Role of secondary cytoreduction in recurrent ovarian cancer

The majority of ovarian cancer patients will recur despite aggressive initial debulking surgery followed by platinum- and taxane-based chemotherapy. At present, there is no standard of care for management of these patients. Secondary cytoreductive surgery may be offered to patients with disease recurrence after a disease-free interval of 6–12 months, during which time they demonstrate a complete response to primary therapy and have no evidence of disease. The key is to be able to accurately predict preoperatively which patients have the greatest likelihood of being completely cytoreduced. Although the existing literature is limited, it does show a consistent survival benefit, specifically in patients undergoing maximal cytoreduction to no gross evidence of disease. This article discusses various selection criteria that have been demonstrated to be predictive of successful surgery, as well as various prognostic factors that influence survival following secondary cytoreductive surgery.

KEYWORDS: cytoreduction ▪ ovarian cancer ▪ recurrent ovarian cancer ▪ secondary cytoreductive surgery

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Theoretical background for primary & secondary surgical cytoreduction

An estimated 21,550 women are diagnosed with ovarian cancer annually in the USA [1]; it is the leading cause of gynecologic cancer-related deaths, with approximately 14,600 deaths per year. For advanced ovarian cancer, the therapeutic role of primary cytoreductive surgery with the aim of complete resection followed by platinum- and taxane-based chemotherapy is well established [2]. The concept of surgical cytoreduction for ovarian cancer can be traced back to Meigs in 1934, who first proposed that the efficacy of postoperative irradiation could be enhanced by surgical removal of as much disease as possible [3]. In 1975, Griffiths published a landmark study that was the first to clearly demonstrate the inverse relationship between postoperative residual tumor size and overall survival [4]. More contemporary studies by Hoskins *et al.*, reporting for the Gynecologic Oncology Group (GOG), further demonstrated that there is a maximal diameter of residual disease above which extensive efforts at cytoreduction do not improve survival, thus helping to define the term 'optimal cytoreduction' in primary ovarian cancer [5]. Moreover, there is a continuum below this threshold, such that progressive reduction in maximal diameter of residual disease is associated with improved overall survival time, with the best survival outcome seen in those patients that have maximal cytoreduction to no gross evidence of residual disease [6].

The survival benefit associated with surgical cytoreduction is thought to be related to several theories of tumor cell kinetics and the development of drug resistance [7–9]. As hypothesized by the Gompertzian cell growth curve model, there is an increased rate of growth in the earlier part of the curve when tumors are relatively small [10]. As a result, the log-kill of tumors by chemotherapy is thought to be greater in small-volume tumors made up of rapidly growing and dividing cells. Theoretically, surgical cytoreduction works by removing large tumors with a relatively small growth fraction and leaving behind much smaller (or microscopic) tumors with a relatively greater growth fraction (higher proportion of actively dividing cells), making them more susceptible to the effects of cytotoxic chemotherapy. In addition, reduction in the tumor size may decrease the adverse metabolic effects of the tumor on the host, potentially leading to improved patient comfort and performance status. Furthermore, tumor debulking may enhance tumor perfusion, resulting in improved drug delivery to the target tissues. Finally, according to the Goldie–Coldman hypothesis, decreasing the number of viable tumor cells will decrease the rate of somatic mutations that often perpetuate drug resistance [11]. Thus, cytoreductive surgery is thought to both remove existing resistant tumor cells and decrease the spontaneous development of additional resistant cells.

Despite aggressive initial primary surgical tumor cytoreduction followed by platinum- and

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taxane-based chemotherapy, the majority of advanced-stage ovarian cancer patients will ultimately recur [12,13]. The theories used to explain the survival benefit of primary cytoreductive surgery are also thought to apply to surgical cytoreduction in the recurrent setting. Berek was the first to introduce the term 'secondary cytoreduction' in 1983 [14]. This initial report included a heterogeneous collection of patients. Subsequent studies have more clearly defined the clinical scenario in which a repeat attempt at surgical tumor removal may provide an associated survival benefit. Specifically, secondary cytoreductive surgery is currently defined as an operative procedure performed in patients with recurrent ovarian cancer after completion of primary treatment and a disease-free interval (DFI) usually longer than 6–12 months, for the purpose of removing as much tumor as possible in order to augment the effectiveness of subsequent chemotherapy. It is this patient population that is the subject of this article. This article will not address surgery for patients with persistent or progressive disease who do not respond to first-line therapy, as secondary surgery is not associated with significant survival benefit but does carry a significant risk of operative morbidity (24%) [15]. Thus, a period of time after initial therapy without any biochemical, clinical or radiological evidence of disease is one of the more important selection criteria in identifying appropriate candidates for attempted secondary surgical cytoreduction.

