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TOPIC HIGHLIGHT

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Peritoneal carcinosis of ovarian origin

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Abstract

Epithelial ovarian cancer (EOC) is the second most common genital malignancy in women and is the most lethal gynecological malignancy, with an estimated five-year survival rate of 39%. Despite efforts to develop an effective ovarian cancer screening method, 60% of patients still present with advanced disease. Comprehensive management using surgical cytoreduction to decrease the tumor load to a minimum, and intraperitoneal chemotherapy to eliminate microscopic disease on peritoneal surface, has the potential to greatly improve quality of life and to have an impact on survival in ovarian cancer patients. Despite achieving clinical remission after completion of initial treatment, most patients (60%) with advanced EOC will ultimately develop recurrent disease or show drug resistance; the eventual rate of curability is less than 30%. Given the poor outcome of women with advanced EOC, it is imperative to continue to explore novel therapies.

Key words: Peritoneal carcinosis; Ovarian cancer; Intraperitoneal hyperthermic chemotherapy; Cytoreduction

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INTRODUCTION

Epithelial ovarian cancer is the second most common genital malignancy in women and it is the most lethal gynecological malignancy, with an estimated five-year survival rate of 39%[1]. Despite efforts to develop an effective ovarian cancer screening method, 60% of patients still present with advanced (Stages Ⅲ-Ⅳ) disease[2]. CA-125 serum levels, transvaginal ultrasound, and pelvic examination have long been thought to be potentially effective screening tools. However, none of them have proved effective in decreasing mortality from ovarian cancer.

An epithelial ovarian tumor arises from the serosal lining of the ovary, which communicates with the serosal lining of the abdomino-pelvic cavity known as the peritoneum. As a consequence of tumor growth, malignant cells exfoliate and shed, becoming free floating in the peritoneal fluid. They typically implant in the pelvis and subdiaphramatic recesses owing to gravity and the incumbent position. This spread of the tumor within the peritoneum is termed peritoneal carcinomatosis, and it is a typical feature of cancer spread in patients with primary advanced or recurrent epithelial ovarian cancers. Intraoperatively, it is characterized by the presence of macroscopic tumor nodules of variable sizes and consistencies that can coalesce to form plaques or masses within

the abdominopelvic cavity. Tumor dissemination from the peritoneal cavity into the pleural cavity might also occur through the lymphatic lacunae within the diaphragmatic peritoneum. This results in severe pleural effusion which compromises lung and cardiac function. It typically presents with vague gastrointestinal symptoms, such as abdominal bloating, distension, weight loss, and fatigue. Due to the heterogeneity and lack of specificity of these early clinical symptoms, diagnosis is often delayed. In the final stages of this disease, patients suffer from severe symptoms of profound anorexia, dyspnea, and severe pain from malignant bowel obstruction, abdominal distension for ascites, and pleural effusion as a result of the extensive burden of tumors that characterizes this fatal deterioration. In the past, peritoneal carcinomatosis was considered a terminal condition and patients were treated with palliatively. However, despite extensive dissemination within the abdominopelvic cavity, this condition is now considered a loco-regional disease.

In many patients, the natural history of ovarian cancer is similar to gastrointestinal tumors with peritoneal surface dissemination. In fact, in both cases, the late consequences of peritoneal carcinomatosis are debilitating ascites and intestinal obstruction. With the full knowledge of the natural history of this progressive disease, the targets of the treatment should be both the peritoneal surface diffusion and the systemic metastases. There is no doubt that the eradication of the peritoneal surface components of this disease would be a major contribution to the overall, and disease-free, survival, as well as improving the quality of life of ovarian cancer patients. Comprehensive management using surgical cytoreduction to decrease the tumor load to a minimum, and intraperitoneal chemotherapy to eliminate microscopic disease on peritoneal surface, has the potential to greatly improve quality of life and have an impact on survival in these patients. In the setting of primary disease, optimal cytoreductive surgery (residual tumor < 1 cm) and platinum-based chemotherapy have been established as the most important determinants of clinical outcome.

