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RESEARCH ARTICLE

DOES TIMING OF TREATMENT HAVE AN EFFECT ON SURVIVAL IN OVARIAN CARCINOMA?

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ABSTRACT

Purpose: Optimal cytoreduction (CRS) is the main treatment modality in epithelial ovarian cancer (OC). Inoperable OC at the time of diagnosis may become eligible for CRS after neoadjuvant chemotherapy (NACT). We aimed to investigate the effect of the time between NACT-CRS and CRS-adjuvant chemotherapy on survival in OC patients.
Material and Methods: Demographic and clinicopathological characteristics of sixty-nine patients with OC who underwent CRS after NACT between December 2009 and May 2020 were analyzed retrospectively.
Results: The median age was 61.1, and the median overall survival (OS) was 75.8 months. The median time from the end of NACT to CRS was 6.53 weeks, and the median time from CRS to initiation of adjuvant therapy was 4.8 weeks. The mean OS was 123.4 months in patients with a NACT-CRS interval of 6.53 weeks or less, and it was 61.6 months in patients above this period ($p>0.05$). The OS was 75.7 months in patients with an interval between CRS and adjuvant therapy of 4.8 weeks or less and 55.1 months compared to those with 4.8 weeks or more ($p>0.05$).
Conclusion: It was shown numerically, although not statistically significant, that a long time between NACT and CRS and CRS-adjuvant therapy had a negative effect on OS.

Keywords: Adjuvant chemotherapy, cytoreductive surgery, neoadjuvant chemotherapy, ovarian cancer

INTRODUCTION

Among gynecological cancers, ovarian cancers have the worst prognosis (1). Therefore, a fully performed surgery (optimal cytoreduction) is the most crucial part of the therapy. What is meant by optimal cytoreduction is visible residual tumor tissue being less than 1 cm. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic-paraaortic lymph node dissection (in the presence of suspected lymph nodes), and abdominal washing should be performed for optimal cytoreductive surgery (2). All the post optimal

cytoreduction ovarian cancers, except stage IA-IB endometrioid type ovarian carcinoma (serous and clear cell ovarian carcinoma including stage IA and ovarian carcinoma of all histological subtypes except stage IA-IB), are candidates for adjuvant chemotherapy (3). Usually, a combination regimen of 3-6 cycles of platinum (cisplatin or carboplatin) and taxane (usually paclitaxel) is used in adjuvant chemotherapy. However, since carboplatin has been shown to be equally effective and less toxic than cisplatin, the standard combination of carboplatin and paclitaxel is preferred (4).

Pre-operative neoadjuvant chemotherapy (NACT) has an important role in locally advanced and metastatic ovarian cancers. A proportion of initially inoperable patients may become eligible for optimal cytoreduction after NACT (5). The postoperative morbidity rate was higher in patients who underwent primary surgery in a randomized clinical trial by Fagotti et al. comparing immediate surgery or interval surgery after NACT, but no difference in survival was found. It has been concluded that the most important prognostic parameter affecting survival in this patient group was optimal cytoreduction (6). In patients with stage IIIC or IV ovarian cancer, no difference in efficacy and survival could be shown between performing surgery after NACT and administering chemotherapy after primary surgery. Therefore, neoadjuvant therapy becomes essential, especially in stage IIIC and IV ovarian cancer, to make unresectable patients resectable after neoadjuvant therapy and to have an optimal chance of cytoreduction. However, chemotherapy cycles should not exceed 3-4 cycles in patients undergoing neoadjuvant therapy (7). As soon as the patient can achieve optimal cytoreduction, surgery should be performed if there is also a response to chemotherapy. In a study conducted by Timmermans et al. in 2018, it was demonstrated for the first time that the time between adjuvant therapy initiation is essential for survival in patients with optimal cytoreduction after neoadjuvant therapy (8). In that study, which included more than four thousand patients and 2485 patients were in the interval surgery arm after neoadjuvant therapy, among the patients who underwent interval surgery after neoadjuvant therapy, the prognosis in those who started adjuvant chemotherapy after 37 days was found to be significantly worse than those who began treatment before 37 days. In this study, researchers emphasized that adjuvant therapy should start within six weeks after interval surgery. We aimed to investigate whether the time from the end of neoadjuvant therapy to surgery and the time from surgery to the start of adjuvant therapy influence survival in patients who received neoadjuvant therapy and were operated in our center.

