Role of cytoreductive surgery in recurrent ovarian cancer

Ovarian cancer is the leading cause of death from gynecologic malignancy in western countries, primarily because over 60% of patients with ovarian cancer will experience disease recurrence. Primary cytoreductive surgery and combination chemotherapy are the cornerstones of the initial treatment for epithelial ovarian cancer. The management of recurrent ovarian cancer is less clear than that of primary disease. The management of recurrent ovarian cancer is largely based on systemic chemotherapy, with surgery being offered only in selected individuals. Despite this, the benefits of surgery has been shown in a meta-analysis by Bristow *et al.* where the survival is influenced by the completeness of cytoreduction. Therefore, epithelial ovarian cancer can be accepted as a chronic disease that consists of multiple recurrence and retreatments such as further surgeries and chemotherapies. The clinical applicability of this secondary surgery remains a controversial topic. Therefore, a trial on secondary surgery for recurrent ovarian cancer and the role of hyperthermic intraoperative peritoneal chemotherapy in addition to the current standard of care of administering systemic chemotherapy alone is warranted. The current data supported that the selection criteria to offer secondary cytoreduction represents one of the most important challenges. There are, to date, no Phase III trials that demonstrate the clinical utility of either secondary surgical cytoreduction or hyperthermic intraperitoneal chemotherapy in epithelial ovarian cancer.

KEYWORDS: gynecologic oncology ▪ HIPEC ▪ hyperthermic intraoperative peritoneal chemotherapy ▪ recurrent ovarian cancer ▪ secondary cytoreduction

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Epithelial ovarian cancer is the second most common genital malignancy in females, and is the most lethal gynecological malignancy with an estimated 5-year survival rate of 46% [1]. Despite efforts to develop an effective ovarian cancer screening method, 74% of patients still present with advanced (stages III–IV) disease [2]. In the setting of primary disease, optimal cytoreductive surgery (residual tumor <1 cm) and platinum-based chemotherapy have been established as the most important components when treating advanced epithelial ovarian cancer [3,4]. The theoretic benefit from cytoreductive surgery relates to removing large tumor volumes that have a decreased growth fraction and poor blood supply, thereby improving the efficacy of chemotherapeutic agents [5]. Indeed, the major determinants of clinical outcome are represented by both residual tumor at first surgery and sensitivity to platinum-based chemotherapy defined on the basis of the interval between completion of first-line chemotherapy and recurrence of disease [6].

Despite achieving clinical remission after completion of initial treatment, most patients (60%) with advanced epithelial ovarian cancer will ultimately develop recurrent disease [7]. The management of recurrent ovarian cancer is less clear than that of primary disease. In patients recurring within 6 months from the completion of first-line chemotherapy, treatment with platinum agents often results in short-lived response duration and survival [8], while in patients considered platinum sensitive, the median survival with platinum or platinum/paclitaxel rechallenge has been reported to range from 24 to 42 months [9–11].

Recently, much attention has been focused on the role of surgery in the management of ovarian cancer recurrence. A consensus regarding the management of recurrent epithelial ovarian cancer, especially the role of secondary cytoreductive surgery, has yet to be reached.

Much of the research is retrospective in nature and limited to small series [2,7,12–26]. Several selection criteria have been correlated with optimal surgery and survival benefit. Among them, disease-free interval (DFI) of at least 6–12 months from completion of initial chemotherapy, tumor size and location and good performance status are the most important [16,21,27,28].

The available data suggest a benefit for secondary cytoreduction in selected recurrent ovarian cancer. Recently, in a meta-analysis, Bristow *et al.* concluded that in view of the optimal effect between residual disease and survival outcome, it

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seems reasonable to adopt complete cytoreduction as the most appropriate surgical objective for women undergoing attempted cytoreductive surgery for recurrent ovarian cancer [7]. After controlling for all other factors, each 10% increase in the proportion of patients undergoing complete cytoreductive surgery was associated with a 3.0-month increase in median cohort survival time.

