



The role of multiple bowel resections in advanced ovarian cancer: survival and surgical outcomes – a narrative review

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Abstract: Ovarian cancer (OC) is the fifth most common cancer-related cause of death in women and the most lethal gynecologic malignancies in developed countries. In more than two thirds of the cases it is diagnosed as an advanced stage disease. The treatment requires a surgical step, aiming to remove the macroscopically visible disease, either as a primary debulking surgery or interval debulking surgery (IDS) after neoadjuvant chemotherapy (NACT). In both cases radical, complex and invasive surgical procedures are needed in order to achieve complete resection of the tumor, frequently involving bowel surgery. Considering the spread of the disease in the abdominal cavity, involvement of multiple bowel segments is common. Multiple bowel resections (MBR) are often needed to a complete cytoreduction but are linked to a higher rate of bowel diversion and postoperative morbidity, including severe postoperative complications, as anastomotic leakage (AL), and even death. These complications not only affect short term morbidity but may even postpone the administration of adjuvant chemotherapy, thus significantly affecting the outcomes of the treatment. NACT may help reducing the aggressiveness of debulking surgery and therefore the rate of its complications. This strategy represents a valid therapeutic option, especially in fragile patients, reducing the surgical related morbidity and the risk of bowel resections, without affecting the overall survival.

Keywords: Ovarian cancer (OC); bowel resection; neoadjuvant chemotherapy (NACT); anastomosis leakage

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Introduction

Ovarian cancer (OC) is the eighth most common malignancy in females worldwide, with an incidence of 6.6:100,000 cases per year and more than 295,000 new cases diagnosed yearly worldwide (1). It represents the fifth cancer-related cause of death and the leading cause of death for gynecologic malignancies, accounting for approximately 14,000 deaths every year in the United States (2). OC is a rare finding in women younger than 40 years and the mean age at the moment of diagnosis is 63 years (3,4). The 5-year survival

rate in OC is 48%. In more than two thirds of the cases distant spread is already present at the time of diagnosis, significantly reducing the overall survival, which drops to 29% in case of advanced stage of disease (2).

Standard of care is upfront surgical cytoreduction, also known as primary debulking surgery (PDS), followed by platinum-based chemotherapy. At present, complete cytoreduction with removal of every macroscopically visible site of disease is the primary goal of surgery in advanced stages (5-8). Optimal cytoreductive surgery improves adjuvant chemotherapy response since reducing the tumor

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load, where chemotherapy drugs operate on, and decreasing the risk of developing resistant clones (9).

Surgery often implies multiorgan treatment and, as a consequence, may lead to extended hospitalization and longer time of recovery, possibly delaying the first course of adjuvant chemotherapy (10). This kind of procedures should be performed in dedicated centers by trained surgeons to achieve the highest rate of complete cytoreduction, while maintaining the rate of postoperative complications to the minimum (11).

When primary surgery is not an option on the basis of compromised clinical condition or unresectable disease, neoadjuvant chemotherapy (NACT), administered as a three course platinum-based chemotherapy, has been included as first line of treatment, since associated with a non-inferior overall survival compared to PDS (12,13), while allowing reduction of surgery-related morbidity and mortality. Following the first three courses of NACT the patient's clinical conditions and the response to medical therapy must be assessed to evaluate the feasibility of interval debulking surgery (IDS). The aim of the surgery remains once again the removal of every site of macroscopically visible disease.

Although several efforts have been done to reduce morbidity for advanced OC patients, multivisceral surgery, including bowel resections, still remains one of the pivotal steps to achieve a complete cytoreduction, both after PDS and IDS. This approach is often associated with severe postoperative complications, including death. In the present review we analyzed the role of multiple bowel resection (MBR), specifically focusing on procedure-related complications, surgical and oncological outcomes.

We present the following article in accordance with the Narrative Review reporting checklist (available at <https://gpm.amegroups.com/article/view/10.21037/gpm-20-63/rc>).

Methods

To write this narrative review, we conducted a non-systematic search of articles about surgery in OC, specifically focusing on the role of bowel resection. MEDLINE was searched using the terms "ovarian cancer" and "bowel resection" from 1975 through November 2020. Moreover, we searched on the Cochrane Database of systematic reviews under the topic "cancer" selecting first "gynecological, ovary" and then "colorectal". We collected evidence from articles which focused on single and multiple (more than one) bowel resections. Moreover, huge importance has been given to the surgical related outcomes

of bowel resection, with specific attention to the occurrence of anastomotic leakage (AL). The impact of NACT on morbidity of bowel interventions for advanced stage OC treatment has been explored. Attention has also been paid to oncological outcomes and survival rates.

The results of this research were selected according to the authors arbitrary evaluation of their relevance and are here exposed in the form of a descriptive review, reporting a comprehensive overview of the most relevant evidences regarding the role of bowel resection within OC surgery.

