Rationale of Cytoreductive Surgery and HIPEC for Management Ovarian Cancer

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Abstract

Ovarian cancer is the second most common genital malignancy in women and it is the most lethal gynecological malignancy. The most common cause of primary ovarian malignancy is epithelial carcinoma; however its exact cause has not yet been identified. Determining the optimal management of patients with advanced ovarian cancer is a significant challenge. The standard of care for ovarian cancer has been surgery followed by systemic chemotherapy. However, treatment with cytoreductive surgery (CRS), and hyperthermic intraperitoneal chemotherapy (HIPEC) is another approach, showing promising results. CRS and HIPEC have become widely accepted as an effective method of treating peritoneal metastases (PM) from various cancers. Therefore, this study aimed to review the surgical management using cytoreductive surgery and HIPEC for treatment of advanced ovarian cancer.

Keywords: Ovarian Cancer; HIPEC; Cytoreductive Surgery

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Introduction:

The second most frequent genital malignancy in women is ovarian cancer, with an estimated five-year survival rate of 39%. The lifetime risk of epithelial ovarian cancer (EOC) is 1 of 70 women; it is the leading cause of death related to gynecologic malignancy (1).

A peritoneal surface malignancy (PSM) is a cancer arising from or spreading to the peritoneal surfaces. It can be a primary disease arising from the peritoneum (such as malignant peritoneal mesothelioma) or a secondary disease (such as metastasis originating from a primary malignant neoplasm). Primary psm is rare; the most frequent forms are primary peritoneal mesothelioma and serous carcinoma of the peritoneum. Secondary psm is by far the most frequent. Its origin is often cancers of the gastrointestinal tract, but it can frequently arise from ovarian cancer and breast cancer. However, many cancers can metastasize to the peritoneum (2).

Cytoreductive surgery (CRS) is performed with the goal of complete removal of all macroscopic disease. This is achieved by peritonectomy procedures and en-bloc resection of the viscera where required. Their use depends on the extent of peritoneal metastases (PM) (3).

CRS aims at removal of macroscopic disease while hyperthermic intraperitoneal chemotherapy (HIPEC) acts on the microscopic disease **(4)**.

Cytoreduction with HIPEC has been recently reported to obtain a median survival of approximately 5 years, as compared with 9–13 months after traditional therapies **(5)**.

Parietal peritonectomy was categorized into six procedures: right diaphragmatic peritonectomy, left diaphragmatic peritonectomy, pelvic peritonectomy, parietal anterior peritonectomy, greater omentectomy, and lesser omentectomy. patients who had < 6 peritonectomy procedures only in anatomic areas with macroscopic evidence of disease constituted the selective parietal peritonectomy (SPP) **(6)**.

Total parietal peritonectomy (TPP) was defined as removal of the entire parietal peritoneum (pelvic, bilateral anteroparietal peritoneum, right upper quadrant and left upper quadrant peritoneum) and the greater and lesser omenta with at least one of them performed in areas free of macroscopic disease at surgical exploration **(7)**.

Treatment of advanced stage disease

Advanced-stage disease means that the disease is extended to pelvic/ aortic lymph nodes, peritoneum, intra-abdominal organs or disease outside the abdominal cavity. A landmark study quantified residual disease and demonstrated for the first time an inverse **(8)**.

Relationship between residual tumor and oncologic outcome **(9)**. The goal of surgery is to resect as much tumor as possible obtaining, ideally, a complete resection. The standard worldwide recommendation consists of primary maximal surgical cytoreduction followed by 6 cycles of intravenous carboplatin plus paclitaxel **(10)**. An alternative strategy is reserved for selected patients and it includes surgical cytoreduction in between chemotherapy courses, usually after three or four cycles. This strategy is called neoadjuvant chemotherapy followed by interval debulking surgery **(11)**.

- **Rationale for primary surgical cytoreduction:**

1. Improvement of oncologic outcomes: a large body of retrospective and non-randomized prospective studies consistently show an inverse correlation between survival and the amount of postoperative residual disease **(12)**. Women affected by advanced stage EOC that were treated with primary surgical cytoreduction and platinum-based neoadjuvant chemotherapy and demonstrated a mean weighted median survival of 29 and 24 months respectively **(12,13)**.

