

## RESEARCH COMMUNICATION

# Role of Appropriate Surgery in Survival of Patients with Epithelial Ovarian Cancer

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### Abstract

**Objective:** Management of epithelial ovarian cancer (EOC) patients is largely based on appropriate surgery. The principle treatment of early stage is competence of surgical staging surgery and surgical management of all patients with advance EOC is approach in a similar manner with cytoreduction surgery. We decided to evaluate the impact of appropriate surgery as a scale on 2 and 5-year survival in EOC patients. **Methods:** In a descriptive analytic study a total 186 patients were divided into 62 with early stage of EOC equivocal FIGO stage I and 124 with advanced disease at Vali-e-Asr Hospital affiliated with Tehran University of Medical Science, Iran, from 1998 to 2008. Two and 5-year disease free survival (DFS) and overall survival rates were determined and compared between the two groups using chi-squared test, Kaplan Meier and Cox regression. **Results:** Five-year DFS in patients with early stage of disease was 85% for the surgical staging group and 38% for non-surgical staging group ( $P=0.037$ ). Two-year DFS and overall survival did not differ between the groups. Also 5-year survival rates in subjects with surgical staging surgery were 42% and 40% for non staging group. For patients assigned to advanced disease group, 5-year DFS in subjects with cytoreductive surgery was 73% and the figure for the remainder was 58%. Five-year overall survival rate in cytoreductive surgery group was 43% in comparison to 38% in the second group. **Conclusion:** Maximal effort for appropriate surgery appears to be a corner stone for optimal survival.

**Keywords:** Epithelial ovarian cancer - appropriate surgery - surgical staging - cytoreduction

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### Introduction

Malignant neoplasms of the ovary are one of the fatal malignancies in women. More than 50% of all deaths from malignancy of the female genital tract occur in women who have gynecologic cancer of ovarian origin (Edward et al., 2008; Ivy et al., 2009).

In contrast to other genital cancers, the best strategy for therapeutic approach for patients with epithelial ovarian cancer (EOC) is undoubtedly surgery (McGuire et al., 2002; Harrison et al., 2008). Probably one of the most important variables influencing the prognosis of these patients is accurate comprehensive surgery with careful attention to extent of disease, which is crucial for successful treatment (Ayhan et al., 2007; Winter-Roach et al., 2009).

In early stage of the disease, a total abdominal hysterectomy and bilateral salpingo-oophorectomy and surgical staging is mandatory. Surgical staging may be curative and definitive in EOC patients (Bell et al., 2006). It does appear that optimal debulking surgery can be accepted as the desired therapy in advance disease of EOC patients (Colombo et al., 2003; Horng et al., 2007).

The importance of careful initial surgical staging in

emphasized by the study of Young and co-worker who indicated that 31% of more advanced disease cases (stage III) was observed in 100 patients with apparent stage Ia- Ib disease (Young, 2003). Based on another study by Young et al., (1990) patients who were found to have stage Ia, Ib disease and did not undergo careful surgical staging surgery, the overall survival rate was 60% whereas five-year survival rate of 90-100% have been reported for other patients who have been properly staged and found to have stage Ia or Ib of the disease. In addition, a study described that approximately 25% of EOC patients whose tumor was confirmed to the ovary (stage I), showed stage II of the disease after surgical staging procedure (Le et al., 2002). An investigation focused on the surgical staging of EOC patients revealed a significant impact of staging on survival time in comparison to patients who did not experience this type of operation (Stewart, 2007).

In advanced cases of EOC, significant palliation may be achieved by reduction of heavy tumor burden (Jemal et al., 2009). Munnell and coworkers demonstrated a 28% five-year survival rate among patients who had undergone a maximal surgical effort compared with 9% five-year survival rate among patients who had biopsy only (Munnell, 1965). The beneficial effects of cytoreductive

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surgery are obvious and this type of surgery can affect the survival of patients (Salani et al., 2005; Gultekin et al., 2009). In advanced disease cases, improved outcome and optimal responses can be achieved with adjuvant chemotherapy in the setting of minimal burden disease (Bookman et al., 2009).

