

# Cytoreductive surgery and ovarian carcinoma

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**Abstract.** *Purpose of investigation:* the aim of this study is to demonstrate if Cytoreductive surgery in patients with ovarian carcinoma increases overall survival. *Methods:* during the period between 1998 and 2008, 60 patients with a relapse of ovarian cancer, were evaluated in order to undergo a cytoreductive surgery. *Results:* an optimal cytoreduction (residual disease <1 cm maximum diameter) was obtained in over half of patients. *Conclusion:* surgery remains the best therapeutic approach in ovarian cancer since it is associated with an increase in survival in all patients undergoing cytoreduction especially in the advanced stages of the disease. These results and those of other studies allow us to determine which patients may benefit from the cytoreductive surgery, improving their survival rate. A disease-free interval > 12 months is the best predictive factor of improved survival rate after surgery. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** Cytoreductive surgery, ovarian carcinoma, overall survival

## Introduction

Ovarian cancer represents 25% of all malignancies of the female genital tract but is the most common cause of death among women who develop gynecologic malignancies (1).

There are different types of ovarian cancer but epithelial tumors are the most frequent ones and represent 80-90% of ovarian cancer.

Diagnosis of ovarian tumors mainly depends on the clinical presentation of the patients, laboratory investigations and imaging modalities (2).

Surgery plays a critical role in the optimal management of all stages of ovarian carcinoma. In apparent early-stage ovarian cancer, a comprehensive surgical evaluation allows stratification of patients into low- and high-risk categories (3).

Surgery remains the fundamental approach for the treatment of advanced ovarian cancer and for recurrences. Cytoreductive surgery has been considered

the standard approach in the surgical treatment for more than 40 years (4). Despite the clinical remission, most patients (75%) with advanced ovarian cancer, develop a relapse.

In the recurrent disease, the therapeutic approach is less clear and precise than in the primary disease. Primary cytoreductive surgery and combination chemotherapy are the cornerstones of the initial treatment for epithelial ovarian cancer (5). Available literature regarding secondary cytoreductive surgery is largely composed of retrospective studies and, more recently, of prospective studies (6-1). Several studies have concluded that patients with platinum-resistant disease (recurrent disease within 6 months of completing treatment) do not benefit from secondary cytoreductive surgery (7-8).

This study was carried out to assess any factors which, associated with cytoreduction, could improve the survival of patients with recurrent ovarian cancer.

## Materials and methods

During the period between 1998 and 2008, 60 patients with a relapse of ovarian cancer, were evaluated in order to undergo a cytoreductive surgery. Two patients with multiple pulmonary and brain metastases were excluded. Patients enrolled for this study had to possess specific characteristics such as: disease-free interval of at least 6 months; maximum 1 or 2 sites of recurrence according to diagnostic imaging; slight increase in Ca-125 serum levels and absence of ascites. The exclusion criteria, however, were represented by stage I and II, patients undergoing second-look surgery without cytoreduction or palliative surgery, and other diseases associated with ovarian cancer. Patients underwent follow-ups each month for 1 year and afterwards every 3 months by performing a physical exam, dosage of Ca-125 and abdomino pelvic CT. Although, as recently published, pre-operative computed tomography (CT) predictors should be used with caution in choosing between surgical cytoreduction and neoadjuvant chemotherapy (9).

## Results

During the study period, out of 58 patients, only 45 were eligible. The mean age of patients was 65 years and the associated diseases were mainly represented by hypertension and diabetes in 75% and 25% of cases, respectively. Ten percent of our patients had a personal history of breast cancer, 20% of cases had a family history of gynaecological malignancies and 5% of cases had a family history of non-gynaecological cancers.

The primary surgery was considered as optimal (residual disease <1 cm maximum diameter) in 66% of patients: 3 of them had not received any neoadjuvant chemotherapy. Patients undergoing chemotherapy, were divided as follows: 58% received a monotherapy (agent platinum), 18% received an association of 2 chemotherapeutic agents and 1% received 3. The mean interval free from disease were 40 months in most cases. Half of the patients presented symptoms at the moment of relapse.

The main symptom was represented by abdomino-pelvic pain associated with sense of abdominal

tension and/or alterations of the intestinal function. In the remainder of patients, relapse was asymptomatic and discovered through high tumor markers, especially Ca-125, or through imaging. Cytoreduction was thus indicated. Localized disease was discovered in 52% of cases, multiple areas of relapse in 23% of cases and multiple disease in 3.8% of cases. The sight of disease affects the type of surgery and type of resection. The resection of the small intestine and colon, following or not following intestinal obstruction, occurs in 8% and 6% of cases respectively. The optimal cytoreduction was obtained in over half of patients and surgical complications were represented by: enterotomy (9%), bleeding (1.5%) with blood loss > to 2600 mL; vascular lesions (1%); abdominal injuries (1%) and cistotomy (1%) as shown in Table 1.

