Digestive resections in advanced-stage ovarian cancer

Nicolae Bacalbasa¹*, Olivia Ionescu², Paris Ionescu³, Irina Balescu⁴

¹ Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
² Bucur Maternity Hospital, Bucharest, Romania
³ Ovidius University of Constanța, Faculty of Medicine, Constanța, Romania
⁴ Ponderas Hospital, Bucharest, Romania

Abstract: The standard frontline treatment for advanced-stage ovarian cancer (ASOC) consists of maximal cytoreduction surgery associated with platinum/paclitaxel-based chemotherapy. Several studies have proven that patients with no gross residual disease (RD) have better survival rates than those with optimal but visible RD (RD ≤ 1 cm). In order to achieve this, more radical cytoreductive procedures such as radical pelvic resection and extensive upper abdominal procedures are performed. However, some investigators have suggested that, although effective, radical surgery cannot fully compensate tumor biology, which is a major determinant in survival and in turn influences the likelihood of surgical cytoreduction. The aim of this review was to present the procedures defining ultra-radical (extensive) surgery and to evaluate its feasibility and morbidity in the management of ASOC.

Keywords: ovarian cancer; residual disease; cytoreductive surgery


*Correspondence to: Nicolae Bacalbasa, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; nicolae_bacalbasa@yahoo.ro

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Introduction

Ovarian cancer is the sixth most common cancer among women and the leading cause of death in women with gynecological malignancies. Globally, there are over 200,000 new cases per year with approximately 6.6 new cases per 100,000 women¹. A woman’s cumulative risk for developing ovarian cancer by the age of 65 years is 0.5%, ranging from 0.4% in less developed countries to 0.7% in developed countries². A majority of women will have advanced-stage disease at initial diagnosis, and this is intimately linked to poor prognosis of the disease. The International Federation of Gynecology and Obstetrics (FIGO) classification of the disease stage is the strongest predicting factor of survival³. Patients with advanced-stage disease will experience relapse and only 20%–25% of patients can be expected to be long-term survivors despite showing a good response to primary treatment⁴. Although the impact of chemotherapy on the survival of advanced-stage ovarian cancer (ASOC) patients is important, the evolution of primary cytoreductive surgical techniques to minimize the amount of residual disease (RD) is important.

Studies have demonstrated that the RD status after an initial surgery is a strong independent prognostic factor for survival, with improvements in both overall and progression-free survival in women with complete or minimal cytoreduction (optimal cytoreduction: RD < 1 cm) at the end of the surgery⁵,⁶. The Gynecologic Oncology Group (GOG) protocols concluded that there is an inverse correlation between the maximal diameter of RD and overall survival (OS) – a maximal diameter of RD above which cytoreductive surgery (CS) has no appreciable effect on survival and the existence of multifactorial survival determinants⁷. Progress in surgical techniques has improved the maximal CS result, therefore decreasing maximal diameters of the residual tumor⁸. However, the extent of surgical resection required
to achieve an optimal cytoreduction remains debatable. The minimum size of RD associated with a significant impact on survival is not exactly known but a large improvement in the prognosis is associated with the removal of all macroscopic tissues. There is a universally diverse surgical practice, with huge variations in the cytoreduction rate between 22% and 98%.[9]

Types of radical cytoreductive surgery

Patients with advanced disease affecting the diaphragm, liver, spleen, and omentum, or widespread disease affecting the bowel, need radical surgery in order to achieve complete or optimal cytoreduction[10,11]. Three types of surgical procedures have been defined with different risks of complications. These are:

- Standard surgery – which includes hysterectomy, bilateral adnexectomy with excision of the pelvic peritoneum, total omentectomy including the supracolic omentum, appendicectomy, removal of bulky pelvic, and lumbo-aortic nodes +/- simple peritonectomies. These procedures can be achieved with minimal risk of complications. It is generally accepted that a maximal cytoreductive effort (which definitely implies more than just standard procedures) resulting in minimal RD is correlated to better survival rates.

  There are still proponents hypothesizing that a less advanced initial disease could equally benefit from standard surgical procedures, as patients with less extensive disease have demonstrated an increased progression-free survival and better prognosis. Hence, the biology of the tumor is a decisive factor in choosing either standard or more radical surgical techniques. In addition, the status of the lymph nodes is also considered to be a determinant factor in disease prognosis. Various studies have supported the idea that the removal of all lymph nodes, either tumoral or non-systematic lymphadenectomy, increases progression-free survival in comparison to lymphadenectomy only of the tumoral lymph nodes.