The perception of oncologic gynecologist regarding the role of appropriate surgery for treatment of EOC patients has undergone considerable emphasis during the recent decades (Morrison et al., 2007). Unfortunately in some areas a considerable number of EOC patients exist who may not receive appropriate treatments. In this study we decided to investigate proper surgery treatments and compare two and five-year survival rates between EOC patients who underwent surgical staging with those who did not have such a surgery.

## Materials and Methods

### Study population

In descriptive analytic study all patients with the diagnosis of EOC who presented to the Tumor Clinic of our Gynecology Oncology Department located at Vali-e-Asr Hospital affiliated with Tehran University of Medical Science, Iran from 1998 to 2008 were eligible.

In the mentioned ten-year period, 186 patents with the diagnosis of EOC had been admitted and received treatments. Those who did not have complete medical records or had not presented for regular follow-ups were not entered into the study. Of 186 patients evaluated, 62 patients had early stage of the disease and 124 cases had advanced stage of the tumor.

The data gathered from medical records of the patients included stage of the disease, surgical staging surgery, cytoreductive surgery, interval and optimal debulking surgery and disease free survival (DFS) and overall survival. DFS was considered as no clinical and para-clinical evidence of tumor recurrence. Also post-treatment survival rate with indicator of recurrence of the disease through tumor marker or CT scan were taken. In addition, impact of the surgery on two and five-year survival rates were obtained. For better evaluation, the participants were divided into two groups: early stage of disease equivocal FIGO stage I, II and advanced stage of disease (stage III, IV). This could lead to better identification role of surgery as a main impact stage of therapy for EOC patients.

### Surgical staging

Standard surgical staging approach which was used in these patients involves a vertical midline incision and total abdominal hysterectomy and bilateral salpingo-oophorectomy, infracolic omentectomy, pelvic and paraortic lymph node sampling which followed by random peritoneal biopsies and four-quadrant washing. Because significant palliation may be achieved by reduction of heavy burden tumor, it is judicious to excise as much tumor as possible, when disseminated of disease is encountered at the time of primary surgery as cytoreductive surgery. Optimal cytoreductive surgery was considered when the largest residual tumor was less than one centimeter in diameter. Interval debulking is classified

for patients who can not undergo technically adequate surgical surgery at the time of diagnosis of EOC. In this Situation it is reasonable to attempt tumor debulking after three cycles of chemotherapy.

### Chemotherapy

Most EOC patients received a number of variably active chemotherapy treatments over their surgery with empiric number of cycles (6-8). The earliest agents utilized in this study were predominantly cisplatin and oyclophosphamid (C+P) and in the recent years taxol and carboplatin (T+C) considered as a gold standard regimen. Substation of gemcitabin and carboplatin or doxil was often attributed to selected cases as a second line chemotherapy.

In patients who did not respond to chemotherapy and those who were not suitable candidates to receive chemotherapy, second cytoreductive surgery was performed. In non responder cases to surgery or chemotherapy etoposide or tamoxifen were considered as palliative therapy.

### Statistical analyses

The data were analyzed using SPSS software for Windows. The chi-squared test was used to compare categorical variables between groups. In order to compare survival rate between groups, the Kaplan-Meier and Cox regression were used.

## Results

Table 1 presents characteristic of the patients. In the group with early stage tumors, 36 patients (58%) were candidate for surgical staging surgery procedure and 26 patients (41.9%) had not received surgical staging. In 124 patients with advanced disease, cytoreductive surgery was performed in 98 cases (79%) and 26 patients (21%) were not candidate for this surgery.

