RESEARCH COMMUNICATION

# Clinical Outcome of Iranian Patients with Advanced Ovarian Cancer with Neoadjuvant Chemotherapy versus Primary Debulking Surgery

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## Abstract

**Objective: The aim of this study is to evaluate the results of neoadjuvant chemotherapy (NACT) and the impact of interval debulking surgery (IDS) on clinical outcomes of patients with advanced-stage ovarian cancer. Methods: We performed a retrospective analysis on 92 patients with advanced ovarian cancer admitted to Vali-Asr Gynecologic oncology departments during 1996–2002. Comparison was made with results of neoadjuvant chemotherapy of 24 patients with unresectable advanced epithelial ovarian cancer treated with platinum- based NACT followed by IDS and clinical outcomes of 68 consecutive stage III and IV ovarian cancer patients treated with primary cytoreduction followed by platinum-based adjuvant chemotherapy. Results: Primary cytoreductive surgery caused longer survival compared to neoadjuvant chemotherapy. Patients who underwent optimal interval debulking surgery (IDS) had a better progression free survival (PFS) (p=0.002) and overall survival (p=0.03) than those who did not. There were not significant differences between the two groups in complications of surgery. Conclusion: NACT followed by successful IDS can lead to high survival percentage in patients with chemoresponsive advanced ovarian cancer; although the result is more effective in those with optimal primary cytoreduction, we still got the same results with those with suboptimal primary cytoreduction.**

**Key Words:** Ovarian cancer - advanced stage - neoadjuvant chemotherapy - interval debulking surgery

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## Introduction

Ovarian cancer is the leading cause of death among all gynecologic cancers in developed countries. The incidence of ovarian cancer has been steadily increasing over the past 10 years in many countries, reaching the overall lifetime risk of 1.8 %( Chi et al., 2001).

Cytoreductive surgery and chemotherapy is the mainstay for the treatment of advanced epithelial ovarian cancer. In order to minimize the tumor burden before chemotherapy, cytoreductive surgery is usually performed first (Griffiths,1975; Hoskins et al.,1994; Chi et al., 2001) Following the landmark publication by Griffiths, more than 30 years ago, nearly every retrospective and prospective study has confirmed that the extent of cytoreductive surgery and the amount of residual disease are among the most important factors affecting the survival of women with advanced ovarian cancer (Chi, et al., 2001; Griffiths,1975). The corollary to this principle, however, is that even extensive surgical efforts that leave residual tumor larger than 1 cm to 2 cm have no meaningful impact on survival (Hoskins,et al.,1994).

Since smaller residual tumor (RT) at the time of surgery happens with higher efficacy of chemotherapy, maximum intensive surgical efforts have been attempted to achieve complete removal of the mass (Fanfani et al.,2003). However, optimal cytoreduction is feasible in only 40-50% of patients with advanced ovarian cancer (Robert et al., 2007). Furthermore, some patients still only undergo exploratory laparatomy because they were not considered to be optimally resectable at the time of first surgery (Fanfani et al.,2003).

Also despite contradictory data on survival outcome, the concept of interval cytoreduction has now evolved into the treatment approach referred to as neoadjuvant chemotherapy. Interval debulking surgery (IDS) can be defined as a surgical procedure with debulking intent preceded and followed by chemotherapy during primary treatment of advanced epithelial ovarian cancer (Griffiths, 1975). So in order to reduce the extent of disease or improve patient performance status, the initial attempt at cytoreduction is abandoned in favor of chemotherapy

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(Pecorelli et al., 2002). In favorable candidates, surgical cytoreduction is then attempted for the first time after some number of cycles of induction chemotherapy.