Bowel resection in advanced OC

Since the majority of patients with OC present in advanced stage of the disease at the time of diagnosis, multiple radical procedures are often necessary to achieve complete cytoreduction. The frequent involvement of the bowel in advanced OC reflects the high rate of bowel resection during cytoreductive surgery, which often represents a crucial part of the debulking procedure. It has been reported that in case of PDS bowel resections are performed in up to 60–70% of the cases to achieve complete resection of the tumor (14).

Rectosigmoid colon and the peritoneum of the pouch of Douglas are most frequently involved by disease; hence rectosigmoid resection is the most common non-gynecological procedure performed, with an estimated rate of 40–60% (14-16). Usually, surgeons have to proceed with an en-bloc resection of recto-sigmoid, uterus, adnexa and peritoneum (15). In case of PDS, the colon is involved in 18–20%, while the small bowel in 6–27% (14).

Advanced OC commonly spreads along the peritoneal surface, frequently involving more than one bowel segment. Therefore, MBR are often required to achieve the complete resection of the tumor.

The rate of MBR during debulking surgery for OC ranges between 14.5% and 30.1% in different series (17,18); they are usually performed in cases with high tumor load in the context of a complex surgical procedure. While bowel resections during debulking surgery significantly increase the rate of successful cytoreduction, these procedures are linked to increased postoperative morbidity and adverse events (19-22).

Salani *et al.* (19) investigated the impact of MBR in debulking surgery, reporting a significantly higher rate of postoperative complications, including severe events such as fistulas, anastomotic breakdown, prolonged ileus, infections and sepsis, presenting twice as frequently compared to patients undergoing one or no bowel resection. Moreover,

the involvement of multiple bowel segments may imply a worse nutritional and performance status, which are independent risk factors for postoperative complications (23,24).

These observations were confirmed by a study conducted by Tozzi *et al.* (23) which showed the association between MBR and increased overall morbidity, with an increase of 19.5% in postoperative complications in patients undergoing MBR compared to those undergoing single bowel resection (SBR). Moreover, MBR significantly increased the rate of bowel specific complications.

AL is the most common severe adverse event after bowel resection. The morbidity associated ranges from wound infections and abdominal abscesses to peritonitis and sepsis, requiring intensive care unit admission and revision surgery (25), and it possibly may result in a life-threatening condition with a mortality reaching 12% (26-28). A systematic review on colorectal surgery showed that ASA score above II, high Charlson comorbidity index (CCI), operating time longer than 4 hours, perioperative blood transfusion and poor nutritional status (hypoalbuminemia) were predictors of a higher risk of postoperative AL (29); moreover, distal anastomosis, especially in the case of rectal resections near the anal verge, were at higher risk of AL.

The reported incidence of AL after advanced OC surgery ranges between 2.9% and 6.9% (16-18,30-32). It has been shown that the rate of AL increases 7-fold if MBR rather than sole rectosigmoid resection are performed, reaching a rate of 8.3% per patient. Moreover, the rectosigmoid resection represents per se a risk factor for increased AL (33).

Grimm *et al.* (18) evaluated rates of AL in a large series of patients undergoing treatment for advanced OC, analyzing its association with type and number of bowel resection performed. They found that MBR were related to a slightly higher rate of AL in comparison to SBR (9% *vs.* 6.9%), even if they failed to demonstrate a significant increase.

They also confirmed that, among patients with MBR, rectosigmoid resection is associated with the highest rates of AL regardless the association of small *vs.* large bowel resection. Conversely, in colorectal surgery (29) it was observed that large bowel anastomoses are linked to a higher rate of AL than small bowel. It should be taken into account this discrepancy may be due to several reasons, including the different biology and pathway of spread of the two malignancies. Indeed, as opposed to colorectal cancer, OC is characterized by a disseminated abdominal spread, often needing a number of additional procedures, particularly extended peritonectomy.

More in line to studies in colorectal literature, an investigation conducted by Kalogera *et al.* (30) showed that the risk of AL increased if rectosigmoid resection was combined with a large bowel resection, proposing large bowel resections as an additional intraoperative risk factor for AL.

AL represents an independent prognostic factor for shorter overall survival (18,23,34), not only affecting short-term mortality, but also delaying the start of adjuvant chemotherapy and even compromising the possibility its administration.

Actually, anastomosis leakage was linked to a significant increased postoperative hospitalization by a median of 19 days (33) and to postpone the administration of the first course of chemotherapy by 20 days (30).

In the aim to avoid possible complications deriving from anastomosis, bowel diversion may be performed in selected cases, but not routinely. A Cochrane systematic review on colorectal surgery showed a relative risk reduction of 67% of clinically relevant AL with protective stomas (35). More than purely affecting AL rates, the diverting stoma may reduce its severe effects, namely peritonitis and sepsis (36,37).

