradiation, etc., were not included in the study, nor were patients who were not followed up at the Institute or Department of Gynecology, whose cause of death was not known or was other than carcinoma, who had ovarian tumors of low malignancy grade or secondary malignancies.

The observation period was three to five years.

Fisher's p-test was used to evaluate statistical significance. Survival was computed by the Kaplan-Meier method and compared with the log-rank test.

Results

The average age of patients who had neoadjuvant chemotherapy (group A) was 65 years and of patients with primary cytoreductive surgery (group B) 63.5 years. The majority of patients had Stage IIIC, poorly differentiated, epithelial carcinoma of the ovarium. The difference between the two groups with respect to age, stage, and differentiation of tumor was not statistically significant (Table 1). In three patients in group A, Stage IV of the disease was established due to metastases detected in the supraclavicular lymph nodes, sigmoid colon and umbilicus. In group B, one patient had distant metastases in the supraclavicular lymph nodes, two in the vagina and three in the umbilical region.

The most frequent pathohistological diagnosis in both groups of patients was serous epithelial invasive carcinoma of the ovaria. In group A, the above diagnosis was confirmed in 95% of patients and in group B in 73%. The incidence (descending order) of other types of carcinoma was as follows: endometroid, mucinous and clear-cell carcinoma (one patient of the group was treated with primary surgery).

A statistically significant difference between the two groups was established only in assessing the success of cytoreduction (Table 1). In group A, 40% of patients were without macroscopic residual tumor after surgery while in group B only 11% were without. The difference ($p = 0.009$) was statistically significant. This difference is still significant even if the group without residual tumor is extended to also include the patients with residual tumor of 1 cm in diameter after surgery. Hence, group A had 12 patients (60%) without macroscopic residual tumor or residual tumor less than 1 cm in diameter, whereas in group B the share of patients without residual tumor after surgery was 12% (22 patients) ($p = 0.001$). Residual tumor larger than 1 cm in group B was observed in 43 cases (78%), whereas in group A eight patients (40%) had residual tumor larger than 1 cm ($p = 0.001$).

Table 1. — *Distribution of patient characteristics in the group of patients with neoadjuvant chemotherapy and in the group of patients with primary cytoreductive surgery.*

Patient Characteristics	Neoadjuvant chemotherapy n=20 (100%)	Primary cytoreductive surgery n=55 (100%)	p
Age at diagnosis (yrs)	65 (40-77)	63.5 (39-78)	0.62
Stage			
III c	85%	87%	0.79
IV	15%	13%	
Differentiation			
1	5%	4%	0.78
2	30%	25%	0.69
3	65%	71%	0.62
Diameter of residual implants:			
no macroscopic RD	40%	11%	0.009*
less than 1 cm	20%	11%	0.20
1 cm or more	40%	78%	0.001*
Chemotherapy - full courses:			
completed	95%	89%	0.43
uncompleted	5%	11%	

P* = statistically significant difference.
RD = residual disease.

Table 2. — *Results of treatment in the group of patients with neoadjuvant chemotherapy and in the group of patients with primary cytoreductive surgery.*

Variable	Neoadjuvant chemotherapy n=20 (100%)	Primary cytoreductive surgery n=55 (100%)	p
Response to first treatment			
CR or PR	80%	73%	0.52
stable disease		7%	
progressive disease	5%	10%	0.26
not assessable	15%	10%	0.49
Relapse:			
yes	85%	84%	0.88
no	15%	16%	
Vital status:			
alive with NED	15%	18%	0.75
Alive with disease		7%	
Deceased	85%	75%	0.33
Medium survival (months)	25 (7-68)	26 (2-69)	0.79