From three different prospective randomized studies (Redman,et al.,1992; van der Burg,et al.,1995; Rose,et al.,2004) two studies (Redman,et al.,1992; Rose,et al.,2004) disagree on the impact of interval secondary cytoreductive surgery on the clinical outcome in patients with advanced ovarian carcinoma that have previously undergone maximal primary cytoreductive surgery with suboptimal residual disease. On the other hand, most studies have shown that response to neoadjuvant chemotherapy (NACT) in primarily unresectable ovarian cancer patients allows cytoreduction to be achieved in 67-84% of the cases. This management can result longer progression free survival (PFS) and overall survival (OS) than in unresponsive patients who are not eligible for interval debulking surgery (IDS) (Vergote et al.,1998; Ansquer et al.,2001; Kayikcioglu et al., 2001; Recchia et al., 2001). Some studies indicate patients undergoning optimal cytoreduction after induction therapy have approximately the same outcome as those optimally cytoreduced during primary surgery (Jacob et al.,1991); however these data have not been confirmed by the other authors (Neijt et al.,1987).

The aim of the present study was to analyze the clinical outcome in patients with FIGO stage IIIc or IV ovarian cancer, considered unresectable at the time of the first laparatomy and undergoing IDS following NACT. Tumor resectability has always been judged at the stage of laparotomy. The ability of preoperative and intraoperative factors to predict the likelihood of resectability has also been analyzed. The role of the extent of IDS has been investigated compared to patients primarily cytoreduced.

## Materials and Methods

The study included 92 patients with advanced ovarian cancer (FIGO stages IIIc or IV) treated in Vali-Asr Gynecologic Oncology department during 1996–2002 .Information regarding the clinical and pathologic characteristics of the patients as well as the response to chemotherapy and follow-up data were obtained from medical records. All patients underwent laparotomy for tumor resectability. Standard surgery included total abdominal hysterectomy, bilateral salpingo-oopherectomy, radical infracolic omentectomy and pelvic and para-aortic lymphadenectomy (Fanfani, et al., 2003).

Patients were divided into two groups according to the type of primary surgery: 68 (74%) underwent primary debulking with an RT of less than 2 cm (group A); whereas 24 (26%) were considered unresectable at primary surgery and experienced only exploratory laparotomy with multiple biopsies (group B). At the time of the first laparotomy, patients were considered unresectable when optimal RT would not be achievable with acceptable morbidity. The same team of gynecological oncology experts determined the tumor resectability in all of the cases.

Group B patients were treated with 3 cycles of chemotherapy combination including either carboplatin (5-6 AUC) plus paclitaxel (175mg/m2, 3h infusion) (n=15), or cisplatin (75-100mg/m2) plus cyclophosphamid (600 mg/m2)(n=9). Courses were repeated every 3 weeks. In order to attempt IDS, in the case of complete or partial clinical response a second operation was performed. Having obtained successful cytoreduction surgery, the size of the RT at the end of surgery was recorded, and 3 cycles of consolidation chemotherapy were administered afterwards. Clinical response was assessed according to SWOG criteria, consisting of gynecological and general physical examination, imaging evaluation (computed tomography and/or sonography), and serum CA125 measurement (Fanfani et al., 2003). Also complication of surgery was compared in two groups.

Fisher exact test was used to analyze the association of clinico- pathological characteristics and extensive of tumor resection between the two groups. The median follow-up period was 29 months for group A and 22 months for group B.

Kaplan–Meier analyses were used to determine disease-free survival and overall survival. All median and life tables were calculated using the product-limit estimate and the curves were compared using log- rank test. Progression free survival (PFS) and overall survival (OS) were calculated from the time of explorative laparotomy to the date of clinical or pathological progression or death. A P value $<0.05$ was considered statistically significant.

## Results

Clinico-pathological and surgical characteristics of groups A and B are shown in Table 1. There were no statistical differences in the distribution of clinico-pathological parameters between two groups with the exception of the presence of ascitis (>500 ml) at first surgery, which was more frequent in group B (72%) than in group A (51%)(p=0.01). Furthermore, there was no significant difference in preoperative CA125 levels between the two groups.