Considering that MBR represent a risk factor for anastomosis dehiscence (18,23,30), it is not surprising bowel diversion is increased in patients requiring two or more resections. It may seem that the formation of the stoma could affect the postoperative complication rate; however, in an analysis conducted on patients receiving bowel diversions, it was found that the rate of postoperative complications was still higher those undergoing MBR compared with patients undergoing a SBR (23). Nevertheless, the stoma itself carries a morbidity related to intestinal obstruction, infection, necrosis, retraction or hernia of the stoma, possible loss of electrolytes and fluids, even if severe complications are usually rare limited to less than 5% (38-40). It must also be considered that bowel diversion may be difficult to be accepted by the patient since significantly affecting their quality of life (41,42). For all these reasons, in patients more likely to receive MBR and bowel diversion, a thorough counselling with a stoma team should be offered, covering the benefits expected and the possible morbidity associated with these procedures.

The role of bowel resections in debulking surgery for OC

The concept of cytoreductive surgery was firstly introduced

Table 1 Surgical complexity score (53)

| Procedure | Points |
|--|--------|
| Total hysterectomy – bilateral salpingo-oophorectomy | 1 |
| Omentectomy | 1 |
| Pelvic lymphadenectomy | 1 |
| Paraaortic lymphadenectomy | 1 |
| Pelvic peritoneum stripping | 1 |
| Abdominal peritoneum stripping | 1 |
| Rectosigmoidectomy – TT anastomosis | 3 |
| Large bowel resection | 2 |
| Diaphragm stripping or resection | 2 |
| Splenectomy | 2 |
| Liver resection | 2 |
| Small bowel resection | 1 |

by Meigs in his work “Tumors of the Female Pelvic Organs” described as a mean to enhance the effects of postoperative therapy, stressing that good practice should be the removal of as much tumor as possible (43). Forty years later, Griffiths analyzed the relationship between presence of post-operative residual tumor and survival, proving the inverse relationship between residual tumor size under 1.5 cm and survival (44). From this study on, the surgical treatment of advanced OC shifted from being limited to simple procedures as hysterectomy with bilateral salpingo-oophorectomy and omentectomy, to a more complex surgery, including bowel resections (10). Following these studies, several investigations analyzed the association between the size of residual tumor and survival, suggesting various thresholds (45-47). Indeed, the Gynecologic Oncologic Group (GOG) defined optimal cytoreduction as a residual tumor <1 cm (48-50), but further analysis demonstrated more benefits from a complete macroscopic resection (i.e., residual tumor equal or inferior to microscopic disease) (5-8), indicating the absence of macroscopically visible residual tumor as the primary goal of any cytoreductive surgery for OC, whenever feasible.

Moving to the surgical aspects, the treatment for advanced OC can be classified in two categories, specifically as simple or radical. Simple procedures are related to a relatively minimal risk of complications and include hysterectomy with bilateral salpingo-oophorectomy, infracolic omentectomy, limited excision of pelvic or para-

aortic lymph nodes, peritoneal excision and segmental bowel resection (51). On the other hand, radical procedures are frequently needed to achieve optimal cytoreduction, which ranges between 50% and 70% in referral centers (11).

However, there may be some limitations to primary cytoreductive surgery. A survey conducted among the Society of Gynecologic Oncologists revealed that the reasons for suboptimal cytoreduction were advanced age or severe morbidities, unstable intraoperative physiology and sites of unresectable disease: most frequently agglutinated bowel mesentery, disease involving the route of mesentery or bulky diaphragmatic disease, porta-hepatis disease, bulky aortic or pelvic lymph nodes, omental disease involving spleen or pancreas, or bulky pelvic disease (52).

Aletti *et al.* (53) developed a surgical complexity scoring system based on number and type of surgical procedures performed, to evaluate their impact on morbidity and overall survival in advanced OC patients (Table 1). They assigned a score between 1 and 3 point to each procedure possibly performed in OC debulking surgery to achieve complete resection, identifying three groups: simple (<3 points), intermediate (4–7 points) and high (>8 points) surgery. In FIGO IIIC stage disease, which includes many different surgical findings, these categories help better reflect the tumor load.

It appears clear that bowel surgery plays an important role in increasing the surgical complexity score, even more if MBR are performed.