Our review will present the most recently evidence regarding the role of cytoreductive surgery in recurrent ovarian cancer and focuses on the following topics:

- What should be the clinical criteria and which type of work-up is recommended to identify the patients suitable for secondary cytoreductive surgery?
- Which patients should be offered cytoreductive surgery for recurrence, and what type of surgical management is required for this type of disease?
- What is the role of hyperthermic intraoperative peritoneal chemotherapy (HIPEC) in the management of recurrence?

We performed a Medline search with the keywords 'ovarian cancer', 'recurrence' and 'secondary cyto-reduction', limited to the English language.

Clinical identification of recurrent ovarian cancer patients suitable for secondary cytoreduction

Early diagnosis and the exact anatomic localization of the metastatic sites, besides the accurate selection of the patient's characteristics, represent a crucial factor in the determination of the best surgical and/or medical treatment for recurrence. In most of the studies reported, surgery has been acknowledged to be possibly beneficial only in selected patients presenting with a single recurrence after a platinum-free interval (PFI) longer than 6–12 months, and likely to be optimally cytoreduced to no visible tumor in the first cytoreductive surgery, although definitive conclusions are far from being reached. The controversies about this issue are due to the heterogeneity of the series and selection bias [7–29], but most importantly, due to the lack of knowledge of the natural history of the recurrence according to the pattern of disease presentation – indeed, it is still not clear whether the duration of PFI or presentation of recurrence as a discrete lesion versus diffuse abdominal carcinomatosis, or site/size of recurrence might differently impact on patient clinical outcome.

The Bristow *et al.* meta-analysis was unable to identify a clinical profile that could be utilized to select appropriate candidates for cytoreductive surgery, at least from the predictor variables utilized in this study [7]. They concluded that such clinical characteristics (DFI, extent of disease or number of lesions and precytoreduction size of largest tumor) might be indeed useful as surgical selection criteria.

Chi *et al.* have published recommendations that may assist surgeons in deciding whether secondary cytoreduction should be offered [25]. These recommendations were based on a multivariate analysis of survival. DFI and number of sites of recurrent disease were the only independent predictors of survival in addition to size of residual tumor. The presence of ascites was significant on univariate but not on multivariate analysis. In total, 157 patients underwent secondary cytoreduction, and 153 of those patients were evaluable. After secondary cytoreduction, the median follow-up was 36.9 months (range: 0.2–125.6 months), and the median survival was 41.7 months (95% CI: 36.0–47.2 months). For patients who had a DFI prior to recurrence between 6 and 12 months, the median survival was 30 months compared with 39 months for patients who had a DFI between 13 and 30 months, and 51 months for patients who had a DFI of over 30 months ($p < 0.005$). For patients who had a single site of recurrence, the median survival was 60 months compared with 42 months for patients who had multiple sites of recurrence, and 28 months for patients who had carcinomatosis ($p < 0.001$). The median survival for patients who had residual disease that measured below 0.5 cm was 56 months compared with 27 months for patients who had residual disease that measured greater than 0.5 cm ($p < 0.001$). On multivariate analysis, DFI ($p < 0.004$), the number of recurrence sites ($p < 0.01$) and residual disease ($p < 0.001$) were significant prognostic factors. This report concluded that secondary cytoreduction should be offered to all patients with a single site of recurrent disease regardless of DFI, as well as to all patients with a DFI of greater than 30 months regardless of the number of disease sites. They recommended that patients with carcinomatosis and a DFI of less than 12 months should not be considered for secondary cytoreduction.