The most frequent histological type was serous adenocarcinoma (80.4%). Seventy-four patients (80%) had FIGO stage IIIC ovarian cancer and 18 (20%) patients FIGO stage IV disease.

Peritoneal carcinomatosis was also observed more frequently in-group B compared to group A (82 vs. 46; p=0.002). In addition, a higher percentage (38 %) of patients who considered as unresectable had mesenteric infiltration vs. only 21 % in the group of patients submitted to primary debulking (p=0.04).

Table 2 shows the association of the presence of ascites and peritoneal carcinomatosis with mesenteric infiltration in the study population: peritoneal carcinomatosis comparing to ascites seems to be more strictly associated with the presence of agglutinated bowel/mesentery. The negative predictive values of ascites and carcinomatosis in predicting the absence of mesenteric infiltration were 61.8 % and 94 %, respectively, while the positive predictive values of these two parameters versus mesenteric infiltration were 49 % and 54 % for ascitis and carcinomatosis.

In the 24 patients initially submitted to exploratory

**Table 1. Clinico-pathological and Surgical Features of the Stage IIIc and IV Ovarian Cancer Patients**

| Characteristics | | Group A | Group B | P-value |
|---|---|---|---|---|
| Age, years | ≤60. | 42 (62.0) | 14 (58.3) | ns |
| | >60 | 26 (38.0) | 10 (41.7) | |
| Stage | IIIc | 61 (89.7) | 21 (87.5) | ns |
| | IV | 7 (10.3) | 3 (12.5) | |
| Histotype | Serous | 58 (85.5) | 19 (79.2) | ns |
| | Mucinous | 2 (2.9) | 1 (4.2 ) | |
| | Endometrioid | 4 (5.8) | 2 (8.3 ) | |
| | Other | 4 (5.8) | 2 (8.3 ) | |
| Grade | G1-2 | 23 (33.8) | 8 (33.3) | ns |
| | G3 | 45 (66.2) | 16 (66.7) | |
| Ascites volume | ≤500 ml | 38 (56.0) | 5 (20.8) | 0.01 |
| | >500 ml | 30 (44.0) | 19 (79.2) | |
| Pre-op CA125 | <500 | 42 (61.7) | 11 (45.8 ) | ns |
| | ≥500 | 26 (38.3) | 13 (54.1) | |
| Peritoneal carcinomatosis | | | | |
| | No | 37 (54.4 ) | 4 (16.7) | 0.002 |
| | Yes | 31 (45.6) | 20 (83.3) | |
| Mesenteric Infiltration | | | | |
| | No | 54 (79.4) | 15 (62.5 ) | 0.04 |
| | Yes | 14 (20.6) | 9 (37.5) | |

**Table 2. Association of the Presence of Ascites and Peritoneal Carcinomatosis with Mesenteric Infiltration**

| Parameter | | Mesenteric infiltration | | |
|---|---|---|---|---|
| | | No | Yes | p value |
| Ascites volume[1] | ≤ 500 | 17 | 5 | 0.086 |
| | > 500 | 52 | 18 | |
| Peritoneal carcinomatosis[2] | No | 41 | 2 | 0.002 |
| | Yes | 38 | 19 | |

[1]Negative predictive value: 62%, positive predictive value: 49%
[2]Negative predictive value: 94%, positive predictive value: 54%

laparotomy only, a higher percentage of complete and partial clinical response to chemotherapy was observed in the group receiving paclitaxel plus carbopltin versus the group that received cisplatin plus cyclophosphamid (84% versus 58.2%, p=0.038). Two out of the 24 patients (8.3%) demonstrated clinical progression and were treated with second-line chemotherapy regimens. The median number of courses of neoadjuvant chemotherapy was 3 (range: 2–4).