- Radical surgery – which, in addition to the above, includes en bloc removal of the uterus, both ovaries, the pelvic peritoneum, and rectosigmoid, with or without simple peritonectomies. Besides radical rectosigmoid resection, it has been shown that in order to achieve a complete resection of the pan-pelvic tumor, other extensive bowel-resections (e.g., rectosigmoid + descending colon + transverse colon + hepatic flexure resections, ascending colon resection, cecum resection) are effective and feasible, and can be performed as part of the maximal cytoreductive surgery. In ASOC, with strict regard to bowel resections, it seems that more than two bowel resections are required in order to achieve minimal RD.

- Supra-radical surgery – a radical procedure which includes at least one of the following: extensive peritonectomies including partial resection of the diaphragm, resection of subcapsular liver metastases, porta hepatitis surgery, cholecystectomy, splenectomy, distal pancreatectomy, other bowel resection, partial gastrectomy, extensive nodal debulking, and intrathoracic surgery[12]. In patients with widespread upper abdominal metastases, radical and ultra-radical procedures are necessary in order to increase complete (RD = 0 cm) or optimal (RD ≤ 1 cm) cytoreduction rates, as well as to increase survival rates.

  On the other hand, when the volume of the abdominal disease is taken into consideration, some authors concluded that women diagnosed with ASOC and high-volume abdominal metastases who underwent radical optimal CS presented the same prognosis and survival rates as women who only had microscopic abdominal metastases[13]. Moreover, it appears that the end-result of the surgical procedures, i.e. no gross RD or minimal RD, is a significant prognostic factor for survival compared to the volume of the abdominal tumor or the types of surgical techniques that are necessary to remove the abdominal disease[14].

  Radical and ultra-radical surgical procedures result in a greater degree of complications but many studies have shown that they are highly effective to achieve complete cytoreduction with survival benefits, and can be safely performed with acceptable levels of morbidity and mortality[15]. Therefore, radical and ultra-radical procedures should be performed on patients with ASOC and abdominal disease if the morbidity and mortality rates are reasonable. Several reasons and conditions of digestive resections are presented in Table 1[16].

Feasibility of the digestive resections

Upper abdominal and bowel resections. To obtain an optimal CS, the incorporation of extensive procedures in the management of ASOC patients with widespread upper abdominal disease is increasingly required[17,18]. Chi et al. reported that as the use of extensive upper abdominal surgical procedures became more widespread, complete and optimal cytoreduction rates increased from
11% to 27% and 46% to 80%, respectively; thus improving the survival rate without significantly increasing the perioperative morbidity and mortality\textsuperscript{[10]}. In their study of 396 stage IIIB–IV ovarian cancer patients, Harter et al. reported that the percentage of patients with complete cytoreduction to microscopic RD had increased from 33% to 62% and the number of patients with RD ≥1 cm decreased from 35% to 14% since radical surgical procedures were introduced. The median overall survival (OS) time significantly increased from 26 to 45 months and the median survival time was 69 months for patients with no gross RD\textsuperscript{[20]}. These reports supported the hypothesis that undergoing upper abdominal resections in managing ASOC is a feasible option, and it can significantly increase complete cytoreduction rates and improve survival.

Bowel resections should not be avoided in managing extensive diseases if an optimal result is achievable and morbidity is controllable\textsuperscript{[21]}. Studies have reported that radical pelvic resection (i.e., radical oophorectomy, en bloc rectosigmoid colectomy, or modified posterior pelvic exenteration) is feasible and effective to completely remove pan-pelvic disease without significant morbidity\textsuperscript{[22,23]}. Extensive bowel resections are also performed as part of cytoreductive procedures\textsuperscript{[24-26]}. Salani et al. reported that multiple (≥2) bowel resections were necessary in order to obtain an optimal or complete RD in ASOC\textsuperscript{[27]}. Tumor biology and radical surgery. Inherent characteristics and biology of the tumor have been regarded as major determinants of survival, which mainly influence the likelihood of surgical cytoreduction\textsuperscript{[9]}. Optimal surgery could be easily performed when the patient has fewer abdominal deposits or a less aggressive form of the disease with an evident survival advantage\textsuperscript{[28]}. Furthermore, researchers have reported that patients with extended abdominal disease who underwent debulking procedures (i.e., bowel resection) did not have a survival advantage compared to patients who have not undergone such procedures and had remaining RD\textsuperscript{[7,29]}. The Scottish Randomised Trial in Ovarian Cancer (SCOTROC)-1 trial results were reviewed by Crawford et al. and the impact of radical surgery on disease-free survival was analyzed\textsuperscript{[30]}. They found an association between radical surgery and survival advantage but the benefit was only observed in patients with a less advanced form of the tumor. In the case of extended high-volume abdominal disease, aggressive surgery was found to be inefficient.