The type of surgery needed, and its possible complications should be carefully evaluated in relation to the expected outcomes of the surgical treatment for every single patient. As a matter of fact, especially considering the higher incidence of OC in patients older than 70 years, sometimes radical surgical procedures cannot be performed without exposing the patient to elevated risks of intraoperative or postoperative complications, that could seriously compromise their quality of life and even lead to death. Several studies have shown that many factors may limit the therapeutic options, including comorbidities, lower performance status, reduced capabilities of tolerating treatment, sometimes even anesthesia (9,53). The radicality and aggressiveness in the surgical treatment are necessarily biased by the surgeon prediction of possible complications. Aletti *et al.* analyzed the complex relation between surgical effort, short-term morbidity and overall survival, showing that age and performance status were related to short-term morbidity and predicted 3 months mortality, while surgical complexity did not. Increased surgical complexity

however predicted overall survival (53). This highlights the difficulties encountered by the physician in trying to find the balance in terms of complications and survival when deciding the best treatment applicable to high risk patients.

The reduction of morbidity and mortality associated with NACT, makes it a valid therapeutic option in women with poor performance status or high tumor load (FIGO stages IIIC–IV) (13,54).

Analyzing the literature about surgery in advanced OC, the introduction of NACT, particularly in patients with high tumor load, allowed a decrease in the rate of MBR and consequently of bowel diversion. Actually, extensive lesions of the small bowel and the need for 2 or more bowel resections have been frequently reported as associated with increased postoperative complications and are more frequently associated with unresectable disease (19,52,53).

Considering only patients in which complete cytoreduction is achieved, platinum based NACT reduces the rate of bowel resection in surgery by 37% (14).

Onda *et al.* (55) conducted a randomized trial analyzing overall survival in PDS versus NACT followed by interval debulking surgery (NACT/IDS), failing to prove non inferiority of NACT. This enlightened the necessity of a strict selection of patients to candidate to NACT/IDS in order to guarantee the best oncological outcomes.

The SCORPION trial (56) was designed to evaluate the morbidity and the progression free survival in PDS versus NACT/IDS in patients with high tumor load. The analysis of perioperative outcomes showed a significantly higher rate of moderate-severe morbidity in PDS rather than NACT/IDS in patients with high abdominal tumor load, as previously illustrated in other randomized clinical trials (12,13,57,58), and demonstrated that the need for MBR significantly decreases after NACT. However, they only reported a 45.5% of complete cytoreduction in PDS with a total rate of severe complications in PDS significantly higher than what reported in other series, ascribing these differences to the fact that the selected population presented high tumor load assessed at laparoscopy. Recent results of the SCORPION trial on survival did not demonstrate a difference in overall and progression-free survival in patients undergoing primary cytoreductive surgery versus IDS after NACT, even if it must be considered that the population was specifically selected for a high tumor burden. A multivariable analysis was conducted aiming to identify factors affecting progression-free survival and overall survival among all patients recruited for the study: only CA 125 levels and residual tumor volume were

independent prognostic factors.

Ongoing randomized trials, the TRUST trial (59) and the Asian SUNNY trial (60), investigating overall survival in PDS versus NACT/IDS, might provide a definitive answer to the question, which is still open.

Conclusions

Bowel surgery is a critical component in advanced OC debulking surgery, often needed to achieve a complete resection of the tumor, but still burdened by a high rate of postoperative complications, related to the resection itself, anastomosis or diversion. The spread of OC along the peritoneal surface often implicates the involvement of multiple bowel segments needing the performance of multiple resections to achieve complete cytoreduction.

MBR increase the surgical complexity score, thus raising the incidence of complications, some of which may negatively influence the survival of the patient.

AL, with its 12% mortality, represents the most severe complications related to bowel surgery, and is more likely to happen if multiple resections are performed. Besides affecting the short-term morbidity and mortality, AL may be responsible for longer hospitalization, need for further surgery and, above all, an important delay of adjuvant treatment, sometimes precluding the possibility of administering it at all.

The majority of data on bowel surgery in OC comes from studies analyzing it in the context of primary debulking surgery. However, NACT followed by IDS has become an option of treatment for advanced OC and has been linked to a decreased rate of postoperative complications without affecting overall survival.

In this setting, the use of NACT reduces the rate of MBR, thus decreasing the rate of postoperative complications and the need for protective stomas. This strategy might be considered specifically in patients with high tumor load, presenting with comorbidities or poor performance status, to offer a less complex surgery and to reduce the risk of MBR.

In conclusion, bowel resections are a fundamental step in advanced OC surgery. They should be performed whenever it is necessary to completely eradicate the tumor, even though, specifically in the case of MBR, they carry a significant rate of surgical complications. Each patient should be evaluated to assess if his performance status allows for a radical surgery. Even if evidence of oncological and survival outcomes related to NACT/IDS are still incomplete, it may

represent an alternative to PDS when the surgery requires multiple complex procedures. A limitation of our study is in its nature of a narrative and descriptive review. In the wait of results from studies about NACT, a systematic review on risks of surgical complications and their impact on prognosis and overall survival may help the clinical decision.

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