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REVIEW ARTICLE

The role of cytoreductive surgery in advanced ovarian cancer: the general surgeon's perspective

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Summary

Ovarian cancer is one of the most common and lethal cancers worldwide and is usually diagnosed at advanced stages. A radical and effective management of advanced ovarian cancer is needed. Cytoreductive surgery followed by intravenous chemotherapy is currently the gold standard for the management of this disease. However, the recurrence rates still remain high. The introduction of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) combined with complete cytoreductive surgery is a well-promising approach for advanced-stage disease, as well as for recurrent cases. This review aimed to present the surgical management of advanced ovarian cancer and the recent literature about the role and the therapeutic effectiveness of cytoreduction.

Key words: *advanced ovarian cancer, cytoreductive surgery*

Introduction

Ovarian cancer is the second most common gynecologic malignancy and the most common cause of gynecologic cancer deaths in the United States [1-3]. Ninety-five percent of ovarian cancer cases derive from epithelial cells and the remainder from other ovarian cells (germ cell tumors, sex cord-stromal tumors) [3,4]. Epithelial type ovarian cancer is estimated to affect annually over 210,000 women globally [5,6]. One of the major problems with ovarian cancer is that 60-70% of the patients present with advanced-stage disease, with 5-year survival rate of 30-55%, compared with early ovarian cancer where 5-year survival exceeds 80% [2,7-9]. The treatment of choice for advanced ovarian cancer includes cytoreductive surgery followed by adjuvant platinum and taxane-based chemotherapy [3,10]. The prognosis depends mostly on the stage of disease at the time of diagnosis and on the quality of treatment [7]. Moreover, the majority of women diagnosed with advanced-stage ovarian cancer develop recurrence after a disease-free period, despite the surgical method used, which is usually aggressive cytoreduction, and the new chemotherapeutic combinations [8,11]. In particular, more than 50% of the patients suffer from disease recurrence within 5 years despite the initial therapeutic management (surgery plus combination chemotherapy) [3]. Currently, cytoreductive surgery followed by platinum and paclitaxel-based chemotherapy is the treatment of choice for patients with advanced-stage ovarian cancer as complete clinical response is expected in over 50% of the patients [7,9,12].

Management of advanced-stage ovarian cancer

Ovarian cancer is a common malignancy that is not easily diagnosed in early stages due to the lack of specific symptoms. Almost 70% of the cases are not diagnosed until the disease reaches advanced stages (FIGO stages IIB to IV) [7,13,14]. An advanced-stage ovarian cancer patient usually

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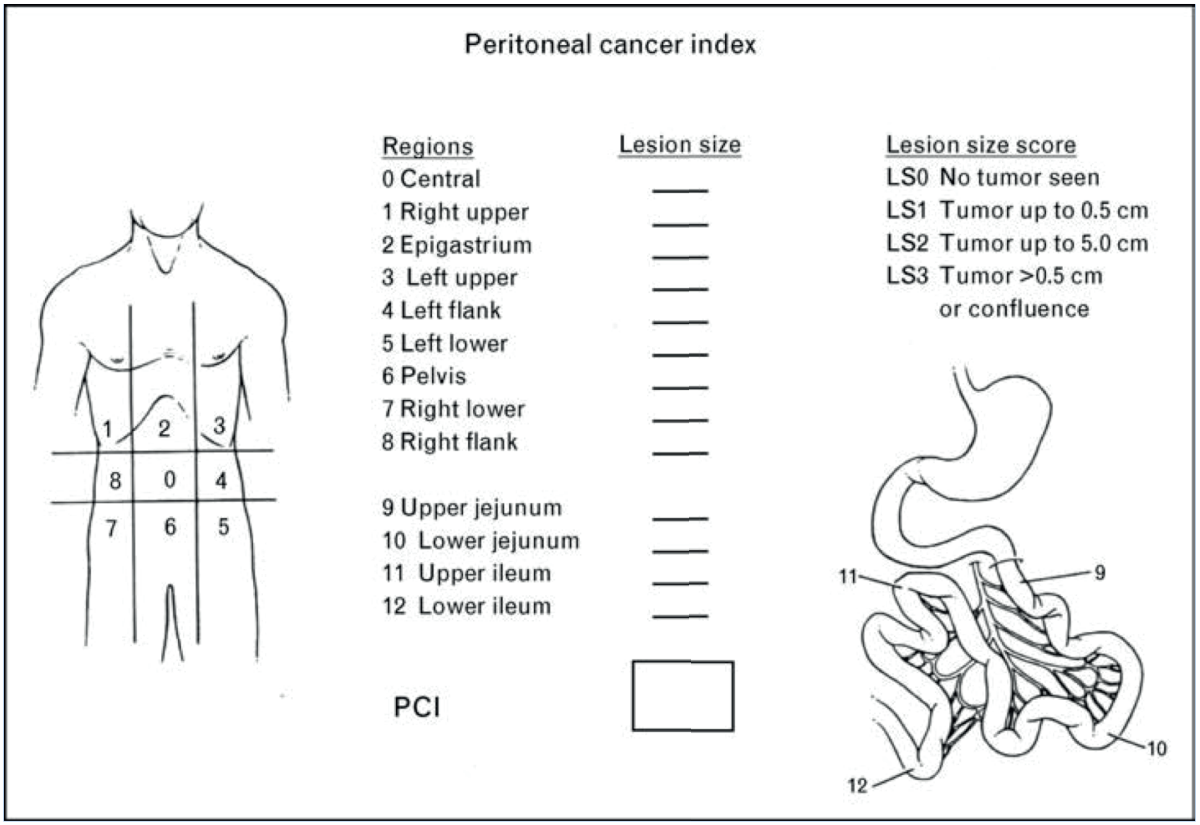