Ferrandina *et al.* reported for the first time in multivariate analysis that the pattern of recurrence might play a role in determining a different clinical outcome in ovarian cancer patients: in particular, ovarian cancer patients suffering

from recurrence with a prevalent pattern of diffuse abdominal carcinomatosis showed an unfavorable prognosis with respect to cases presenting with discrete lesions [28]. They found no difference in the survival of cases presenting with early (PFI < 12 months) discrete nodule recurrence versus late (PFI > 12 months) recurrence as diffuse abdominal carcinomatosis: possible therapeutic alternatives aimed at improving the clinical outcome of these 'intermediate prognosis' groups could be represented, as in the case of discrete lesions by surgical removal plus chemotherapy, although there is no general agreement on the duration of PFI (6 vs 12 months) that should be taken into consideration in the prediction of survival benefit from surgery. On the other side, in cases of late (PFI > 12 months) recurrence as diffuse carcinomatosis, a more aggressive multimodal approach combining peritonectomy and chemotherapy could be explored. They concluded that not only the duration of PFI, but also the type of recurrence may independently influence post-relapse survival in ovarian cancer patients, and both should therefore be taken into great consideration when evaluating the treatment options in the salvage treatment of recurrent patients.

Interestingly, results from the DESKTOP OVAR trial [30], a large multicenter retrospective review, led to the design of an algorithm that will be used in a nonrandomized prospective trial. The algorithm suggests that patients with a good performance status and a DFI greater than 6 months should undergo secondary cytoreduction. In addition, these patients must have had no residual disease after initial surgery, and also currently have no large-volume (>500 ml) ascites. These factors were associated with a favorable surgical outcome in 81% of the patients. This predictive score will be evaluated prospectively (AGO-DESKTOP II).

Predicting preoperatively which patients can be optimally cytoreduced may be challenging. Although current radiologic procedures should help the clinician in the proper selection of the cases submitted to surgery, they have shown unsatisfactory results in the prediction of optimal cytoreduction [31–33].

Recently, several studies have been produced for the use of fluorine-18-fluorodeoxyglucose positive emission tomography (FDG-PET) and FDG-PET/computed tomography (FDG-PET/CT) in the early diagnosis of recurrence in ovarian cancer patients [34–37].

Recently Fulham *et al.* reported in a prospective, multicenter study, that for women with previously treated ovarian carcinoma with recurrent disease, FDG-PET/CT can alter management in close to 60% of patients; detect more sites of disease than abdominal and pelvic CT; and is superior in the detection of nodal, peritoneal and subcapsular liver disease [38].

Nevertheless, this technique is still limited by small-nodule carcinomatosis. Moreover, no data are available regarding the ability of FDG-PET/CT to assess diffusion of advanced intra-/retro-peritoneal disease, and its correlation with the possibility of complete cytoreduction. In this context, staging laparoscopy (S-LPS) has proved to offer a reliable evaluation of occult peritoneal carcinosis, and a good prediction of the possibility of optimal cytoreduction in primary advanced ovarian cancer patients [39].

Recently, Fagotti *et al.* reported for the first time the accuracy rate of FDG-PET/CT to predict the possibility to achieve an optimal cytoreduction in a large prospective series of recurrent ovarian cancer patients, which corresponded to 78.6% [40]. Combined radiological and laparoscopic evaluation showed a negative predictive value of 88.9%, a specificity of 59.3%, a positive predictive value of 78.8%, a sensitivity of 95.3% and an accuracy rate of 81.4%.

They concluded that the combination of FDG-PET/CT and staging laparoscopy has a significant effect on the multimodal approach to the population of patients with recurrent ovarian cancer. Such techniques should be considered complementary because of the potential of each one to identify a different setting of the disease. S-LPS can improve FDG-PET/CT sensitivity versus small-nodule carcinomatosis, as well as the accuracy in the detection of the number of nodules. On the other hand, FDG-PET/CT can provide a more accurate evaluation of retroperitoneal and/or intraparenchymal disease. Moreover, the logistic advantage of FDG-PET/CT, which means that only a single diagnostic test is necessary to exclude distant metastases by an 'all in one' examination, has to be emphasized. Finally, based on various modalities used in assessing the patient, laparoscopy still seems to be the gold standard in the final decision-making process. They suggested that both procedures could be useful before secondary cytoreduction, when compared with all laparotomies performed, including unnecessary ones. In fact, preventing unnecessary laparotomies could shorten the hospital stay and enable patients to start chemotherapy earlier. In addition, the ability to accurately plan surgery preoperatively is of great value, since it allows the surgeon and the odds ratio to be fully prepared and the patient to be well-counseled in advance.