MATERIAL AND METHODS

Inclusion criteria were being older than 18, diagnosed with epithelial ovarian cancer, performed NACT, and patient data from electronic databases and files. Exclusion criteria, on the other hand, were the presence of a diagnosis of non-epithelial ovarian cancer (such as sarcoma, germ cell tumor, metastasis of another tumor), the presence of a diagnosis of another malignancy other than synchronous or metachronous endometrial carcinoma (except for carcinomas in situ), surgery as first-line therapy, and inaccessibility of electronic database or file data. One hundred fourteen patients diagnosed with ovarian carcinoma and received neoadjuvant therapy in our hospital between December 2009 and May 2020 were screened. Forty-five of them were excluded from the study because they were excluded from follow-up after neoadjuvant therapy, neoadjuvant therapy was not completed, and healthy data could not be obtained from the electronic database of our hospital. The remaining 69 patients were included in our study. The patients were divided into two groups those under 65 years of age and those aged 65 and over. Differences in survival between these two age groups were examined with the Kaplan-Meier test. The time between the end of neoadjuvant therapy to surgery and the date of surgery to the start of adjuvant therapy was calculated in weeks. ROC curve was created to determine the most appropriate cut-off point; however, since reliable results could not be obtained due to the small number of patients ($p>0.05$), the median values for both periods were accepted as the cut-off point. Patients below (including) these cut-off points and those above the cut-off points were analyzed by comparing them in terms of survival. The obtained data were evaluated by nonparametric Chi-Square, Mann-Whitney U, Kruskal-Wallis, Wilcoxon tests, parametric analyzes T-test, ANOVA, and Paired T-test according to the normal distribution and data characteristics, using Statistical Program for Social Science (SPSS) version 24.0. Survival analysis was evaluated with Kaplan Meier. Median follow-up time was calculated by reverse Kaplan

Meier analysis. The statistical significance level was accepted as p<0.05. The study protocol was approved by the decision of the Beykoz University Non-Interventional Research Ethics Committee, dated 14.08.2020 and numbered 2020 / 01-03.

RESULTS

The median follow-up period in the study was 51 months. The median age of 69 patients included in the study was 61.1 (range: 35.8-82.8). The median disease-free survival (DFS) was 26.6 months, and the median overall survival (OS) was 75.8 months. The patients were divided into groups under 65 years old and 65 years old and over, based on geriatric oncology practice. Accordingly, the median OS was 75.7 months in the <65 years old group, and the OS duration was 53.2 months and shorter in the ≥65 years old group, although it was not statistically significant (p=0.352). No comorbidity was found in 26 of the patients (37.7%), only one comorbidity was present in 23 (33.3%) patients, and two or more comorbidities were present in the remaining 20 patients (29.0%). The most common comorbid diseases were type 2 diabetes and hypertension. In 87% of the patients, the tumor was in serious carcinoma histology. 4 patients (5.7%) included in the study had stage 1 or 2 diseases, and the remaining 65 patients (94.3%) had stage 3 or 4 diseases. Since four patients with stage 1 or 2 were considered medically inoperable, therapy was initiated with NACT. The sociodemographic and clinical characteristics of the patients are given in Table 1. The patients received a median of 3 cycles of NACT, and 62 (89.9%) of the patients received a carboplatin-paclitaxel combination regimen every three weeks, and 7 (10.1%) of the patients received a weekly carboplatin-paclitaxel regimen. The median CA 125 value before neoadjuvant therapy was 1051.5 (range: 7-5147). The median CA 125 value after neoadjuvant therapy was 35.5 (range: 4.8-11549), and the median CA 125 value after surgery was 29.1 (range: 5.8-4022). The pre-operative radiological acid level of 30 (43.5%) of the patients was below 500 cc, and 39 (56.5%) were 1000 cc and above. At the time of diagnosis, 13 (18.8%) patients had pleural effusion, and 56 (81.2%) patients had no pleural effusion. All 69 patients in the study were operated after NACT. Optimal cytoreductive surgery could be performed in 48 patients (69.6%) after neoadjuvant therapy, while it could not be performed in 21 patients. (30.4%). The median operative time is 270 minutes (±140 minutes).

Table 1. Patient characteristics

Characteristic	n (%)
Performance Status	
ECOG PS -0-1	58 (%84)
ECOG PS -2-3	11 (%16)
Comorbidity	
None	26 (%37,7)
Only one comorbidity	23 (%23)
≥ 2 comorbidities	20 (%29)
Age	
<65 years	58 (%84,1)
≥ 65 years	11 (%15,9)
Body mass index (BMI)	
<18,5	2 (%2,9)
18,5-24,9	15 (%21,7)
25.0-29,9	23 (%33,3)
30.0-34,9	29 (%42,0)
Menopause Status	
Post menopause	54 (%78,3)
Premenopausal	15 (%21,7)
Histological Subtype	
Serous	60 (%87)
Endometrium	3 (%4,3)
Carcinosarcoma	2 (%2,9)
Low grade serous	1 (%1,4)
Undifferentiated carcinoma	1 (%1,4)
Ovarian+endometrial	1 (%1,4)
carcinoma(endometroid)	1 (%1,4)
Not determined	