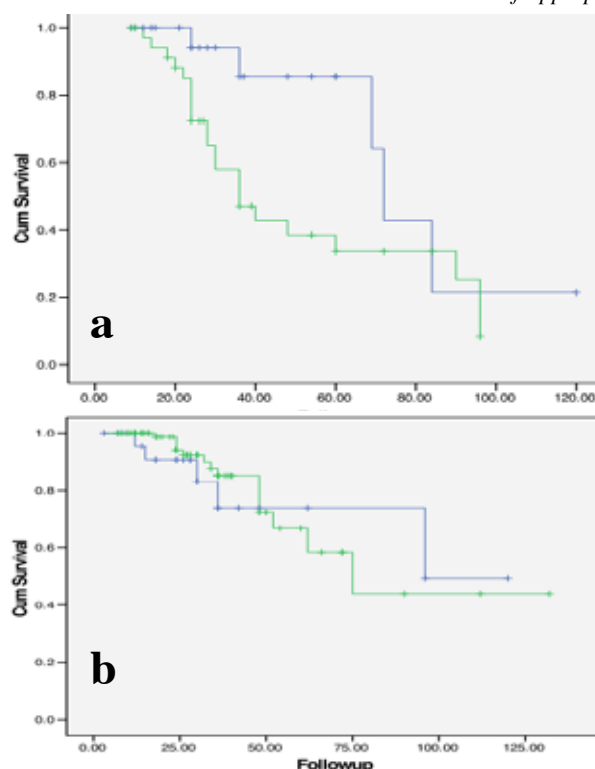
### Recurrence rate and DFS (see Figure 1)

Mean ( $\pm$ SD) time of tumor recurrence was 16.0 ( $\pm$ 23.9) months in surgical staging group and 5.6 ( $\pm$ 12.6) months in non-surgical staging group ( $P=0.31$ ). In surgical staging group, 5-year DFS was 85% in comparison to 38% in non-surgical staging group ( $P=0.037$ ); However, two-year

**Table 1. Characteristics of Early and Advanced Stage Epithelial Ovarian Cancer**

|              | Early<br>Surgical staging |         | Advanced<br>Cytoreduction |         |
|--------------|---------------------------|---------|---------------------------|---------|
|              | -                         | +       | -                         | +       |
| Pathology    |                           |         |                           |         |
| Serous       | 21/95.5                   | 26/86.7 | 19/95.0                   | 73/89.0 |
| Mucinous     | 1/4.5                     | 4/13.3  | 1/5.0                     | 9/11.0  |
| Chemotherapy |                           |         |                           |         |
| C+p          | 14/53.8                   | 11/30.6 | 9/34.6                    | 20/20.4 |
| T+c          | 10/38.5                   | 23/64   | 15/57.7                   | 75/76.5 |
| Recurrence   |                           |         |                           |         |
| CT-Scan      | 8/44.4                    | 4/30.8  | 9/52.9                    | 34/50.7 |
| Tumor marker | 7/31.8                    | 5/25.0  | 9/47.4                    | 31/51.7 |

Data are n/%



**Figure 1. Disease Free Survival of Epithelial Ovarian Cancer Patients. a) Early Stage; b) Advanced Stage**

DFS between two groups was not statistically different (83% vs. 95%, respectively). Mean (SD) tumor recurrence time in cytoreductive surgery group was 5.56 ( $\pm 10.88$ ) and in cases who had not this surgery was 5.69 ( $\pm 15.93$ ) months ( $P=0.96$ ). Five-year DFS in patients who received cytoreductive surgery was 73% and for group without this surgery that data was 58% ( $P=0.847$ ). Two-year DFS in both group was similar (83% vs. 85%).