Complete resection as the goal of secondary cytoreductive surgery

The concept of 'optimal debulking' in primary ovarian cancer refers to removal of tumor burden below a certain threshold of maximal diameter of residual disease, above which there is no survival advantage to surgical cytoreduction despite the amount of surgical effort invested. In the primary surgery setting, it is well accepted that 'optimal cytoreduction' is most commonly defined as residual disease measuring a maximum of 1 cm, although recent literature indicates that maximal cytoreduction to no gross evidence of disease is associated with the greatest survival benefit [16]. The ideal surgical objective, in terms of the maximal diameter of residual disease, is not as well defined in the setting of cytoreductive surgery for recurrent ovarian cancer.

Consequently, the question is often posed: what should the goal be for surgical cytoreduction in recurrent ovarian cancer? Much of the literature on secondary cytoreductive surgery for recurrent ovarian cancer consists of small, retrospective, single-institution studies with a range of optimal debulking definitions from no gross evidence of disease to residual disease smaller than 2 cm. The larger studies reported on at least 100 patients having some period of complete clinical remission before undergoing secondary surgical cytoreduction [17–21]. Eisenkop *et al.* looked at 106 patients and found that maximal cytoreduction to no gross evidence of disease was possible in 82% of patients and was associated with a significant improvement in survival [17]. In the largest series addressing surgery for recurrent ovarian cancer, Harter *et al.*, reporting for the Descriptive Evaluation of preoperative Selection Kriteria for Operability in Recurrent Ovarian Cancer (DESKTOP) trial, studied 267 patients and concluded that only complete resection was associated with a prolonged survival after secondary cytoeduction [18]. A total of 50% of patients were completely cytoreduced in this study. Scarabelli *et al.* and Zang *et al.* demonstrated a survival benefit for both complete cytoreduction to no gross disease as well as 'optimal cytoreduction' to less than 1 cm in greatest dimension, with a complete resection rate of 36 and 9%, respectively [19,20]. Other investigators have advocated that residual disease less than 0.5 cm should be the surgical objective for secondary cytoreductive operations [21]. For example, in a study of 153 patients in which 41% of patients were completely cytoreduced, Chi *et al.* noted a significant survival benefit for residual disease measuring a maximum of 0.5 cm [21]. Based on the totality of the available data, the most reasonable and objectively verifiable surgical objective for secondary cytoreductive surgery for recurrent ovarian cancer seems to be no gross evidence of disease. If complete resection is not possible, the surgeon can aim to cytoreduce the patient to less than 1 cm, bearing in mind that anything above this would instead be considered palliative surgery.

Selection criteria to predict successful surgical outcome

The selection criteria to predict successful surgical outcome are outlined in **Box 1**. The key to maximizing survival outcome and minimizing the number of unnecessary or unsuccessful surgical procedures is accurate patient selection. It is important to counsel patients appropriately regarding the morbidity associated with further surgery followed by chemotherapy versus chemotherapy alone. In 1998, five groups of experts met at the Second International Ovarian Cancer Consensus Conference to provide guidelines on various topics based mainly on expert opinion rather than the literature [22]. The criteria