Figure 1. Peritoneal Cancer Index described by P. Sugarbaker. The Figure is adaptred from ref no.5

presents with diffuse abdominal pain; other possible symptoms are meteorism, changes in bowel habits, unexplained weight loss, fatigue, anorexia or ascites [7].

A United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) developed an algorithm for early detection and screening for ovarian cancer, preventing thus the diagnosis at advanced stages, which consists of regular transvaginal ultrasound and CA125 serum levels [7]. However, it has been recently shown that these measures do not lead to a reduction in mortality [3,14]. This lack of reliable screening examinations and the accompanying tumor ability to spread in extraovarian organs results in 75% metastatic disease at the time of diagnosis [15]. Moreover, it is also known that women with BRCA1 mutation have 36-46% risk of developing ovarian cancer and those with BRCA2 mutation have a risk of 10-27% [5,7,14]. According to this genetic knowledge, there is a possibility that prophylactic bilateral salpingo-oophorectomy in healthy mutation carriers could result in 80% reduction in the risk of developing ovarian cancer [7]. Therefore, early detection of ovarian cancer is far from being satisfactory so that efforts should focus on the radical and effective management of this disease.

Independent prognostic factors for advanced ovarian cancer are tumor stage, patient age, performance status and postoperative residual tumor after the initial surgery [7]. In particular, postoperative residual tumor is the strongest prognostic parameter after disease stage and is the only one that can be effectively addressed by the specialized general surgeons in that field [7]. The prognosis of advanced-stage ovarian cancer mainly depends on the degree of tumor reduction at the initial operation, as complete resection can achieve a 5-year survival of 40-50% [7,9]. The target of surgeons is to attain the most optimal residual tumor, which can be achieved in 50-85% of the patients with advanced ovarian cancer [7].

The surgical approach to advanced ovarian cancer is totally different from the treatment of early ovarian cancer (FIGO stages I to IIA), which consists of complete resection of the primary tumor and detailed inspection and biopsies of the abdominal cavity for staging [7,14].

The concept of cytoreductive surgery for ovarian cancer has evolved since Meigs, in 1934, proposed that as much tumor as possible should be removed to enhance the effects of postoperative irradiation [12,14,16]. The surgical goal in the management of patients who present with advanced disease is the resection of all visible tumor [2]. According to the Gynecologic Oncol-

ogy Group (GOG), there are two significant factors with respect to residual disease after primary surgery for advanced-stage ovarian cancer (FIGO stages IIB to IV) [12]. First, there is a maximal diameter of residual disease above which even extensive efforts at cytoreduction will not impact the survival. Second, patients with no gross residual disease have the most favorable survival rates [7,12]. There is no clarification about the term ''no gross residual disease''. Some authors describe no gross residual disease as absence of visible disease at the end of the operation; others use less than 0.5cm, less than 1cm, less than 1.5cm or less than 2cm residual disease [9]. However, patients with no residual tumor following the primary surgery have the best prognosis [7].