By achieving a complete cytoreduction and similar survival outcome in both extensive abdominal disease (via ultra-radical surgery) and less extensive disease (via less radical surgery), the emphasized benefits of cytoreduction over the adverse effects of aggressive tumor biology on survival outcomes are self evident\textsuperscript{[31]}. Morbidity according to the extent of surgery. Ultra-radical surgery implies a prolonged operating time and exposure to anesthesia, which increases the risk of hypothermia, respiratory complications (atelectasis), infections, adult respiratory distress syndrome, blood loss and intraoperative ureteric, as well as bowel and bladder injury\textsuperscript{[32]}. After colorectal anastomosis, digestive fistulae could occur but it can be generally treated by conservative means (percutaneous drainage plus antibiotic therapy)\textsuperscript{[33]}. Postoperatively, patients may require longer hospital stay and recovery time, and would be prone to infections (chest, wound, urine), venous thromboembolic disease, as well as poorer mobility and nutritional status\textsuperscript{[34]}. In spite of the complications, many reports have shown that digestive resections in ASOC have acceptable rates of morbidity and mortality, which implies that the procedure imparts a survival benefit. The outcomes of some recent studies are summarized in Table 2\textsuperscript{[35]}. Neoadjuvant chemotherapy followed by optimal surgical resection. Taking into consideration the scientific evidence concerning the evolution of patients with advanced but operable tumor, it can be concluded that applying neoadjuvant chemotherapy (NAC), followed by an optimal CS is a reasonable option in cases associated with a good survival rate, low post-operative morbidity rate, and good quality of life\textsuperscript{[26,41]}. However, patient prognoses were not clearly defined. These facts were revealed in Bristow and Chi’s meta-analysis of 834 women with stage IIIIC–IV ovarian cancer from 22 cohorts, who underwent interval debulking surgery (IDS) after NAC\textsuperscript{[42]}. The volume of RD at the end of the surgery was the most important prognostic factor for survival. The

Table 1. Digestive resections in ASOC

<table>
<thead>
<tr>
<th>Reasons</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>An optimal RD at the end of surgery increases the overall survival rate.</td>
<td>• After bowel resection and colorectal anastomosis, a temporary colostomy is usually required while a definitive one is obsolete.</td>
</tr>
<tr>
<td>In the case of bulky pelvic disease, a posterior pelvic exenteration with colorectal anastomosis on soft tissue is frequently required.</td>
<td>• Large, extensive digestive resections which may burden the normal bowel function should be avoided.</td>
</tr>
<tr>
<td>• The digestive resection should be performed by experienced, highly-specialized surgeons. Post-operative complication rate (especially fistula) should be low and the patient should have a good quality of life.</td>
<td></td>
</tr>
</tbody>
</table>

Bacălbasă N, et al.
reported overall median survival after NAC and IDS was 24.5 months, which seemed to be inferior to those reported after primary CS. Moreover, women who received more than four cycles of NAC presented a four-month decrease in survival, which means that the median overall survival is inversely proportional with the number of pre-operative chemotherapy cycles. This can be potentially explained by the fact that patients selected for NAC either had advanced disease or worse prognostic factors. Moreover, some may develop tumors resistant to chemotherapy owing to late diagnoses, hence resulting in the impossibility of performing the initial CS.

In the case of patients requiring NAC, a biopsy from the peritoneum (especially from the mesenteric and small intestine peritoneum) that is frequently performed through laparoscopy is essential in order to predict the operability of the tumor. If a patient is selected for NAC, IDS should be effectuated as soon as possible after the pre-operative chemotherapy cycles.

Impact of extensive abdominal surgery on survival.

Several single institution studies have evaluated the impact of complete cytoreduction on the survivability of ASOC patients with optimal RD after maximal CS. In 2006, Chi et al. analyzed 465 patients with bulky stage IIIC ovarian cancer who underwent attempted maximal cytoreductive surgery with extensive abdominal resections (diaphragm stripping/resection, splenectomy, distal pancreatectomy, liver resection, and resection of tumor from porta hepatitis), followed by a minimum of six cycles of postoperative platinum-based systemic chemotherapy. Patients with no gross RD after primary cytoreduction had a median survival of 106 months, and it was proposed that the resection of all visible disease significantly improved survival and should be the surgical goal of CS.