THE CLINICAL AND BIOLOGICAL RATIONALE FOR MAXIMAL CYTOREDUCTION IN OVARIAN CANCER

More than 20 years after Griffiths' major paper[3], a recent meta analysis by Bristow *et al*[4] examined the effect of maximal cytoreductive surgery on survival in advanced ovarian cancer. The author concluded that maximal cytoreduction was one of the most powerful reasons of cohort survival for patients with this disease. Eisenkop *et al*[5] found that cytoreduction had a more significant influence on survival than the extent of metastatic disease observed before surgery. Incorporating extensive upper abdominal debulking procedures with standard pelvic cytoreduction (rectosigmoid resection, peritoneal stripping, diaphragm stripping, extensive bowel resection, splenectomy, partial gastrectomy, and resection of liver and kidney) not only significantly improved the disease-free survival rate of patients left with optimal residual disease (85%), but also led to a significant improvement in overall survival.

The apparent value of primary cytoreductive surgery is based on the following reasons: (1) Surgery is thought to remove resistant clones of tumor cells and thus decreases the likelihood of the early onset of drug resistance; (2) The removal of large masses likely to be associated with poorly vascularized areas of tumors supposedly improves the probability of delivering adequate drug doses to the remaining cancer cells; (3) The higher growth fraction in better vascularized small masses enhances the effect of chemotherapy; (4) In principle, smaller masses require fewer cycles of chemotherapy and thus decrease the likelihood of drug resistance; (5) Removal of bulky disease theoretically enhances the immune system; (6) The patients feel better after removal of ascites and large tumor masses, particularly from the omentum; and (7) Surgery alleviates the associated nausea and satiety these patients feel.

PREOPERATIVE SELECTION CRITERIA TO EVALUATE THE INTRAPERITONEAL DIFFUSION OF THE DISEASE

Residual disease after primary surgery is one of the most important prognostic factors in advanced ovarian cancer patients. However, a certain percentage of women, ranging between 25% and 90%[6,7], are not suitable for optimal cytoreduction after exploratory laparotomy, and are treated by neoadjuvant chemotherapy. To preoperatively identify patients with unresectable tumors, which can be spared an unnecessary exploratory laparotomy, several approaches have been attempted, including the evaluation of CA-125 serum levels and the radiological assessment of tumor spread. However, the accuracy of these parameters has been unsatisfactory, and has been limited by the retrospective nature of the studies and the highly variable rates of optimal cytoreduction in different series[7]. In this context, a genetic analysis by microarrays has been attempted to identify some biologic characteristics underlying the possibility of optimal debulking, resulting in a low predictive accuracy[8]. Laparoscopy is well known for offering a direct and magnified vision of the peritoneal cavity and a better view of the upper abdomen. It allows the pathological assessment of the disease without an open surgical procedure, with a shorter operating time, and better results in terms of postoperative morbidity. Indeed, it has been demonstrated to be an effective procedure for restaging early ovarian cancer[9-11]. A recent pilot study by Fagotti *et al*[12] demonstrated that laparoscopy is an adequate and reliable procedure for the assessment of the chances of optimal cytoreduction (RT < 1 cm) in clinically advanced ovarian cancer patients. Since then, other investigators have been confirming the role of laparoscopy in the evaluation of the possibility of achieving optimal residual disease in the same clinical subset[13,14]. Subsequently, in a consecutive prospec-

tive series of 113 advanced ovarian cancer patients, the presence of omental cake, peritoneal and diaphragmatic extensive carcinomatosis, mesenteric retraction, bowel and stomach infiltration, and spleen and/or liver superficial metastasis were investigated by laparoscopy. Each parameter received a score based on a specificity > 75%, positive predictive value (PPV), negative predictive value (NPV) > 50%, and accuracy > 60% with respect to the chances of achieving an optimal cytoreduction. By summing the scores relative to the presence of every aforementioned parameter, an overall laparoscopic value for each patient (total predictive index value = PIV) was calculated. Sensitivity, specificity, PPV, NPV, and accuracy with respect to optimal RT were calculated for each PIV. Finally, the authors concluded that the proposed laparoscopic model appears a reliable and flexible tool to predict optimal cytoreduction in advanced ovarian cancer. More recently, this model has been applied in a different center from that in which it was developed[15]. The results from this study have shown that even when utilized in a different setting of patients, the laparoscopic PIV can identify advanced ovarian cancer cases that are likely to be suitable for optimal debulking.

SURGICAL PROCEDURES IN THE MANAGEMENT OF ADVANCED OVARIAN CANCER

Worldwide, there are more than two hundred thousand new cases of ovarian cancer diagnosed annually, accounting for about 4% of female cancers.