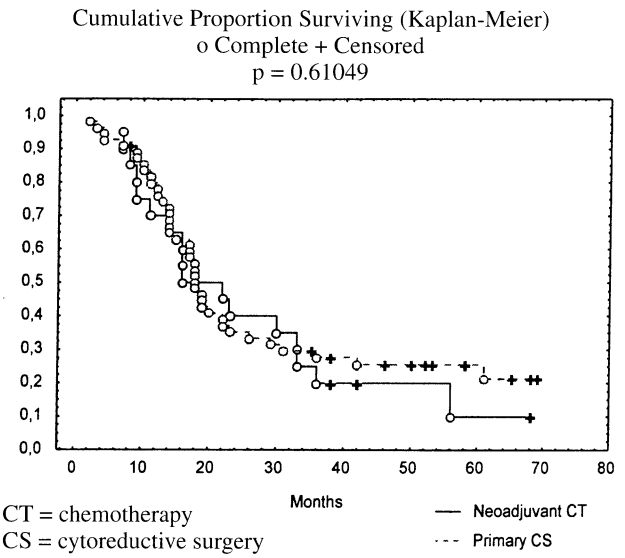
P* = statistically significant difference.
RD = residual disease.
CR = complete response.
PR = partial response.
NED = non residual disease.

In group A one or no residual implant was found in five cases (25%) after cytoreductive surgery, while in group B one or no residual implant was detected in six cases (11%). Six or more residual implants were observed in 35% of patients of group A and in 58% of patients of group B. A unilateral or bilateral oophorectomy was performed in one patient (5%) of group A and in 11 patients (20%) of group B. Hysterectomy, bilateral oophorectomy and omentectomy were performed in ten patients (50%) of group A and in 38 patients (68%) of group B. Paraaortal and/or pelvic lymphadenectomy in addition to hysterectomy, bilateral oophorectomy and omentectomy was performed in 40% of patients in group A and in 5% of patients in group B.

Complete chemotherapy of six cycles was applied in 95% of patients of group A and in 89% of patients of group B. The difference between the two groups was not statistically significant (p = 0.43) (Table 1). Complete or partial response to treatment was observed in 80% of patients of group A and 73% of patients of group B. As to the response to treatment, the difference between groups A and B was not statistically significant either (p = 0.52) (Table 1).

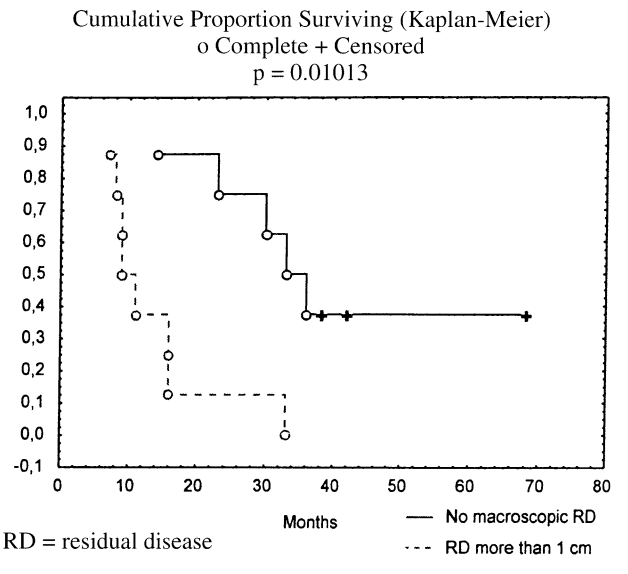
Relapse was observed in 17/20 patients (85%) of group A and in 45/55 patients (84%) of group B. The difference was not statistically significant (p = 0.31) (Table 2), neither was it in the case of disease-free survival from diagnosis of the disease to relapse (p = 0.56107). Simultaneous local and systemic relapses were observed in both groups at a similar percentage; in 50% of patients in group A and in 41% of patients in group B.

By the end of the observation period, 3/20 patients (15%) survived in group A and 10/55 patients (18%) in group B (Table 2). Among the survivors in group B, four had relapsed, whereas among the survivors treated with neoadjuvant chemotherapy no one had relapsed. In group A 17/20 patients (85%) died and in group B (treated with primary cytoreductive therapy) 41/55 patients (75%) died. In all cases the cause of death was the progression of ovarian cancer. As for survival, the difference between both groups was not statistically significant (p = 0.50). The median survival of group A and group B was 24.7 months (7-68 months) and 26 months (2-69), respecti-



CT = chemotherapy
CS = cytoreductive surgery

Figure 1. — Cumulative proportion survival in the group of patients with neoadjuvant chemotherapy and in the group of patients with primary cytoreductive surgery as estimated by the Kaplan-Meier method.