2. Surgical reduction of tumor burden prior to chemotherapy: it has been postulated that the proportion of tumor cells destroyed with each cycle of chemotherapy is constant. Thus, in cases of tumor cells not resistant to chemotherapy, fewer cycles would be necessary to eradicate them if the absolute number were less **(14)**. In addition, tumor size is correlated with an increased spontaneous mutation rate of malignant cells. Animal models have also demonstrated that drug exposure allows the resistant cells to outgrow the sensitive tumor cells population **(14)**. Primary surgical cytoreduction, thus, reduces the number of cancer cells decreasing the chance of inducing drug resistance **(15)**.

3. Improved drug diffusion: large bulky tumors may have hypoperfused areas where concentration of chemotherapy agents can be suboptimal, increasing the possibility of drug resistance **(16)**.

4. Increased tumor cells growth rate: During initial tumor growth, cancer cell division is almost exponential. But then, cell growth reaches a plateau. Thus, the great majority of cells in large tumoral masses are not dividing, being in G0 phase of the cell cycle, which is essentially resistant to chemotherapy **(17)**. Primary surgical cytoreduction may stimulate G0 residual tumor cells to re-enter in the normal cell cycle, increasing the chemotherapy efficacy **(18)**.

Residual Tumor Disease:

Residual tumor disease is commonly described as the diameter, in millimeters, of the biggest nodule left after surgical debulking. The importance of residual disease after surgery in women with ovarian cancer. They demonstrated an inverse relationship between residual disease and patient survival. In 1994, the Gynecology Oncology Group (GOG) published a sub-analysis of two retrospective series (GOG protocol 52 & 97) of patients affected by advanced stage EOC who underwent primary cytoreduction followed by chemotherapy. The study showed significant differences in OS in women with microscopic disease or less than 2 cm in comparison with of residual disease of more than 2 cm diameter. The maximum diameter of residual disease was firstly found to be an independent predictor of OS after controlling other variables. Thus, surgery with residual disease of less than 2 cm was defined as "optimal" cytoreduction; while more than 2 cm was called "suboptimal" **(19,18)**.

The GOG collective experience analyzing the data of seven trials (GOG 11, 114, 132, 152, 158, 162 and 172) that studied the efficacy of chemotherapy in 1895 stage III and 360 stage IV ovarian cancer patients. All patients underwent primary debulking surgery followed by 6 courses of cisplatin and paclitaxel. Residual disease after surgery was an independent prognostic factor. The median OS reported was 79.1, 42.4 and 35 months in patients with microscopic, 1-10 mm and > 10 mm of residual disease, respectively. The authors suggested a modification of the term "optimal residual disease" from < 1 cm to microscopic **(20)**.

Feasibility of complete primary cytoreduction:

In the presence of a preoperative suspected adnexal mass with ascites and peritoneal carcinomatosis, the feasibility of complete cytoreduction should be determined by exclusion of multiple liver or pulmonary metastases by imaging studies such as computed tomography (CT). In the absence of extra-peritoneal lesions and surgical contraindications, patients should undergo primary debulking surgery **(11)**. The feasibility of optimal cytoreduction depends on the disease distribution, the patient´s overall medical condition and the surgeon's expertise. However, obtaining an optimal cytoreduction ≤ 1 cm of residual disease is not an easy task. In highly specialized centers, the rate with optimal primary cytoreduction is over 75 %. But this rate falls down to 25% when low-volume ovarian cancer surgeries centers are included in the analysis.

Nevertheless, as it was previously mentioned, primary debulking surgery is beneficial if complete cytoreduction is achieved. According with the literature, this is achievable in only 30% of patients when a gynecologist oncologist performs the surgery, a higher rate when compared with general gynecologists or general surgeons **(21,22)**.

Neoadjuvant chemotherapy followed by interval debulking surgery:

Despite upfront primary debulking surgery (PDS) for newly diagnosed patients with advanced stage ovarian cancer is considered the standard of care[156], limitations to this strategy have been postulated **(22,23)**. For instance, patients with incomplete primary cytoreduction seem to have no meaningful impact on OS[11, 174]. Furthermore, only experienced surgeons with extended formal training in cytoreductive techniques obtain an acceptable complete primary cytoreduction rate **(24)**.