The post-surgical complications that in most cases increased the hospitalization of patients were: fistula (5%); wound infection (4%) ileus (2%); bowel obstruction (1%) and renal failure (1%) as shown in Table 2.

The factors that seemed more related to better survival rate were: a disease-free interval > 12 months, residual disease after primary surgery < 2 cm, the staging and the grade at the time of primary surgery.

The median follow-up was 28 months and the median survival of 30 months with a relapse present in 75% of patients during the period of follow-up. For patients with a disease-free interval between 6 months and 1 year, the median survival was 35 months com-

**Table 1.** Operative complications

Complication	Frequency (n)	Percentage (%)
Enterotomy	7	9
Haemorrhage	1	1,5
Vascular lesions	1	1
Diaphragmatic lesions	1	1
Cistotomy	1	1

**Table 2.** Postoperative complications

Complication	Frequency (n)	Percentage (%)
Fistula	2	5
Wound Infection	4	4
Ileus	4	2
Bowel Obstruction	1	1
Renal failure	1	1

pared to patients who had a disease-free interval between 15 months and 30 months and for those who had a disease-free interval > 30 months. The average interval free of disease was approximately 25 months.

In conclusion, the 5-year survival is 50%.

## Discussion

The rationale for an aggressive approach to the treatment of advanced stage and recurrent ovarian cancer is that the disease tends to recur in large volume in the peritoneal cavity (10). For this reason surgery remains the best therapeutic approach in ovarian cancer since it is associated with an increase in survival rate in all patients undergoing cytoreduction especially in the advanced stages of the disease. These were once considered as inoperable, but nowadays there is a marked improvement in survival after cytoreductive surgery (11-12).

Factors that affect survival in the setting of the secondary cytoreduction can be divided into preoperative factors and operative factors (13-14). A key for survival is the interval free of disease. The longer the time between the remission of cancer and the occurrence of relapse, the longer the survival of patients.

In our study patients who had a disease-free interval > 12 months showed an improvement in survival rate compared to patients with disease-free interval < 12 months, since the first group had survived more than 4 years while the second had not exceeded 18 months of survival.

The volume of residual disease after primary surgical Cytoreduction (definition of which varies from < 1-2 cm) has been shown in several studies, including in this series, to significantly affect survival (15-16). The large extension of cancer at the time of recurrence has an unfavourable impact on survival although this varies from 5 to 10 cm depending on the study (13-15). The expanded size of abdominal metastases influences the success of cytoreductive surgery reflecting perhaps, the total volume of tumor making the surgical resection difficult. However, the marginally significant influence of size of recurrence and failure of any specific procedure to adversely effect survival, as well as the significant influence of the cytoreductive outcome

on survival, all suggest that biologic aggressiveness had a minimal influence on the survival outcome (17).

Based on the number of recurrent disease our patients were divided into 3 groups, 38% had only one site of relapse, 10% of patients had 2 sites of relapse and 5% of patients had multiple sites of recurrence. The optimal cytoreduction was performed only in patients with 1 or 2 sites of relapse while in the remaining 5% of surgery was not carried out satisfactorily given the extent of the disease. The presence of multiple sites of relapse represents an unfavourable factor for survival in spite of a disease-free interval > 12 months. For patients with multiple sites of recurrent disease secondary cytoreduction may be considered and the decision could depend on different factors such as the exact interval free from disease, the age of the patient and the general conditions.

According to Berek et al. histology, tumor grade and radiographic and physical findings before surgery had little or no effect on survival.

The optimal secondary cytoreduction is the main factor that may improve the survival, although the survival of patients varies from one study to another. The patients that are selected for secondary cytoreduction should present certain characteristics such as 1 or 2 sites of relapse that may not otherwise be cytoreductive.

Hospitalization of patients undergoing secondary cytoreduction is around 7 days as in other studies (18-19). The intestinal resection proved to be a valid approach for removing the tumor that invades the intestine. Our patients underwent resection of the colon in 40% of cases, the small bowel in 5% and 6% in cases increasing survival at the expense of quality of life that has proved worse than the medical palliation. In 15% of cases ostomies were performed. For the patients who could not undergo a secondary cytoreductive surgery the only possible treatment was represented by 6 cycles of platinum-based chemotherapy but the long-term results are still being studied.

## Conclusions

These results and those of other studies determine which patients may benefit from cytoreductive

surgery and improve their survival rate. A disease-free interval > 12 months is the best preoperative predictive factor of improved survival after surgery.

The factors that are deemed unfavorable in terms of survival are essentially represented by a less than optimal cytoreductive surgery, an increase in the volume of the tumour and an extensive disease at relapse. After an optimal cytoreduction an aggressive surgical approach may be performed to improve survival.

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