RD = residual disease

Figure 2. — Cumulative proportion survival, estimated by the Kaplan-Meier method, in the group of patients with no macroscopic residual disease and in the group of patients with more than 1 cm residual disease after surgery (both with neoadjuvant chemotherapy).

vely. Again, the difference was not statistically significant (p = 0.79) (Table 2). The survival curves of both groups were calculated by the Kaplan-Meier method. Both curves are shown in Figure 1.

In both groups, the one treated with neoadjuvant chemotherapy and the one treated with primary cytoreductive surgery, longer survival was observed in patients who were without macroscopic residual tumor after cytoreductive surgery than in those with residual tumor larger than 1 cm. In both cases the difference was statistically significant (Figures 2, 3).

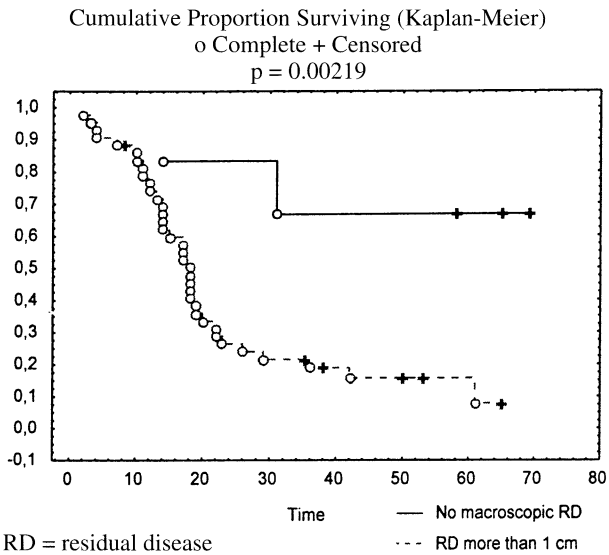


Figure 3. — Cumulative proportion survival, estimated by the Kaplan-Meier method, in the group of patients with no macroscopic residual disease and in the group of patients with more than 1 cm residual disease after surgery (both with primary cytoreductive surgery).

Discussion

From the non-randomized research studies that have been thus far performed on patients with ovarian cancer, it may be concluded that the size of residual tumor has a major influence on prognosis. [19, 20]. Patients without residual tumor have the best prognosis with regard to survival and to quality of life [2-7, 21]. In some patients with very advanced disease (Stages IIIC and IV) complete excision of the tumor is not feasible despite the high skill and effectiveness in cytoreductive surgery of the personnel in certain centers [22]. Even after a strongly mutilating surgical intervention and application of the latest cytostatics, the survival and quality of life of these patients is usually low [15].

In addition to radical cytoreductive surgery, the responsiveness of tumor to chemotherapy also has a strong effect on the prognosis of patients with ovarian cancer. From a pathohistological view, cytoreductive surgery improves the effectiveness of chemotherapy, particularly on account of its capacity to reduce the whole tumor mass, thereby also limiting the number of spontaneous mutations and improving the general performance status. However, recent findings have shown that survival of patients who are non-responsive to chemotherapy is extremely low, regardless of the radicality of the surgical intervention [17].

Regarding the results of the latest studies, neoadjuvant chemotherapy entails the exclusion of patients who are non-responsive to chemotherapy, thereby allowing a more radical cytoreduction – in most cases in only one intervention [23, 24]. The principal question of all non-randomized studies that have been published so far on this topic was whether the survival of patients after cytoreductive surgery and several cycles of neoadjuvant chemotherapy was worse, the same, or better in comparison to the survival after standard treatment. In the majority of these studies, it has been concluded that the survival of patients after neoadjuvant chemotherapy followed by cytoreductive surgery is no worse than the survival of the patients after primary cytoreduction [8-14]. The latest studies even assume that survival is even better after neoadjuvant chemotherapy and cytoreductive surgery [15-18]. Nonetheless, we cannot give any definitive answer because we do not have the results of prospective non-randomized studies that are still going on.