In 1994, the National Institutes of Health[16] convened a 14-member panel of experts in the management of ovarian cancer to generate a consensus statement of recommendations. The panel concluded that: "Adequate and complete surgical intervention is a mandatory primary therapy for ovarian cancer, permitting precise staging, accurate diagnosis, and optimal cytoreduction. The procedure is best conducted by a qualified gynecologic oncologist, when there is a high probability of ovarian cancer. All women with suspected ovarian cancer should be offered a preoperative consultation with a gynaecologic oncologist". During the past decade, compelling published work has accumulated to lend support to these consensus recommendations. These reports show that initial surgery for ovarian cancer is most appropriately done by gynaecological oncologists, preferably in centers with expertise in the multidisciplinary management of this disease. Engelen *et al*[17] recently described a population-based observational study of patterns of care for 680 women with ovarian cancer in the northern Netherlands. The patients were treated between 1994 and 1997. The main objective of the study was the effect of surgery performed by a gynaecological oncologist on the quality of surgery and survival outcome compared with surgery by a general gynaecologist without subspecialty training. In all disease stages, patients received surgical treatment according to prevailing surgical guidelines more frequently when operated on by a gynaecological oncologist. The risk of death for patients who did not have surgery according to accepted guidelines was almost twice that for patients who had surgery according to the guidelines. In this study, patients with stage Ⅰ / Ⅱ disease were more likely to be staged by gynaecological oncologists than general gynaecological surgeons, resulting in a more accurate assignment of disease stage and administration of adjuvant treatment. For patients with stage Ⅲ disease, five-year survival was 32% when the guidelines were followed and 11% when guidelines were not (hazard ratio 1.97, 95% CI: 1.45-2.68, $P < 0.001$). Furthermore, more patients with stage Ⅲ disease had complete debulking (24% *vs* 12%) and reduced residual disease (< 2 cm) (62% *vs* 45%) by a gynaecological oncologist when compared to a gynaecologist. These data, as well as similar population-based studies, lend support to three main conclusions about the delivery of cancer care services for women with suspected ovarian cancer[18-21]: (1) the disparity in survival outcomes according to the specialty of operating surgeon, after confounding factors have been accounted for, supports the long-held hypothesis that the surgically-attained maximum diameter of residual disease is inversely proportional to survival outcome. Consequently, primary cytoreductive surgery offers the best opportunity for achieving extended survival and should be considered the standard of care for women with advanced-stage epithelial ovarian cancer; (2) the consistent and positive effect of a surgeons' specialty on survival provides irrefutable evidence that surgical care in ovarian cancer should be concentrated in centers with gynaecological oncologists. These surgical subspecialists have the necessary expertise to stage patients with early-stage disease as well as to perform the cytoreductive surgery necessary to achieve minimal residual disease in patients with advanced-stage tumors. Adequate and complete initial intervention is among the most powerful clinician-driven determinants of survival for women with ovarian cancer; and (3) the above conclusions call for widespread and consistent support by the medical community and governmental organizations in recognising specialty training in gynaecological oncology as a necessary component for comprehensive health care for women[22].

The standard of therapy in patients with advanced ovarian cancer is the surgical exploration of the pelvis and the upper abdomen and a maximum cytoreduction. The aim of surgery is to remove all tumor-infiltrated organs including the peritoneum, bowel, spleen, hepatic tissue *etc*., thus surgery is not limited to the pelvis, the omentum and the lymph nodes. Bristow *et al*[23] showed that even in patients with un-resectable liver metastasis, optimal de-bulking of extra-hepatic disease is associated with a significant survival advantage. Therefore, the intent of surgery is not to leave any macroscopic intraabdominal disease[24]. In a high percentage of patients, this aim can be reached by an encouraged, ultraradical, consequent, multivisceral surgery. Eisenkop *et al*[24] achieved 85% of optimal cytoreduction in a series of 163 patients with

stage Ⅲ and Ⅳ ovarian cancer. In our opinion, the limit of resectability can be defined by the extent of miliaric carcinomatosis on the serosa of the small bowel and by the infiltration of the major abdominal vessels. In conclusion, we should answer a crucial question to support the role of cyto-reduction in the management of advanced ovarian cancer: is attainment of an optimal outcome largely related to philosophy and skill of the surgeons or does it reflect a less aggressive tumor biology? These issues are still being studied and debated after more than 20 years. We believe that the better understanding of tumor biology can help in the planning of surgical strategy in cases of recurrent ovarian cancer, but the patient's general health, the presence of diffuse carcinomatosis, and the surgical philosophy are correlated with the achievement of an optimal surgical outcome.