Surgical management of recurrent ovarian cancer & technique aspects

Secondary cytoreduction is possible technically in a significant proportion of patients who have tumors that are eradicated by primary surgery and first-line chemotherapy. The secondary cytoreduction include enterolysis, visualization of all peritoneal surface and intraperitoneal or retroperitoneal tumor resection. The techniques used in abdominal, urologic and gynecologic surgery, such as bowel resection, pelvic exenteration, retroperitoneal lymphadenectomy, upper abdominal surgery (splenectomy, liver, gastric or partial pancreas resection and diaphragmatic surgery) and urinary tract resection, are applied in secondary surgery. In published series, the technical success rate of secondary cytoreduction vary widely, from 37–47% to 83% [7,27]. With currently available surgical techniques, secondary cytoreduction can be accomplished with significant but acceptable morbidity. The mortality risk is negligible.

Two recent groups published their experience with hepatic resection for recurrent ovarian cancer, and they concluded that parenchymal liver metastases should not preclude secondary surgical efforts. Merideth *et al.* reported on 26 patients who underwent hepatic resection for metachronous liver metastases from recurrent ovarian cancer [41]. Yoon *et al.* reported on 24 patients who underwent hepatic resection as part of their surgery for recurrent ovarian cancer [42]. Perioperative complications occurred in five patients, but there were no operative deaths and the median survival of their patients was 62 months. It would seem logical that the decision to perform hepatic resection should be only made if optimal cytoreduction can be achieved, and should be individualized and performed by surgeons with the necessary technical expertise and knowledge of the natural history and treatment algorithms for recurrent ovarian carcinoma.

Magtibay *et al.* reported the largest series of 46 patients who had undergone splenectomy as part of cytoreductive surgery for recurrent ovarian cancer [43]. They concluded that parenchymal splenic metastasis does not portend a poor prognosis and should not preclude a maximal surgical effort to minimize residual disease.

Recently, Bristow *et al.* reported a series of 56 patients who underwent a rectosigmoid colectomy for recurrent epithelial ovarian cancer, and they concluded that this type of surgery can contribute to a maximal cytoreductive surgical effort [44]. The morbidity is comparable to rectosigmoid colectomy performed for primary cytoreduction and the associated survival outcome appears favorable. Previously, Tamussino *et al.* reported a larger series of 110 patients undergoing rectosigmoid colectomy and 137 patients undergoing small-bowel resection for recurrent ovarian cancer [45].

Relapsing epithelial ovarian cancer exclusively located in the lymph nodes has recently gained attention concerning specific clinical characteristics, course of the disease and the patient management [46–48]. Isolated nodal recurrence is uncommon, but not exceptional. Legge *et al.* concluded that complete surgical resection of lymph node stations should be attempted in the absence of diffuse peritoneal disease [48].

In conclusion, we should ask the same questions for the secondary cytoreduction as for the primary cytoreduction: is attainment of an optimal outcome related to surgical philosophy and skill, or largely the reflection of less aggressive tumor biology? These issues are still being studied and debated after more than 20 years of inquiry. We believe that the better understanding of tumor biology can help in the planning of surgical strategy in the case of recurrent ovarian cancer, but the patient's general health, the presence of diffuse carcinomatosis and the surgical skill are correlated with the achievement of optimal surgical outcome.

Recently, Chi *et al.* demonstrated that the incorporation of extensive upper abdominal surgery into the operative strategy can lead to a significant increase in optimal cytoreduction rates and consequent improved progression-free survival and overall survival for advanced ovarian, tubal and peritoneal carcinoma [49]. The modified approach included diaphragm peritonectomy and/or resection, splenectomy, distal pancreatectomy, partial liver resection, cholecystectomy and resection of tumor from the porta hepatis in cases where the primary surgeon deemed them necessary to achieve optimal cytoreduction. A paradigm shift toward more complete primary cytoreduction can improve survival for patients with advanced ovarian, tubal and peritoneal carcinomas.