The impact of radical abdominal CS procedures (splenectomy, liver resection, extensive peritonectomy) on RD and the associated survival outcome of 194 patients with stage IIIC epithelial ovarian cancer receiving adjuvant platinum-based chemotherapy (including paclitaxel or cyclophosphamide) for six to eight cycles after undergoing primary surgery were analyzed. A total of 131 (67.5%) patients were found to have RD ≤1 cm in maximal diameter. The median survival times of patients with no gross RD and optimal but visible RD (0.1–1.0 cm) were more than 84 months and 34 months, respectively. Overall survival of patients who underwent radical procedures significantly improved compared to those who did not undergo radical procedures (38% versus 9%, p < 0.001). Moreover, patients’ outcomes were affected by the surgeon’s tendency to utilize radical procedures as part of maximal CS, as patients treated by surgeons who frequently utilized radical procedures had significantly longer median OS times compared to patients treated by surgeons who infrequently performed radical surgeries (42 months versus 24 months, respectively, p < 0.001).

The obtained results showed that a complete cytoreduction to afford no gross RD was associated with sig-

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Table 2. The outcomes of digestive resections in ASOC

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Stage</th>
<th>Surgery</th>
<th>RD = 0</th>
<th>RD ≤1 or ≤2 cm</th>
<th>Overall perioperative complications</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radical oophorectomy, en bloc rectosigmoid colectomy, or modified posterior pelvic exenteration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aletti[36]</td>
<td>57</td>
<td>IIIC–IV</td>
<td>Rectosigmoid colectomy</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Park[37]</td>
<td>46</td>
<td>III–IV</td>
<td>Rectosigmoid colectomy</td>
<td>20 (43.5%)</td>
<td>25 (54.4%)</td>
<td>15 (32.6%)</td>
<td>2 (4.2%)</td>
</tr>
<tr>
<td>Houvenaeghel[38]</td>
<td>168</td>
<td>II–IV</td>
<td>Posterior pelvic exenteration</td>
<td>85 (51.2%)</td>
<td>NA</td>
<td>45 (26.8%)</td>
<td>NA</td>
</tr>
<tr>
<td>Bowel resections</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bristow[39]</td>
<td>33</td>
<td>IIIC–IV</td>
<td>Transverse colectomy</td>
<td>11 (33.3%)</td>
<td>19 (57.6%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Silver[40]</td>
<td>19</td>
<td>IIIC</td>
<td>Extended left colon resection</td>
<td>18 (94.7%)</td>
<td>1 (53.6%)</td>
<td>3 (15.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Song[39]</td>
<td>22</td>
<td>IIIC–IV Total colectomy</td>
<td>10 (45.5%)</td>
<td>10 (45.5%)</td>
<td>7 (31.8%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Porta hepatitis or celiac axisSong[38]</td>
<td>2</td>
<td>IIIC–IV</td>
<td>Tumor resection</td>
<td>1 (50.0%)</td>
<td>1 (50.0%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hoffman[41]</td>
<td>6</td>
<td>IIIC</td>
<td>En bloc LUQ resection</td>
<td>NA</td>
<td>6 (100.0%)</td>
<td>3 (50.0%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Kehoe[42]</td>
<td>17</td>
<td>IIIC–IV</td>
<td>Splenectomy/distal pancreatectomy</td>
<td>NA</td>
<td>16 (94.1%)</td>
<td>NA</td>
<td>4 (23.5%)</td>
</tr>
</tbody>
</table>

NA = not available
nificantly longer OS, and that the survival outcome of patients with ASOC was strongly influenced by the surgeon’s ability to undertake radical surgical procedures.

**Conclusion**

Ovarian cancer is the most common cause of cancer-related death in women. The survival of patients with ASOC is mainly influenced by the extent of the disease at the time of diagnosis, tumor biology and its chemosensitivity, and the size of RD after surgery, which is the only modifiable factor by therapeutic approach. The removal of all macroscopic tumors as soon as possible in the therapeutic sequence seems to be elemental for improving chemotherapeutic efficacy and patient survival. In order to accomplish optimal or no gross RD, the need for extensive abdominal resections increases in the management of ASOC with widespread abdominal disease.

These procedures considerably increase complete cytoreduction rates and improve patient survival. Data in existing literature have concluded that for patients with advanced but operable disease (i.e., patients without poor performance status, stage IV disease, or extensive mesenteric involvement), radical surgery followed by chemotherapy, with the goal of removing all macroscopic tumors, is the recommended therapeutic approach to afford better disease-specific survival. With dedicated institutional support and multidisciplinary efforts, significant improvement in optimal and complete cytoreduction rates could be an achievable goal.

**Conflict of interest**

The authors declare no potential conflict of interest with respect to the research, authorship and/or publication of this article.

**References**