Cytoreduction includes a variety of surgical procedures such as bowel resection, especially rectosigmoid (necessary in approximately 30-50% of cases of advanced ovarian cancer), diaphragm stripping, peritoneal resection, splenectomy, partial hepatic or pancreatic resection, cholecystectomy, hysterectomy and salpingo-oophorectomy [2,7,8,14]. Many studies report that more aggressive surgical procedures are associated with increase in disease free and overall survival rates [17].

Preoperative tumor assessment is possible with the usage of the Peritoneal Cancer Index (PCI) described by Sugarbaker (Figure 1) [3,16]. PCI includes tumor size and distribution [16]. The abdomen is divided into 13 areas and, depending on tumor size, each area is rated on a scale of 0-3 [3,16]. It is stated that a PCI lower than 15 is a determinant factor in performing an optimal cytoreduction but a PCI higher than 15 does not promise a successful cytoreductive surgery [10].

The aim of a surgeon is to achieve maximal resection of the tumor [5,18]. Bristow et al. have stated that a 10% decrease of residual tumor leads to a 5.5% increase in median survival [15]. A score proposed by Sugarbaker and Chang can estimate the Completeness of Cytoreduction (CC) (Table 1) [3,5,17]. According to this, CC-0 indicates no residual tumor, CC-1 indicates residual nodules <2.5mm, CC-2 indicates residual nodules >2.5mm and <2.5cm and CC-3 indicates residual nodules >2.5cm [3,5]. The GOG defines optimal cytoreduction as residual disease that is < 1cm in maximum diameter, but also currently, it states that cytoreduction to <1cm or to no visible disease is associated with improved response to chemotherapy [14,18,19]. Another important benefit of cytoreduction is that removal of the tumor rapidly improves the patients' symptoms that are disease-related [20].

Table 1. Completeness of cytoreduction (CC); a score proposed by Sugarbaker and Chang [3]

CC	*Definition*
CC-0	No residual tumor after cytoreduction
CC-1	Residual nodules < 2.5mm
CC-2	Residual nodules >2.5mm and <2.5cm
CC-3	Residual nodules >2.5cm

Despite the fact that cytoreduction is the treatment of choice for the management of advanced ovarian cancer, there are some factors that make it difficult to achieve complete cytoreduction [21]. These factors may be the presence of extraabdominal or retroperitoneal disease, bowel obstruction in more than 3 places and very poor performance status [21,22].

Although the role of cytoreduction is incontestable for surgeons, there are some special issues in which the medical opinion about this treatment is controversial. Many arguments have been raised about the proper primary treatment of choice. The accepted treatment for the patients is complete cytoreduction followed by adjuvant postoperative chemotherapy. The special target is to offer proper preoperative disease extent investigation as well as the necessary postoperative care. Also, the surgeon should collaborate with other specialties [23].

Cytoreduction can cause surgically-induced infertility. It is recommended that a conservative approach is favorable for early-stage ovarian cancer (FIGO IA-IB), especially in women who are in reproductive age. However, many studies showed that this does not apply to advanced ovarian cancer as the survival with conservative surgical management is poor, even for FIGO IC stage [24].

Currently, minimally invasive surgery has developed and proves to be beneficial in many cases. However, according to the literature, there is no satisfactory evidence about the usefulness of laparoscopic surgery for the management of advanced-stage ovarian cancer. In well selected patients, it is not recommended for staging or debulking. Although there is a risk of port site metastasis while performing laparoscopy in patients with known malignancy, this rate is about 1-2% and it is more common in patients with advanced ovarian cancer accompanied with peritoneal carcinomatosis. Moreover, CO_2 pneumoperitoneum seems to affect tumor growth. In particular, some studies claim that prolonged exposure to CO_2 in-

Table 2. Advantages and disadvantages of primary cytoreductive surgery followed by intravenous platinum and paclitaxel-based chemotherapy

	Benefits		*Disadvantages*
1	Cytoreduction aims to maximal tumor reduction, stating that no residual disease has the best prognostic survival rates. It is stated that a 10% decrease of residual tumor leads to a 5.5% increase in median survival rate (Bristow et al), [12].	1	This management presents lower prognostic rate when advanced ovarian cancer is associated with any of the following: presence of ascites, poor nutritional status, poor performance status, extraabdominal disease or bowel involvement.
2	Cytoreduction removes large tumor volume and enhances tumor chemosensitivity.	2	Chemo-toxicity (thrombocytopenia, anemia, neutropenia, alopecia, neuropathy).
3	This therapeutic algorithm is feasible to 75% of the patients and effective even in advanced ovarian cancer cases associated with peritoneal carcinomatosis.	3	Surgically-induced infertility after cytoreduction.
4	This management is equally effective to the elderly patients with advanced ovarian cancer.	4	Even in successful therapeutic approach, the recurrence rate remains more than 50% within 5 years from the primary treatment.

creased cell growth and metastatic capacity, while others state that increased apoptosis [25].