Consequently, an alternative approach such as neoadjuvant chemotherapy (NACT) has been proposed by several authors **(22, 23)**.This strategy of treatment consists in the administration of at least 3 courses of platinum-taxanes chemotherapy followed by an interval debulking surgery (IDS) and further adjuvant treatment in patients responsive to chemotherapy. The goal of this modality is to reduce the extension of the disease and, by performing a less radical surgical procedure, to improve the complete cytoreduction rate reducing the surgical time and complication rate, while improving the PFS and OS rate **(25)**.

Objective indications for neoadjuvant chemotherapy are patients with poor performance status and with significant medical co-morbidities making them unsuitable for an aggressive debulking surgery. These indications include, however, the smallest proportion of patients who underwent neoadjuvant chemotherapy **(11, 26)**. The majority of women receive either NACT or PDS based on tumor extension and on estimated tumor resectability **(27)**. The latter is a subjective and highly surgeon-dependent indication **(28)**.

Although several criteria have been tested for predicting the surgical resectability of ovarian tumors, its accuracy and clinical applicability is still controversial\. Some of these criteria include ascites volume, serum CA 125 values and computer tomography scan parameters **(27)**. For example, terms like “dense adhesion between bowel and omentum”, “large diaphragm disease”, and “large tumor nodules adherent to abdominal structures” have been postulated by some authors as criteria of unresectability **(28)**. These terms show how subjective is the definition of a patient as debulkable or not. These criteria are mostly based on CT scan findings but, sometimes, a direct laparoscopic assessment of is recommended **(29)**.

On the other hand it is a common belief to associate NACT with less complex surgical procedures, shorter surgical time, and lower incidence of complications after IDS **(25,26)**. However, this strategy does not exclude the necessity of performing complex surgical procedures at the time of IDS in order to obtain an optimal cytoreduction. Thus, referring these patients to a specialized gynecologist is mandatory **(30)**.

Recently, the results of a randomized, controlled, prospective trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) included six hundred and seventy patients with stage IIIC and IV ovarian cancer were assigned to primary cytoreductive surgery group or neoadjuvant chemotherapy group **(31)**. There were no significant differences in OS (29 months for primary cytoreductive surgery group versus 30 months for neoadjuvant chemotherapy group) between the two groups. Complete cytoreduction with no gross residual disease was possible in 20% of patients who underwent primary cytoreduction and 52% of those who had neoadjuvant chemotherapy. On multivariate analysis, the strongest independent predictor factor of prolonged survival was the absence of residual tumor after surgery ($p<0.001$). The authors concluded that neoadjuvant chemotherapy followed by interval debulking surgery has similar efficacy compared with primary debulking surgery followed by chemotherapy for patients with stage IIIC or IV ovarian cancer and complete resection of all gross lesions remains the objective of the cytoreductive surgery whether performed as primary or after neoadjuvant chemotherapy. However, optimal cytoreduction (<1cm residual disease) was achieved in only 41.6% of patients in the PDS arm, a substantially lower rate than the published by expert series. The PFS and OS for patients randomized to the PDS arm were substantially lower than those reported in previous studies, including prospective trials of the Gynecologic Oncology Group (GOG) **(11,32,33)**.

Surgical cytoreduction technique:

Women should be placed on supine position with legs spread apart. Vertical midline incision is recommended in order to access to the entire abdominal cavity **(34)**. Ascites is evacuated and sent for cytological evaluation. As described above, a careful inspection and palpation of the entire peritoneal cavity and retroperitoneum is carried out in order to assess the extent of the primary and metastatic disease. The localization and diameter of the primary tumor and its extension into surrounding organs is described as the diameter of the larger metastases. Sometimes, there are regions that cannot be accessed before larger tumor masses are removed. This careful inspection and palpation is essential in order to establish the feasibility and extension of surgical cytoreduction. Complete cytoreduction may by difficult in cases of bulky suprarenal nodes, extensive disease in the liver parenchyma, along the root of the small bowel mesentery and in the bowel serosa, close to the origin of the superior mesenteric artery, or in the porta hepatis. If complete surgical cytoreduction is not feasible, neoadjuvant chemotherapy is preferred **(35)**.

Radical omentectomy use to be the first surgical step because it is the first tumor encountered upon entering the peritoneal cavity. The infracolic omentum is separated from the transverse colon and resected. If the omental metastases involve the gastrocolic omentum, it is resected **(Figure 1)**. The next step is to remove the primary tumor in the pelvis with the other adnexa and the uterus in the usual fashion if no extension to other pelvic organs is present. However, advanced ovarian cancer often involves the uterus, rectosigmoid, cecum, ileum and bladder. Metastases of the pelvic peritoneum sometimes completely obliterate the anterior and

posterior cul-de-sac. In this case, the retroperitoneal approach is the most reasonable way for removing *in block* the entire tumor. This procedure is accompanied by performing a rectosigmoid resection with an end-to end mechanical anastomosis **(33)**.