Regarding the surgico-pathological status after NACT, 22 out of the 24 patients (91.6%) showed clinical response and were further submitted to a second laparotomy. Six (27.3%) patients did not show any macroscopic disease, while 8 (36.3%) patients showed RT<2cm and 4 (18.2%) had RT>2cm. After IDS 10 patients (45.3%) were completely cytoreduced (RT=0), 8 (36.3%) underwent a cytoreduction with macroscopic RT<2 cm and the remaining 4 patients (18.2%) were still unresectable and thus were treated with second-line chemotherapy.

Tumor resectability at IDS was related to the pattern of disease spread rather than to the volume of the RT. In particular, the presence of diffuses bulky peritoneal carcinomatosis in the upper abdomen and diaphragm and an agglutinated bowel /mesentery caused limitations in obtaining complete debulking.

There were 31 vases of progression and 22 deaths in group A and 15 of progression and 10 deaths in group B.

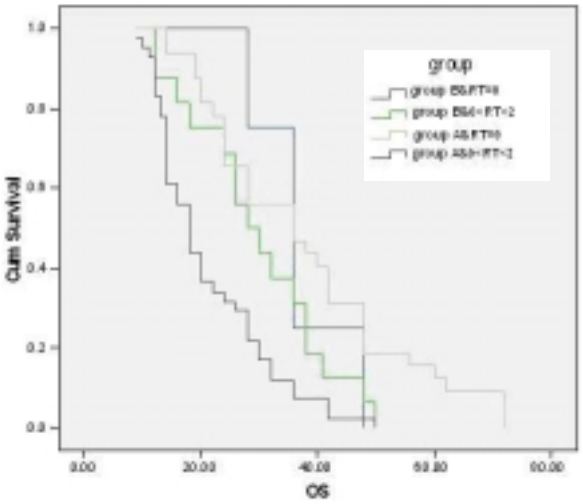


**Figure 1. OS Curves of Stage IIIc and IV Ovarian Cancer with Primary Cytoreductive Surgery and Interval Debulking According to RT**

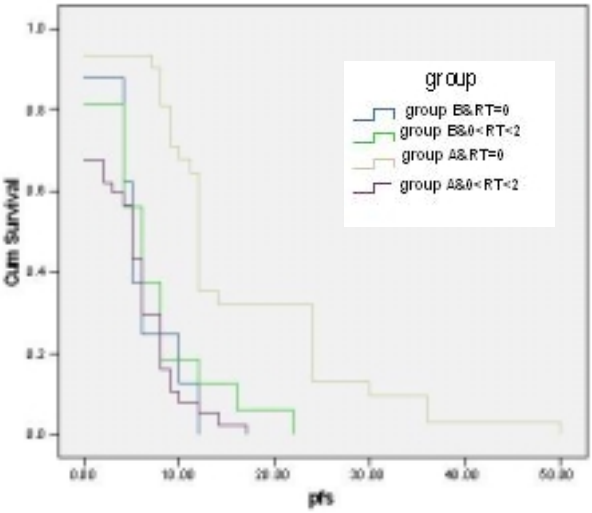


**Figure 1. PFS Curves of Stage IIIc and IV Ovarian Cancer with Primary Cytoreductive Surgery and Interval Debulking According to RT**

In patients primarily cytoreduced with RT=0, survival outcomes were significantly better than those patients who cytoreduced with RT between 0 and <2 (median PFS 43 vs 24 months p=0.0046; median OS 54 vs. 30 months, p= 0.003) (Figures 1 and 2). In-group B, patients who underwent debulking showed a more favorable prognosis than those who did not, in terms of PFS (median PFS 18 vs. 4 months, p=0.002) and OS (median OS 25 months vs. 12 months, p=0.03). We analyzed survival curves in clinically responsive patients, according to residual disease before IDS, and did not find any significant difference in terms of PFS and OS. No differences of PFS were observed according to the extent of the residual disease at second surgery (median PFS: 18 months, in patients with no residual disease vs. 14 patients with macroscopic residual disease<2 cm; p= 0.7). Similar results were obtained analyzing OS according to the extent of the RT following IDS (median OS: 25 vs. 22 months, in patients with no RT vs. patients with macroscopic RT<2cm; p=0.53). Although surgical morbidity was lower in group B, but there was no significant difference in complications of surgery in two groups.