It is sensible to select the patients in whom primary cytoreduction is presumed to be unsuccessful. The application of neoadjuvant chemotherapy might improve their quality of life or even their survival [4, 7].

In our study, we therefore included only the patients who, with reference to their absolute as well as to their relative indications, met the criteria to be selected for neoadjuvant chemotherapy proposed by Verboten [4]. All our patients with Stage IV disease had cytologically confirmed distant metastases in addition to positive cytology for pleural effusion.

The main deficiencies of our research, as well as of others dealing with similar subject matter, are the small number of patients and retrospective approach. In order to avoid the risk of bias, we selected two highly comparable and homogeneous groups of patients. The comparison of both groups of patients – the group of patients treated with neoadjuvant chemotherapy (group A) and the group treated with primary cytoreduction (group B) – showed no significant difference for patient age and tumor stage, grade, treatment modality (chemotherapy and surgery, without irradiation) applied cytostatics and total number of chemotherapeutic cycles.

As for the age of patients [14], tumor stage [8-18], treatment modality [10, 14, 17, 18] and applied cytostatics [15-18], the patients from other similar studies were more heterogeneous than those from our study.

In the majority of published studies on the treatment of patients with the advanced ovarian carcinoma, better treatment results were reported with cytoreductive surgery after neoadjuvant chemotherapy than with primary cytoreductive surgery alone [8-18]. The data from our study also confirm more extensive radicality of cytoreduction when applied in combination with neoadjuvant chemotherapy than when applied as primary cytoreductive surgery; this may be noted in a significantly greater percentage of patients without macroscopic

residual tumor or with residual tumor less than 1 cm in diameter and in a larger percentage of patients with a minimum number of residual implants as well in a larger percentage of patients with optimal radical surgical intervention.

The aim of our study was not to assess the morbidity of patients. However, from the data that an additional surgical intervention due to resection of the colon or bladder was less frequent in our patients who were treated with neoadjuvant chemotherapy, and that the majority of patients could continue with chemotherapy the 10^{th} or 14^{th} day after surgery, we may conclude that the morbidity of these patients was lower, thereby their quality of life much higher.

The results of other studies aimed at evaluating the morbidity and mortality of patients speak in favor of lower morbidity [9, 13, 17, 18] and an unchanged or even reduced mortality rate of patients treated with radical surgery after neodjuvant chemotherapy [17, 18].

In our study as well as in a number of other similar studies, no statistically significant difference was found between the survival of the group of patients treated with neoadjuvant chemotherapy (median survival 25 months) and the group treated with primary surgery (median survival 26 months). (8-14) We did not observe any statistical difference between the two groups as regards the response to primary treatment (CR, PR, progress), relapse or disease-free survival.

In contrast to more recent studies that also took into account the patients treated with taxanes in the data analysis, [14, 17, 18] we excluded these patients from our study in view of a more objective, unbiased comparison, and uneven distribution in both groups. The assumption made in some of the latest studies that the patients treated with platinum-taxane-based chemotherapy have better survival, will be proven true only after obtaining the results of the prospective randomized studies that are still going on [15].

The question concerning the biology of tumors which may affect the outcome of cytoreductive surgery as well as the efficiency of chemotherapy has remained unanswered [4, 14]. Although the number of patients included into our study is small, we may nevertheless conclude that our data speak in favor of a better survival in patients without macroscopic residual disease than in those with residual tumor larger than 1 cm. In both groups of patients – the one treated with neoadjuvant chemotherapy and the one treated with primary cytoreductive surgery – the survival was statistically significantly better in the patients with no macroscopic tumor residue after surgery.

Conclusion

From the findings of our study and from the literature review, we may conclude that chemotherapy followed by interval debulking surgery in patients with advanced epithelial ovarian carcinoma does not worsen the prognosis.

There is substantial evidence that neoadjuvant or cytoreductive chemotherapy (two to four courses) followed by interval debulking surgery is a valid alternative in a selected group of patients with advanced ovarian carcinoma. Neoadjuvant chemotherapy should be applied in advanced stages of ovarian carcinoma (bulky disease) when radical surgery is most unlikely to be successful. This assumption should be confirmed in a prospective randomized trial before it is accepted as valid

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