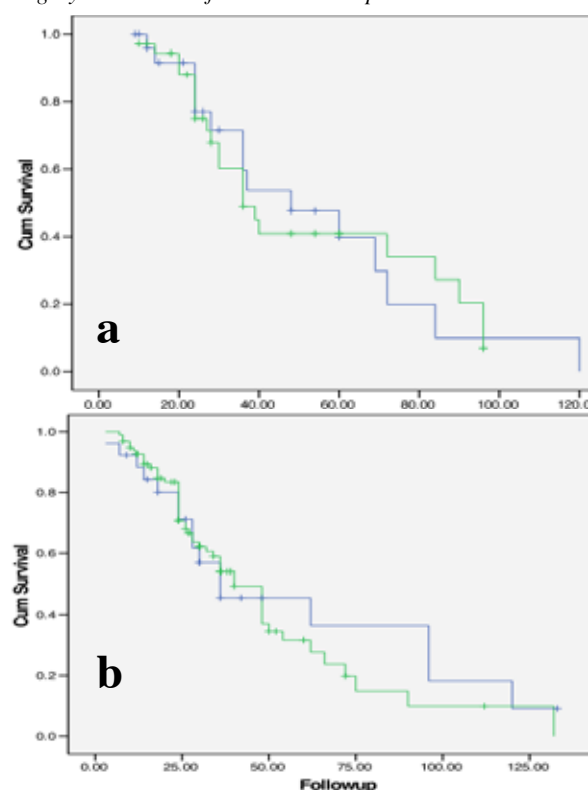
#### Overall survival rate (see Figure 2)

In patients with early stage of disease two-year overall survival rate in both groups was similar (90%). Also 5-year overall survival rate in surgical staging group was 42% comparable with other group was 40% ( $P=0.97$ ).

Five-year overall survival rates in patients with and without cytoreductive surgery were 43% and 38%, respectively ( $P=0.62$ ). There was no statistically significant difference between the two groups regarding cytoreductive surgery. This was also observed in 2-year survival rate between cytoreductive surgery-received patients and those who did not (83% vs. 80%, respectively).

Interval debulking surgery was performed in 30.1% of cytoreductive surgery group and in this situation 56% of them had died at the time of study. 5-year DFS in participant with interval debulking surgery was detected only in 20% of patients. There was no statistically significant difference between patient with and without interval debulking surgery with respect to 5-year DFS ( $P=0.86$ ) and 5-year overall survival rate ( $P=0.49$ ).

Also findings of results of this study in subject recipient optimal debulking surgery showed that 5-year DFS  $P=0.165$  and 5-year overall survival rate  $P=0.507$  'were not significant differences between groups with and



**Figure 2. Overall Survival of Epithelial Ovarian Cancer Patients. a) Early Stage; b) Advanced Stage**

without optimal debulking surgery.

4% of subjects in optimal surgery group and 9% in non-optimal group received a secondary surgery due to recurrence of the disease. Optimal debulking in secondary surgery was unable in all of non-optimal surgery group patients ' but successful results observed only in two cases of optimal surgery group.

Generally majority of recurrence disease cases received second-line chemotherapy and in un curable disease salvage chemotherapy regimen with etoposide or tamoxifen was performed.

35% of patients with advanced stage disease were classified as persistent disease group. Most of these patients subsequently received combination chemotherapy with taxol and cisplatin or gemistabin and carboplatin or doxil and with 6 to 8 empiric cycles. Also many of these patients had a prolonged period of stable disease with minimal side effects of cytotoxic chemotherapy treatment. Based on type of chemotherapy there was no statistically significant improvement in 2 and 5-year overall survival rates in these groups.

## Discussion

Based on this study, subjects who received surgical staging surgery showed improvement in 5-year DFS survival rate. DFS in this group was significantly different from another group which did not undergo surgical staging procedure. Generally surgical staging is essential for successful treatment in early stages of the disease (Leblanc et al., 2000). Trumbo's et al., (2006) described 5-year DFS as 100% for extensive surgical staging surgery in stages I and II of the disease and DFS of 88% in inaccurate staging surgery group. In this study, despite decreased recurrence

of disease ( $P=0.31$ ) 5-year overall survival rate with surgical staging surgery no greater than group non-surgical staging. Findings of cooperative national study of Young and colleagues revealed that 100 patients with apparent stages I and II of EOC, who were referred for subsequent therapy underwent additional surgical staging surgery. In this series, 28% of them initially thought to have stage I disease were upstaged as were 43% of those thought to have stage II disease and 77% were reclassified as having stage III disease (Young et al., 1983). Based on these data, they concluded that initial surgical staging approach with inexperienced surgeon may be incomplete and inadequate (Young et al., 1983). The impact experience of surgeons as prognostic factor in many of studies was noted and with regard to above mention 'because inadequate surgery in our referral cases, this factor considerable in our study.