The surgeries performed on the patients and the details of these surgeries are given in Table 2. The median time from the end of neoadjuvant chemotherapy to cytoreductive interval surgery was 6.53 weeks. The median time from interval cytoreductive surgery to the start of adjuvant therapy was determined as 4.8 weeks. While the mean OS was 123.4 months in patients with a NACT-surgery interval of 6.53 weeks or less, it was 61.6 months in patients above this time. However, this difference was not statistically significant (p> 0.05). When the effect of timing of postoperative systemic chemotherapy on survival was analyzed, OS was numerically longer in patients with a time between surgery and adjuvant therapy of 4.8 weeks or less compared to the group with a duration of over 4.8 weeks. However, it was not statistically significant (75.7 months vs. 55.1 months, p=0.837) (Figure 1). Sixty-one of the patients (88.4%) received adjuvant chemotherapy after interval surgery, and the median number of chemotherapies cycles they received was 3. In the adjuvant period, three weeks of the carboplatin-paclitaxel protocol was applied to 57 (82.6%) patients, weekly carboplatin-

Table 2. Characteristics of surgical therapies

Characteristic	n (%)
Optimal Cytoreduction	
Yes	48 (%69,6)
No	21 (%30,4)
Surgical complexity	
Low	17 (%24,6)
Moderate	16 (%23,2)
High	33 (%47,8)
Not determined	3 (%4,3)
Peritonectomy	
Yes	39 (%56,5)
No	30 (%43,5)
Appendectomy	
No	43 (%62,3)
Yes	24 (%34,8)
Unknown	2 (%2,8)
Splenectomy	
Yes	66 (%95,7)
No	3 (%4,5)
Sigmoid Colon Resection	
Yes	58 (%84,1)
No	11 (%15,9)
Ostomy status	
Yes	60 (%87)
No	9 (%13)
Diaphragm Striping	
Yes	53 (%76,8)
No	16 (%23,2)
Omental Implant	
Yes	55 (%79,7)
No	14 (%20,3)
Peritoneal Implant	
Yes	58 (%84,1)
No	11 (%15,9)
Ascites Cytology	
Negative	35 (%50,7)
Positive	34 (%49,3)

paclitaxel therapy to 3 (4.3%) patients, and capecitabine-carboplatin therapy to 1 (1.4%) patient.

DISCUSSION

There is no large-scale study of the initiation time of adjuvant therapy after interval cytoreductive surgery. The timing of chemotherapy has often been discussed for initiating adjuvant chemotherapy in patients undergoing primary cytoreductive surgery. Many studies have emphasized that late initiation of chemotherapy after immediate cytoreductive surgery is associated with unfavorable survival (9). However, a definite time for the initiation of postoperative adjuvant therapy in patients who underwent primary cytoreductive surgery has not yet been defined. Tewari et al. concluded in their study that the prognosis for patients with a therapy initiation time longer than 25 days was worse than those who started therapy earlier than this period (10). Hofstetter et al., in a similar study, determined this period as 28 days (11). In a study by Lee et al., which included 711 patients, it was shown that longer than ten days after optimal cytoreductive surgery until the start of adjuvant therapy was associated with statistically significantly worse survival (12). Although many studies have been conducted on this subject, it has not been possible to determine an optimal time. Moreover, the fact that we are far from determining an optimal duration in this patient group emerges. There are much fewer data in the literature on the time from the end of neoadjuvant therapy to interval cytoreduction and from interval cytoreduction to the initiation of systemic therapy.

Although some studies have been conducted to determine the optimal adjuvant chemotherapy initiation time after interval cytoreductive surgery, no consensus has been reached on the optimal time. The median time was determined for each study group in the studies conducted. It was revealed that if the therapy start time was longer than the determined time, it had a negative effect on overall and disease-free survival. After revealing the negative impact of long adjuvant therapy initiation time after primary cytoreductive surgery on survival, the effect of the time elapsed until interval cytoreductive surgery after NACT on survival has also been a matter of interest. However, when we look at the literature, it has been noticed that there are no prospective randomized controlled studies on this subject. In a retrospective study of 224 patients in the literature, in which Liu et al. included patients with stage 3 and 4 ovarian cancer, it has been demonstrated that prolonging the duration of NACT-interval cytoreductive surgery has a negative effect on OS. Still, it has been reported that there is no significant shortening in OS when analyzed according to age, stage, and complete resection rate (13). In another retrospective study, it has been demonstrated that longer than 35.5 days between the end of NACT and the start of postoperative chemotherapy has a negative effect on progression-free survival (PSC) and OS (14). In the studies mentioned, the impact of time between the end of NACT and the start of postoperative chemotherapy on OS and PSC was investigated. Still, the effect of the time between the end of NACT and interval cytoreductive surgery, which we analyzed in our study, on OS has not been investigated before. Our study demonstrated that if the time between NACT-interval cytoreductive surgery was over 6.53 weeks, the OS was numerically shorter, although not