NOVEL APPROACHES AND THE ROLE OF INTRAPERITONEAL CHEMOTHERAPY IN THE MANAGEMENT OF ADVANCED OVARIAN CANCER

Only about 50% of patients show a complete clinical response to systemic platinum/taxol based chemotherapy, and 30% of them have microscopic metastasis at second look surgery. Despite achieving clinical remission after completion of initial treatment, most patients (60%) with advanced epithelial ovarian cancer will ultimately develop recurrent disease or show drug resistance, and their rate of curability is less than 30%. The recurrence rate ranges between 30% and 50% for patients who show no lesion at the time of second look surgery[25]. In these patients, the median disease-free survival is only 24 mo.

These factors are major limitations in treatment of patients with ovarian cancer[26]. Different treatment modalities have been attempted to overcome these limits, such as secondary cytoreduction, second-line chemotherapeutic drugs, high-dose chemotherapy, intraperitoneal chemotherapy (IP), radiotherapy, immunotherapy, and hormone therapy. In fact, it is conceivable that recurrences in platinum-responsive patients might be prevented by higher doses of drugs to eradicate less sensitive clones of tumor cells that became resistant to platinum when lower doses are given during initial treatment[27].

To date, except for IP chemotherapy, none of these approaches has been found to have a significant impact on survival. IP chemotherapy refers to the administration of cytotoxic agents directly at the predominant disease site: the peritoneal cavity. The rationale is that a higher concentration of cytotoxic drugs and longer duration of exposure can be achieved while reducing the toxicity normally associated with intravenous therapy. In fact, cytotoxic drugs administered IP can directly target tumor masses confined to the abdominal cavity, thus bypassing the poor vascularization of small-volume disease and, therefore, increasing peri- and intra tumoral drug concentration. Cisplatin can penetrate small-volume tumors to a maximum depth of 1-3 mm; therefore, a benefit of this schedule can be obtained only for patients with microscopic residual disease. By the use of large doses of intraperitoneal cisplatin, the surface of the tumor can be exposed to high concentrations of cisplatin with a sufficient amount of drug leaking into the circulation. Thus, the level of drug reaching the tumor through capillaries is doubled compared with a maximally tolerated dose of cisplatin delivered intravenously[28].

Two large phase Ⅲ trials published in 1996 and 2001 have documented some outcome advantages for IP therapy[29,30]. Recently, a 3rd randomized trial showed that IP chemotherapy provides better long-term outcome than Ⅳ drug delivery in patients with advanced ovarian cancer[31]. In the United States, the National Cancer Institute and the Society of Gynecologic Oncologists have endorsed the use of intraperitoneal chemotherapy in recent position papers. However, some concerns have been raised about the use of IP therapy: (1) the effectiveness of IP therapy depends on uniform drug distribution. It is essential that fluid circulates freely throughout the peritoneal cavity. After cytoreductive surgery, the risk of IP adhesion formation is increased, which might limit the access of the active drug to the tumor areas; and (2) various complications have been attributed to IP catheter, such as infections.

The intraoperative administration of intraperitoneal chemotherapy has been designed to overcome such obstacles. The use of intraoperative intraperitoneal chemotherapy avoids the pitfalls of postoperative adhesions and inconsistent drug distribution. Overall, intraoperative chemotherapy allows optimal drug distribution to all peritoneal surfaces. This produces a regional pharmacokinetic advantage with the amount of drug delivered to the tumor greater than that delivered systemically.

Intraperitoneal hyperthermic chemotherapy (HIPEC) is a new treatment modality that is based on increasing the sensitivity of cancer cells to the direct cytotoxic effect of chemotherapeutic agents at high temperature and increasing the concentration of chemotherapeutic agents that penetrate cancer tissues[32-34]. In fact, it has been proved that high temperature damages cancer cell membranes and promotes cellular apoptosis by increasing the intracellular calcium concentration and DNA fragmentation. Another mechanism is the destabilization of thymidine kinase 1, which is involved in DNA synthesis in cancer cells[35]. At 42℃, hyperthermia is cytotoxic by itself, increasing membrane permeability, inhibiting DNA repair, and promoting macrophage lysosomal exocytosis with consequent apoptosis[36]. The treatment modulates the activity of cytokines[37], and increases the antigenicity of tumor cells by the production of heat shock proteins and the activation of natural killer cells[38]. In conclusion, the biophysical effects of HIPEC are: membrane protein denaturation, increased vascular permeability, and alterations of multimolecular complex for DNA synthesis and repair. Moreover, the architecture of the vasculature in solid tumors is chaotic, resulting in regions with low pH, hypoxia, and low glucose levels. This

microenvironment makes solid tumors more susceptible to hyperthermia[39].