## Discussion

The reason for the good results in terms of response to NACT in this study is mainly due to having a homogenous series of patients; however these series showed inferior survival after neoadjuvant chemotherapy than after primary cytoreductive surgery.

Appropriate surgery remains the cornerstone of management for patients affected by advanced epithelial ovarian cancer. Cytoreduction is defined as maximum tumor debulking in order to debulking in order to improve the effectiveness of further chemotherapy. The hypothetical rational for debulking surgery is an increase in chemo sensitivity of the residual tumor lesions. With the removal of the relatively insensitive large tumor masses with poor central blood supply and low growth fractions, the sensitivity to cytotoxic drugs is increased by a better perfusion of the small residual tumor lesions and a higher growth fraction. Moreover, the chance of developing primary drug-resistant clones by spontaneous mutations is lower in small tumor foci. Finally, a significant decrease in tumor volume improves the general conditions of the patient, resulting in a higher quality of life, possibly in an enhanced immunocompetence and thus a better outcome (Van Dalen et al.,2000 ).

Surgical debulking followed by platinum-based chemotherapy is the standard care for patients with stage III ovarian carcinoma. Neoadjuvant chemotherapy followed by interval debulking surgery may reduce the tumor burden and allow for an easier and complete surgical cytoreduction; specifically 91.6% of patients with chemo sensitive disease after NACT had complete or partial clinical response achievement. In this series Chemotherapy was platinum based. NACT achieved complete or partial clinical response in 91.6% of patients. Secondary cytoreduction was possible in 81.6% of these cases, leaving at least an RT <2 cm in all of them. Fanfani et al showed similar results in the sense that 85% of their patients had complete or partial response after NACT with 85% chance of secondary cytroreduction. In this series, similarly, the decision as to whether to proceed with cytoreduction at IDS or not was related to the pattern of disease spread rather than to RT volume.

After many debates concerning the optimal integration of surgery and chemotherapy, we can undoubtedly re-affirm the strong correlation between chemo sensitivity, successful debulking surgery and survival from this disease. This correlation strongly supports the concept that it is the biological characteristics of the tumor that allow the patient to have successful cytoreductive surgery rather than the aggressiveness of surgery (surgeons skills and attitude) itself (Van Dalen et al., 2000).

It is well known that a rapid decrease in CA125 levels during first line chemotherapy is associated with a good prognosis (Pecorelli et al., 2002). Even though high CA125 levels before primary surgery have been proposed as potentially helpful in predicting advanced ovarian cancer resectability, the most appropriate cut-off has yet to be defined (Van Dalen et al.,2000). Furthermore, at a threshold level of 500U/ml the preoperative CA125 levels were shown to have a specificity of 62%, meaning that 38% of patients may have been unexplored inappropriately (note: 1- specificity is the probability of false positive) (Modares Gilani, et al.,2007). Similar to Fanfani et al. (Fanfani et al.,2003 ) we failed to find any statistical differences in the distribution of CA125 levels according to the feasibility of cytoreduction at first surgery at any of the cut-off levels tested.

CT-scan-derived criteria are also reported to be a reliable indicator of ovarian cancer resectability, resulting in specificity values of 66.7-100%( Fanfani, et al.,2003; Bristow, et al.,2000), therefore leaving a certain percentage of patients who would possibly have been successfully cytoreduced. Some authors have advocated an initial assessment of disease extent via laparoscopy in order to predict surgical outcome more accurately (Angioli et al., 2006; Deffieux et al., 2006).