The role of intraperitoneal hyperthermic chemotherapy in the management of recurrent ovarian cancer

Recurrent ovarian carcinoma is a logical target for directed intraperitoneal therapy in combination with heat, and there are reports of

clinical studies looking at HIPEC following cytoreductive surgery in this disease [50–56]; however, there are few studies published, and those that are contain relatively small numbers of patients. With regard to analogous situations with ovarian carcinoma, in which disease may be widespread within the peritoneal cavity, studies in gastric cancer [57], malignant mesothelioma [58], appendix cancer [59,60] and colorectal cancer have shown promising results [61]. The reason to use HIPEC is that recurrent ovarian cancer is often a locoregional disease, involving only the peritoneum and adjacent intra-abdominal organs, making it ideally suited for locoregional therapy. Intraperitoneal delivery of chemotherapy in ovarian cancer has been shown to be effective in front-line treatment. Hyperthermia, on its own, is tumoricidal. In addition, it increases the cytotoxicity of cisplatin and other chemotherapeutic agents both in human cell culture and animal models, and may reverse cisplatin resistence. While the precise underlying molecular mechanism of this effects is unknown, studies of hyperthermia in combination with chemotherapy have demonstrated increased DNA cross-linking and increased DNA adduct formation [62–70].

In intraperitoneal chemotherapy the cytotoxic drugs can directly target tumor masses confined to the abdominal cavity, which offers the possibility of bypassing the poorly developed vasculature of small-volume disease and, therefore, increasing peri- and intra-tumoral drug concentration. Since intraperitoneal cisplatin can penetrate small-volume tumors (1–3 mm), maximum chemotherapeutic benefit could be derived for patients with microscopic residual disease or very small volume. Consequently, optimal cytoreductive surgery is a prerequisite for intraperitoneal chemotherapy, because of its limited penetration depth into tumor deposits.

As far as ovarian carcinoma is concerned, the few clinical studies looking at HIPEC following cytoreductive surgery [71–73] suffer from some limits: relatively small numbers of patients, retrospective studies, different clinical settings and drugs.

Since randomized studies regarding this topic have found some difficulties in the accrual of the patients, at present much information should be obtained throughout prospective studies focused on strictly selected patients during specific steps of the natural history of their disease. In fact, published data show that different groups of patients have often been mixed together, in terms of number of recurrence (persistent, first, second, third), type of recurrence (single, multiple, carcinosis) and PFI (platinum-sensitive or -resistant).

Bijelic *et al.*, in a systematic review, analyze the morbidity, mortality and survival benefit of cytoreductive surgery combined with HIPEC or early postoperative intraperitoneal chemotherapy [50]. They have identified 14 publications from the Medline search and, overall, 294 patients. The evidence presented in this systematic review indicates that cytoreductive surgery and heated intraoperative intraperitoneal surgery are a viable option in the management of recurrent ovarian cancer. Two different methods of administration of the heated intraoperative intraperitoneal chemotherapy were described in these studies. The open technique was used in seven studies [74–80]. This method involves the instillation of the chemotherapy solution into the open abdominal cavity with manual stirring to assure even distribution of the chemotherapy agents and heat. In the closed technique, the abdominal fascia is either temporarily or permanently closed after completion of the surgery, including all the anastomoses, and the chemotherapy solution circulated into the cavity through several catheters with the aid of a pump. Current data indicates that vigorous agitation of the intraperitoneal fluid increases the contact area of the peritoneum and may indicate that the open technique is superior to the closed method [81]. The survival reported with cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy may be superior to the results of conventional treatment. With systemic chemotherapy, patients with platinum-sensitive recurrent disease have an overall median survival of 29 months [16], while patients with platinum-resistant disease have an overall survival of only 17 months [82]. In contrast, overall survival of 22–45 months in patients treated with cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy is promising considering that most of the studies included a large number of patients with recurrent disease. The rates of significant morbidity associated with this combined treatment were low, ranging from 5 to 36%. The median mortality was 3% (range: 0–10%). These results indicate that selected patients with recurrent ovarian cancer could be considered as candidates for salvage therapy with cytoreductive surgery and heated intraperitoneal chemotherapy, and the efficacy of this combined treatment should be evaluated in a prospective Phase III trial.