Cisplatin has been shown to penetrate deeper into tumor tissue under hyperthermic conditions compared to normothermic conditions. At 40-43℃, neoplastic cells become more chemo-sensitive due to an enhancement of intracellular concentrations of drugs and to alterations in the DNA repair process, especially for alkylating agents[40,41]. In addition, it has been shown that these events have a greater intensity in cisplatin-resistant rather than cisplatin-sensitive ovarian cancer cells lines. Formation of platinum-DNA adducts after cisplatin exposure is enhanced in heated cells, thus resulting in relatively greater DNA damage[42].

The critical point of this approach is cytoreduction down to nodules of less than few millimetres, to allow HIPEC to act. The possible synergy between hyperthermia and chemotherapy agents has sparked clinical trials utilizing this combination in many disease types. With regard to situations analogous with ovarian carcinoma, in which the disease may be widespread within the peritoneal cavity, studies in gastric cancer, malignant mesothelioma, appendix cancer, and colorectal cancer have shown promising results. A phase Ⅲ randomized study of hyperthermic intraperitoneal chemotherapy following cytoreductive surgery compared with traditional iv chemotherapy in patients with peritoneal spread of colorectal carcinoma showed a statistically significant prolongation of life in the experimental arm[43]. In addition, this combined treatment has been suggested as the standard of care for peritoneal dissemination from neoplasm of the appendix[44,45] and diffuse malignant peritoneal mesothelioma[46]. With long-term follow-up, cytoreductive surgery plus HIPEC is the only treatment associated with a cure for these diseases.

EOC is a logical target for directed intraperitoneal therapy in combination with heat, and there are reports of clinical studies looking at hyperthermic intraperitoneal chemotherapy following surgical debulking in this disease[47-56]. In 2001, Hager *et al*[54] reported that HIPEC significantly increased the survival and response rates, and improved the quality of life, in 36 stage Ⅲ and Ⅳ ovarian cancer patients who showed resistance to systemic chemotherapy. Deraco *et al*[57] reported that HIPEC significantly increased two-year survival to 55% and delayed tumor progression in 27 patients with recurrent ovarian cancer after extensive surgery to nodules less than 2.5 mm in diameter. Nevertheless, the few clinical studies looking at HIPEC following surgical debulking suffer from some limitations: relatively small numbers of patients, retrospective studies, different clinical settings and drugs. In fact, published data show that different groups of patients have been often mixed together, in terms of number of recurrence (persistent, first, second, and third), type of recurrence (single, multiple, and carcinosis) and PFI (platinum-sensitive or -resistant). More recently, we reported an interesting series on the use of HIPEC and cytoreductive surgery in a specific setting of patients, where ovarian cancer women at their first recurrence with a PFI of at least 6 mo presented to a gynecological oncology referral centre[58]. All cases were strictly selected before inclusion in the protocol, utilizing AGO-DESKTOP Ⅱ criteria for secondary cytoreduction and performing an FDG-PET/CT and S-LPS in all cases before attempting surgery. The preoperative evaluation allowed a complete cytoreduction in 100% of the patients (23 CC-0 and two CC-1), that is an excellent result when compared to 50% of complete cytoreduction shown in a recent meta-analysis on secondary surgery[4]. As might be expected, this satisfying result was achieved at the cost of multiple organ resections, but peri-operative mortality and morbidity rates were 0% and 30%, respectively, which are well balanced with data reported in the recent literature, even if cytoreductive surgery alone is considered[59]. In conclusion, considering the potential advantages of HIPEC associated with cytoreductive surgery and the low morbidity and mortality rates, such a promising approach should be encouraged for long-term survival in platinum-sensitive recurrent ovarian cancer patients. We await larger prospective randomized studies with longer follow-up times.

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