It is apparent advantage outcome of 5-year DFS and 5-year overall survival time in participant cytoreductive surgery group, however it is not statistically significant differences  $P=0.84$ , but these results may be reasonable considered for ovarian cancer patients as a selected cases. This study could not show increase 5-year survival rate in patients who received cytoreductive surgery. This finding may be attributed to the small number of cases and essentially poor outcome advance stages of this diseases .

Whether prognosis for patients who had sub optimally cytoreductive surgery may be improved if chemotherapy followed by a second attempted of surgical cytoreduction surgery as a interval debulking surgery is unclear (Bristow et al., 2007; Cheng et al., 2009). In this study, overall survival time in subjects with interval surgery was less than those without this surgery ( $P=0.49$ ). We have not encountered no set of criteria performed well enough for clinical use predicted which patients can optimally debulked in interval debulking surgery (Díaz-Montes et al., 2005).

Previous reports on the impact of maximal tumor reduction in cytoreductive surgery have shown favorable effects on overall survival time (Dizon et al., 2003; Heinz et al., 2007). The most important predictive factor in DFS has been proved to be diameter of largest residual disease after primary surgery. Each 10% increase to cytoreduction surgery equated to as 5.5% increase in overall survival rate (Ozols et al., 2002).

Aure and colleges demonstrated significant improvement in survival time among patients with stage III disease only if all gross disease can be resects (Munkarah et al., 2004). However, despite the high rate of optimal surgery and improved our techniques may be due to advanced stage of the disease' we did not find statistically differences in 5-year overall survival rate in optimal surgery group. We thinks few months survival must be considered as an improved in life of an ovarian cancer patient even it is not statistically significant.

In disease recurrence, second cytoreductive surgery is mainstay of therapy for these patients. In an investigation review of previous studies recommendation was, discouraged some individual surgeon from secondary cytoreductive surgery (Bristow et al., 2000). It is not clear to confer an additional benefit from secondary surgery for patients with recurrent of disease 'or followed by

a second-line chemotherapy regimen (Bookman, 2003; Rose et al., 2004; Zang et al., 2004; Ayhan et al., 2006). Also negative physical, emotional and social effects which are imposed on patients by these surgeries should be considered (Fagotti et al., 2010). The policy of this hospital teams in early years of this study based on secondary cytoreduction surgery in many of subjects, but data not showed an improvement on survival. So in majority of cases treatment planning focused on second line chemotherapy regimen.

This imperative to considered cytoreductive surgery should be performed by sciences judgments, experience and aggressiveness of surgeons as a gynecologist oncologist (Ghaemmaghami et al., 2009). In agreement with this issue improvement in achieving optimal cytoreduction surgery and availability multidisciplinary team along with careful integration between surgeon chemotherapists especially in teaching hospital, has correlated with optimal and effective guideline of therapy (Bristow et al., 2004; Vernooij et al., 2009). We considered these parameter in this research.

There are several limitation of the current study that must be considered in the interpretation of data. The one is unavailability some of patients who did not return for follow-up, and the second one we encountered was incompleteness data in some of files.

Finally based on this study we also have noted that in early stages of EOC careful surgical surgery is important for providing an accurate prognosis. Without this procedure, occult metastasis may be present and missed and this may be lead improper treatment. In advanced disease, optimal cytoreductive surgery with experienced surgeon, gynecologic oncologist could lead to a successful therapy.

Clearly these findings require confirmation and more in depth exploration using databases with more patients to allow for more meaningful adjustments.

In conclusion, maximal effort for appropriate surgery appears to be a corner stone of potential effect on survival rate.

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