Fagotti *et al.* reported an interested series on the use of HIPEC and cytoreductive surgery in a specific setting of patients – that is, women

with ovarian cancer at their first recurrence with a PFI of at least 6 months, presenting to a gynecologic oncology referral center [83]. All cases have been 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 has allowed a complete cytoreduction in 100% of the patients, which is an excellent result when compared with the 50% complete cytoreduction that was demonstrated in a recent meta-analysis on secondary surgery [7]. As may be expected, this satisfying result has been achieved at the cost of multiple organ resections, but perioperative mortality and morbidity rates have been 0 and 30%, respectively, which are well balanced with data reported in the recent literature, even if cytoreductive surgery alone is considered [26].

Recently, deBree *et al.* reported that the use of paclitaxel for HIPEC following cytoreductive surgery seems feasible and relatively safe, with acceptable morbidity in patients with primary and secondary peritoneal tumors [84]. Its administration is associated with a highly favorable pharmacokinetic profile, despite the short treatment duration of HIPEC. Very high local drug exposure, which is approximately 50- to 60-times higher than achieved after intravenous administration, and low systemic drug levels, make paclitaxel a very attractive drug for HIPEC. They concluded that larger studies with a more homogeneous patient cohort and prolonged follow-up should be performed to demonstrate its definite efficacy.

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, and larger prospective randomized studies with a longer follow-up time are awaited.

Conclusion & future perspective

During the past 20 years, secondary cytoreduction has emerged as an accepted treatment option for a select group of patients with recurrent ovarian cancer. Despite a growing body of retrospective literature illustrating an inverse relationship between residual disease and postrecurrence survival, the clinical applicability of secondary cytoreduction remains a controversial topic. The current data supported that the selection criteria to offer secondary cytoreduction represents one of the most important challenges, and we believe that for this issue in the future the role of laparoscopy combined with FDG-PET/CT will play a more interesting role.

Moreover, numerous variables are responsible for the improvement in the surgical outcome, such as advances in surgical effort and training, advances in perioperative management, and a multidisciplinary surgical team. These findings emphasize the importance of comprehensive training, preparation and referral to centers that specialize in the surgical management of patients with advanced disease.

However, there has not been a prospective randomized trial that confirmed the benefits of secondary cytoreduction combined with adjuvant therapy compared with chemotherapy alone. Until more definitive Phase III data are made available, our current philosophy is that surgical cytoreduction plays a determinant role in the management of selected patients with recurrent ovarian cancer.

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Executive summary

- The role of secondary cytoreduction in ovarian cancer and its clinical outcome are discussed in this review.
- The definition of the selection criteria to offer secondary cytoreduction represents one of the most important challenges.
- The pattern of recurrence and the platinum-free interval should be included in the selection criteria to identify candidates for secondary cytoreduction. The preoperative work-up of secondary cytoreduction should be performed with use of positron emission tomography/computed tomography and explorative laparoscopy.
- The role of hyperthermic intraoperative peritoneal chemotherapy associated with optimally secondary cytoreduction should be evaluated by a prospective clinical trial.
- There has not yet been a prospective randomized trial that confirmed the benefits of secondary cytoreduction combined with adjuvant therapy compared with chemotherapy alone.
- Comprehensive training, preparation and referral to centers that specialize in the surgical management of recurrent ovarian cancer patients are essential for the treatment of these individuals.

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