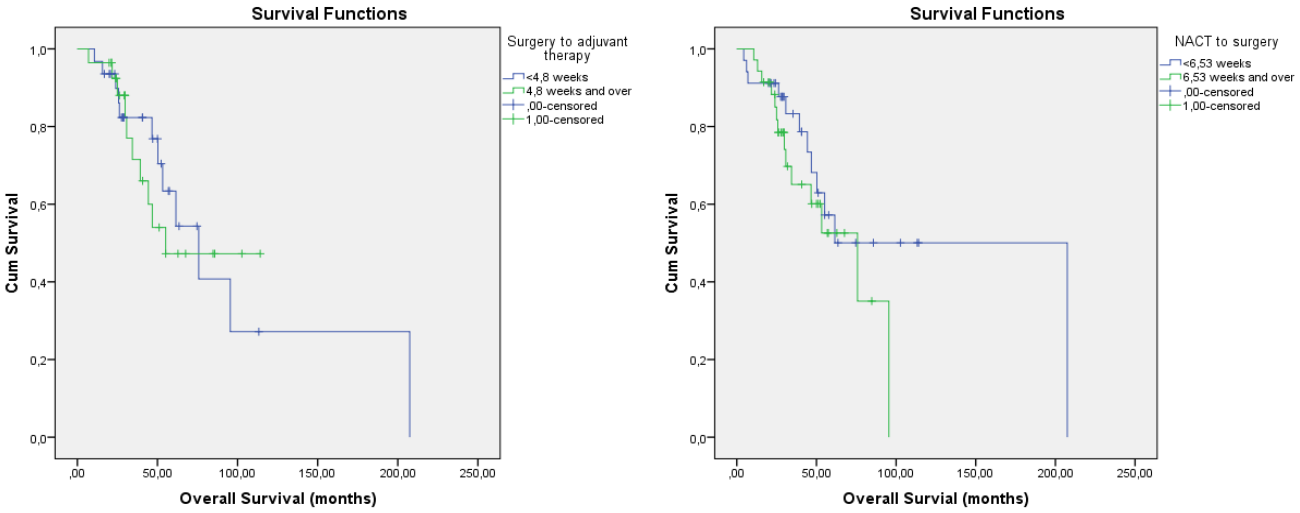

Figure 1. Effect of therapy timing on overall survival (Kaplan-Meier analysis)

statistically significant. It is known that the operation time of patients who underwent interval cytoreductive surgery after neoadjuvant chemotherapy was shorter than the group who underwent primary cytoreductive surgery. Moreover, in a study comparing the results of interval cytoreductive surgery and immediate cytoreductive surgery after NACT, the operation time of patients who underwent interval cytoreductive surgery was 253.2 minutes (6), which was similar to the operation time in our study. Some studies have shown that pre-operative average CA 125 value and low body mass index (BMI) have a positive effect on PSC and OS (14), and obesity is poor prognostic in patients diagnosed with ovarian cancer at an early age (15).

On the contrary, studies in the literature state that height, weight, and BMI are not associated with prognosis in ovarian cancer (16). Furthermore, there is no relationship between the CA 125 value measured before interval surgery and groups with different therapy times (12). Contrary to this issue, with contradictory results in the literature, it was not possible to demonstrate any effect of pre-operative CA 125 and BMI value on survival in our study.

International guidelines state that in patients diagnosed with stage 3-4 ovarian cancer, interval cytoreductive surgery should be performed after three cycles of NACT, that at least three cycles of postoperative chemotherapy should be applied after surgery, and that the number of pre-operative chemotherapy cycles should not exceed 6-8 cycles in total (17). However, Akıllı et al. showed that administration of more than three cycles of NACT in advanced-stage epithelial ovarian cancer caused chemotherapy resistance and did not contribute to the resectability status or the pathological complete response rate (18). Additionally, in another study investigating the effect of the number of NACT cycles on survival, it was reported that the R0 rate was similar in patients who were given 3,4 and 5 cycles of chemotherapy and that even five cycles or more of NACT were associated with a worse prognosis than those given 3 and 4 cycles (19). Therefore, although the number of NACT cycles does not have a clearly defined standard value, such as the timing of therapy, according to many authorities, it seems more appropriate to plan NACT in such a way that it does not exceed 3-4 cycles in ovarian carcinoma patients (20).

CONCLUSION

This study has revealed that the prolongation of the time between NACT-interval cytoreductive surgery and interval cytoreductive surgery-adjuvant chemotherapy in patients diagnosed with advanced-stage epithelial ovarian cancer, although not statistically significant, has a numerically negative effect on overall survival. The findings from this study need to be confirmed by more extensive studies.

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