Locoregional dissemination involving the peritoneum alone is noticed in the case of non effective initial treatment, as the epithelium of the ovary, peritoneum and fallopian tube are considered to be a single clinical and histological entity [5,18].

PCI is usually estimated intraoperatively [26]. In peritoneal carcinomatosis, PCI is the strongest independent prognostic factor for overall and disease free survival [27]. The success of cytoreduction depends on the extent of tumor dissemination intraabdominaly [26].

Postoperatively, a total of 6 cycles every 3 weeks of intravenous carboplatin (AUC 5) and paclitaxel (175mg/m^2) over 3 hours are usually the adjuvant chemotherapy of choice [7]. The significance of cytoreduction prior to chemotherapy is that it removes the large tumor volume which contains poorly oxygenated cells that are either resistant or potentially resistant to chemotherapy and finally leaves small residual tumor, making them more susceptible to chemotherapy [11]. However, increase of the number of chemotherapy cycles, dose escalation or addition of other drugs are not recommended by current guidelines, as no trials exist that report prolonged survival [7].

Neoadjuvant chemotherapy refers to the administration of systemic chemotherapy prior to definitive surgery. This therapeutic approach is preferred mainly for patients who are poor operative candidates because of medical comorbidities or poor performance status, as well as for patients with advanced ovarian cancer and clinically apparent unresectable tumor to whom an optimal cytoreduction is unlikely [28,29].

The two modalities used in postoperative treatment of newly diagnosed advanced ovarian cancer are intravenous chemotherapy alone or in combination with intraperitoneal chemotherapy. The choice between these two options depends on the amount of the residual disease after the primary operation [30].

Primary cytoreduction followed by platinum (carboplatin or cisplatin) and paclitaxel-based chemotherapy is the treatment of choice for patients with advanced-stage ovarian cancer as complete clinical response is expected in > 50% of the patients (Table 2) [5,9,11-13,16,31].

Managenent of recurrent ovarian cancer

Despite the effectiveness of the primary cytoreduction followed by platinum and paclitaxel-based chemotherapy in patients with advanced ovarian cancer, the majority of them (about 80%) will recur [2,11,12,32]. These patients require immediate surgical treatment [13]. The most significant prognostic factor for recurrent ovarian cancer is the time interval from the initial treatment of disease to the time of recurrence (recurrence free period and the residual disease after secondary cytoreduction [8,11].

No optimal strategy for salvage treatment of recurrent ovarian cancer exists but there are reports about the role of secondary cytoreductive surgery [2,8,9,13,33]. The alternative options are new chemotherapeutic agents and new biologic therapies that target specific cellular pathways [8].

The term "secondary cytoreduction for recurrent ovarian cancer" has been used since 1983 and was defined as an operative procedure performed in patients with disease-free interval > 6 months from the completion of primary treatment, aiming at tumor reduction [9,12]. The term "secondary cytoreduction" refers to a variety of surgical procedures, however there are controversial views

about visceral resections [2]. There are many studies that focus on the role of secondary cytoreduction in recurrent ovarian cancer in comparison with other managements [8]. Although many of them are not randomized, they are retrospective and have heterogeneity, it cannot be ignored the fact that in women who underwent secondary cytoreduction, the size of residual disease significantly impacted survival [8]. Reports show a 75% probability of a range from 41-month to 60-month overall survival with secondary cytoreduction, especially in women whose macroscopic disease was totally resected [8,11]. The outcome after secondary cytoreduction is impacted by many factors. The disease-free interval prior to recurrence is a significant factor as a longer disease-free interval is associated with longer survival after surgery. Moreover, the number of recurrent disease sites impacts overall survival, since patients with few metastatic lesions in well-defined sites have complete secondary cytoreduction in contrast with the low survival of patients who suffer from extended peritoneal carcinomatosis [8].