Tumor spread to the hilum of the spleen may be carefully inspected as well. Splenectomy may be sometimes indicated to achieve maximal tumor debulking. Any peritoneal implants should be removed, particularly if there are large, isolated masses and their removal will render the patient optimally cytoreduced. Diaphragm peritoneum should be visualized and resected if the disease is present. Sometimes, it can involve muscle resection that can be sutured with non-reabsorbed monofilament continuous suture. Pelvic and /or aortic lymph node involvement is seen is approximately 60% of patient with advanced stage disease. Despite controversial, pelvic and aortic lymphadenectomy should be completed starting form aortic bifurcation up to the renal veins. The incidence of complications and morbidity of this approach should be also taken into consideration for patient selection. The most common complications include: infections, cardiac morbidity, pulmonary thromboembolism, coagulopathy, gastrointestinal, renal failure, re-laparotomy and death **(34)**.

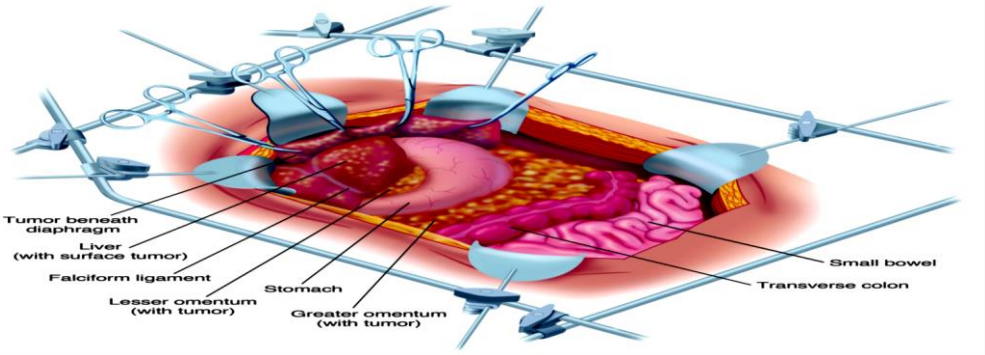

Figure (1) Self-retaining retractor provides continuous exposure of all quadrants of the abdomen including the pelvis [33].

- **Intraperitoneal chemotherapy**

Advanced ovarian cancer is predominantly a disease of the peritoneal surfaces, and this has prompted investigation into delivery of chemotherapy directly into the peritoneum. This increases the intensity of the dose delivered to the tumor without compromising plasma drug levels and potentially spares normal tissues such as bone marrow from increased toxicity **(36)**. Evidence to support the use of intraperitoneal (IP) chemotherapy is derived from three randomized trials **(18)**.

In fact, IP therapy is generally associated with higher treatment-related complications such as catheter complications (obstruction, infection, bowel perforation, and fistula formation), nausea abdominal discomfort and pain (related to the infusion of chemotherapy in the abdomen), metabolic imbalances and neurotoxicity (due to the higher drug absorption from the peritoneum) **(36)**.

Ongoing trials are evaluating the use of intraperitoneal carboplatin (GOG 252 and iPocc/JGOG 3019) and the use of intraperitoneal therapy with either carboplatin or cisplatin and intraperitoneal paclitaxel after NACT and IDS (NCIC-CTG OV21/NCRI-PETROC) **(37).**

The incorporation of hyperthermia together with IP chemotherapy (hyperthermic IP chemotherapy) had been introduced. Hyperthermia alone is tumoricidal, and it increases the cytotoxicity of many chemotherapeutic agents in human cell culture and animal models **(38).**

Conclusion:

Peritonectomy provides further superior outcome at the time of interval CRS for advanced ovarian cancer.

Total parietal peritonectomy provides an effective and efficient outcome with improved survival rate in patients with advanced ovarian cancer compared to selective parietal peritonectomy.

The use of HIPEC, the severity of the condition, and the degree of cytoreduction all have an impact on how long patients with recurrent ovarian cancer survive.

Conflict of interest: The authors declare no conflict of interest.

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