We showed that peritoneal carcinomatosis was more predictive of tumor-free mesenteric structures compared to the presence of ascites at first surgery. Therefore the possible preoperative role of ascites in determining the likelihood of achieving complete cytoreduction, as proposed by several authors (Kuhn et al., 2001; Fanfani et al., 2003) should be evaluated in the light of these findings; moreover, while the negative predictive value of carcinomatosis in excluding mesenteric infiltration was very high, leaving only 4% of the cases theoretically unnecessarily explored; the positive predictive value was 48.6%, which would leave almost 51% of the cases inappropriately unexplored. These results were similar to another study (Fanfani et al., 2003).

There are ten reports published on neoadjuvant chemotherapy between 1989 and 2003. For example, in 2001, Ansquer et al. reported on 54 patients who were seemed to be optimally unresectable at primary surgery ( Ansquer, et al.,2001). Patients received a median of 4 cycles of platinum-based chemotherapy; 46 of 54 patients (85.2%) underwent interval surgery, with 39 patients being left with optimal (<2 cm) residual disease. This represented 72.2% of the entire study group and 84.8% of patients actually undergoing surgery. Also only 24.1% (13 of 54 patients) of the total cohort derived a potential surgical benefit from the neoadjuvant approach. The median overall survival time for the entire group of neoadjuvant chemotherapy patients was 22 months. In a retrospective comparison study, Shibata et al. reported on 29 patients who were treated with 6 cycles of mostly platinum-based neoadjuvant chemotherapy after exploratory laparotomy only. Although this study did not report the aggregate survival outcome for all neoadjuvant patients, the 13 patients (44.8%) undergoing optimal interval cytoreduction had a median overall survival time of 23.0 months, while patients left with suboptimal residual disease after interval surgery had a median survival time of just 11.0 months. In a comparative analysis with 90 patients treated with up-front cytoreductive surgery, the authors noted that the median survival of optimally debulked neoadjuvant chemotherapy patients was similar to patients undergoing primary debulking leaving large volume residual disease (> 5 cm) (Shibata et al.,2003).

In addition, our data indicate that the extent of RT can play a different prognostic role in patients primarily cytoreduced versus those cytoreduced following IDS. This result was also showed by Fanfani et al (2003). In particular, while completeness of primary cytoreduction was shown to play a prognostic role in patients eligible to being debulked at primary surgery, there were no significant differences in overall survival and time to progression according to completeness of cytoreduction at IDS. Although the favorable prognostic role of maximal cytoreduction at first surgery is generally accepted (Ansquer et al., 2001), very few data are available regarding the prognostic value of maximal cytoreduction surgery at second surgery in primarily unresectable patients responding to NACT. Schwartz et al (1999) showed that secondary cytoreduction to a nonvisible RT has been reported to confer a survival advantage compared to patients with a residual disease. The most reasonable explanation of our findings relies on the assumption that tumors of ovarian cancer patients susceptible to second surgery are characterized by chemo sensitivity, which in turn could make the amount of the tumor cell clones after IDS less relevant from a clinical point of view. This may be compared to patients primarily cytoreduced, in whom the presence of resistant cellular clones in the tumor cannot be excluded.

Another advantage of NACT is the achievement of an optimal cytoreduction by means of a less aggressive surgery with lower morbidity (Ansquer et al., 2001; Fanfani et al.,2003) and a better quality of life (Chan et al., 2002). All these suggest that, although primary cytoreduction to no visible RT is the target in advanced stage ovarian cancer patients, NACT followed by IDS can represent a suitable approach in those patients in whom complete debulking is not primarily available. In this study although surgical morbidity was lower in group B, but there was no significant difference in complications of surgery in two groups.

In conclusion, neoadjuvant chemotherapy followed by successful IDS can lead to a high survival percentage in patients with chemoresponsive advanced ovarian cancer; although the results are more effective in those with complete primary cytoreduction, we still got the smae results with those with suboptimal primary cytoreduction.

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