Chemotherapy is an alternative option for recurrent ovarian cancer . Single-agent platinum compounds, single-agent nonplatinum drugs, platinum- and non-platinum-based combinations are the chemotherapeutic options for recurrent disease [8]. There are some chemotherapy trials that reveal a 15-18 month overall survival with single-agent or combination chemotherapy [12]. However, chemotherapeutic agents have some characteristics concerning their effectiveness as it seems to produce similar responses to recurrent ovarian cancer compared with the responses of the initial treatment, always according to the sensitivity of cancer cells. Nevertheless, tumor cells show drug resistance after many cycles of chemotherapy [8]. It has been stated that when the disease-free interval is ≤ 6 months, the disease seems to be platinum-resistant, but when this interval is > 6 months, the disease seems to be platinum-sensitive with response rates up to 77% [2]. The absence of ascites and the reintroduction of platins as postoperative adjuvant treatment are generally associated with increased survival [9].

Also, many studies have shown longer survival in patients who underwent secondary cytoreductive surgery followed by chemotherapy, similar to the approach adopted in primary treatment [8]. For patients who recurred after 6-12 month disease-free interval, repeating the tumor cytoreduction has been advocated as a means of augmenting the duration of response to subsequent adjuvant chemotherapy. Each 10% increase in complete secondary cytoreduction is associated with an incremental increase in median overall survival of 3 months. Complete secondary cytoreduction in patients surgically rendered free of macroscopic residual tumor is 50% [12]. Successful secondary cytoreductive surgery increases the patient survival rate when there has been a long disease-free interval, localized recurrent sites, such as pelvic or intra-abdominal recurrences, and an optimal performance status. A role of collaborative surgery with different but complementary areas of expertise in recurrent ovarian cancer may achieve resection of as much tumor as possible to improve the quality and duration of life in these patients [2]. Early intervention with cytoreductive surgery in asymptomatic patients with recurrent ovarian cancer detected only on the basis of serum CA 125 or imaging techniques offers increased survival rates in contrast with early chemotherapy which is reported not to affect survival [9]. Patients who achieve a complete secondary cytoreduction (approximately 79%) usually have a complete resection at the primary surgery and good performance score (positive Arbeitsgemeinschaft Gynaekologische Onkologia/ AGO score which is independent predictive score for complete resection and is identified by the DESKTOP trial I). Other predicting factors are the presence of cancer-related symptoms, tumor excision burden and increasing levels of CA 125 [9,11].

Secondary cytoreduction is considered for patients who have a long progression-free interval of at least 12 months, have responded to first line chemotherapy, have a good performance status, a locally recurrent disease and who are good candidates for potentially complete disease elimination [34].

Ovarian cancer can recur after the secondary cytoreductive surgery, so tertiary cytoreduction followed by chemotherapy has been established as a therapeutic choice in some cases of secondary recurrences. At secondary recurrences, the ovarian tumors usually involve at least two regions of the abdominal cavity. Tertiary cytoreduction is an aggressive surgical procedure for which excellent candidates are considered to be ovarian cancer patients with a recurrence after secondary cytoreduction and in whom the tumor is thought to be preoperatively completely resectable. Platinum-resistant tumors were thought to be an exclusion criterion but this statement is questionable. Factors such as ascites, advanced FIGO stage and peritoneal carcinomatosis do not

present a burden for tertiary cytoreduction. However, the postoperative residual disease is the most important prognostic factor for this surgical procedure as well. Patients with a disease-free period of more than 24 months after the secondary cytoreduction up to the secondary recurrence have a greater possibility for a complete tertiary cytoreduction. Moreover, chemosensitive recurrent tumors present more favorable prognostic management in tertiary cytoreduction. The median survival rate after tertiary cytoreduction is estimated to be about 19 months with a residual tumor of less than 1cm [35].

Conclusion

In conclusion, primary cytoreductive surgery followed by intravenous chemotherapy is a gold standard for the management of advanced ovarian cancer. The survival rates are associated with the completeness of cytoreduction. The surgeon's priority should be the least possible residual disease after primary or secondary cytoreduction. The surgical management of advanced ovarian cancer is an example of the need of multidisciplinary approach, particularly the cooperation of surgical oncologists and gynecologic oncologists in a specialized team.

Authors' contributions:

KR, EAN and EH have contributed to the conception and design of the article, acquisition analysis and interpretation of data, as well as writing of the article.

MP reviewed the manuscript and provided the final comments.

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