established for candidates for secondary cytoreductive surgery were as follows: DFI longer than 12 months, response to first-line therapy, potential for complete resection based on preoperative evaluation, good performance status and younger age. While these empiric criteria are intuitively accurate, they lacked verification from the scientific literature. As a result, subsequent investigators have made more rigorous attempts to define clinically useful parameters by which to select patients for attempted secondary surgical resection. The largest series addressing surgical selection criteria are the DESKTOP I and II trials [18,23]. In the largest study, which was completed in 2006, the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) group published the DESKTOP I trial, a multi-institution retrospective study of 267 patients that identified the following predictors for successful surgical cytoreduction: good performance status (Eastern Cooperative Oncology Group [ECOG] performance status 0), no residual disease after surgery for primary treatment or initial International Federation of Gynecology and Obstetrics (FIGO) stage I/II disease, and absence of ascites greater than 500 ml in the preoperative workup [18]. Complete resection was achieved in 79% of patients who met all of these criteria compared with 43% in patients who did not meet all criteria. The DESKTOP II trial was undertaken to prospectively validate the AGO scoring system [23]. Patients who had a good performance status, complete resection of disease at primary surgery and absence of ascites were defined as having a positive score. A positive score resulted in a complete resection rate of 76% in the setting of recurrent ovarian cancer, thereby validating the score. However, the original study reported a 43% complete resection rate in patients who did not meet these criteria, demonstrating that patients who do not meet criteria should be informed of the lower success rate of complete resection but should not be excluded from secondary cytoreductive surgery based strictly on their preoperative AGO score. AGO is planning a randomized Phase III trial comparing secondary surgery plus chemotherapy versus chemotherapy alone in patients with platinum-sensitive recurrent ovarian cancer, the results of which will be valuable in validating the use of secondary surgery.

A follow-up article of the DESKTOP trial determined that the presence of peritoneal carcinomatosis was associated with a decreased likelihood of complete surgical resection, with rates of 26 and 74% in the presence and absence of carcinomatosis, respectively [24]. Importantly, carcinomatosis had no adverse effect on prognosis if complete resection was achieved. The 2-year survival rate of patients with peritoneal carcinomatosis who were completely debulked was 77%, which is similar to the 2-year survival rate of 81% in patients without peritoneal carcinomatosis whose disease was completely resected.

Box 1. Proposed selection criteria to consider for successful secondary surgical cytoreduction.

- Disease-free interval longer than 12 months.
- Response to first-line therapy.
- Potential for complete resection based on preoperative evaluation.
- Good performance status.
- Younger age.
- No residual disease after surgery for primary treatment.
- Initial International Federation of Gynecology and Obstetrics stage I/II disease.
- Absence of ascites greater than 500 ml.
- Absence of peritoneal carcinomatosis.
- Size of largest recurrent tumor less than 10 cm.
- Absence of preoperative salvage chemotherapy.
- Solitary site of recurrence.

A significant number of single-institution studies have offered additional criteria that may be useful in selecting appropriate surgical candidates for secondary cytoreduction, although they remain controversial. Upon multivariate analysis, Eisenkop *et al.* found that the following factors were predictors of complete resection: size of largest recurrent tumor smaller than 10 cm, absence of preoperative salvage chemotherapy and a good performance status [17]. A retrospective review of 38 patients by Gronlund *et al.* reported that a solitary site of tumor recurrence was independently associated with complete cytoreduction [25]. Improved resection rates with solitary versus multiple sites of recurrence have been supported elsewhere in the literature [7,20].

One of the most well-studied factors to be used as a preoperative selection criterion is the DFI, or the time from the completion of chemotherapy to the diagnosis of recurrence. The precise DFI is variable depending on the study. Interestingly, the DESKTOP trial did not detect any impact on predicting successful surgical cytoreduction when comparing DFIs of 6–12 months versus longer than 12 months [18]. Although the DFI has not been shown to be a good predictor of successful surgical cytoreduction, there is some evidence to support its role as a prognostic factor for survival following surgical cytoreduction, which will be discussed later [17,21,26–28].

How frequently can successful surgery be performed?

The likelihood of successful secondary surgical resection for recurrent ovarian cancer depends on both the patient selection criteria employed,

which can be variable, and the complexity of the operation required to achieve the stated surgical objective. Most patients with recurrent ovarian cancer are already status posthysterectomy and bilateral salpingo-oophorectomy, and many nongynecologic procedures are often required to achieve complete surgical cytoreduction, which include bowel resection, lymph node dissection, diaphragm stripping or resection, liver resection and splenectomy. Repeat laparotomy after extensive initial tumor debulking and chemotherapy for secondary cytoreduction is challenging and the rates of resection vary widely. Most series reported optimal debulking rates, defined as no gross evidence of disease to less than 2 cm, between 40 and 60% [8,21,22,29–32], although two series have described optimal resection rates of greater than 80% [28,33]. In terms of complete resection, studies have reported rates ranging from 40% [21,25,26,34] to as high as 80% [17]. This wide variation is probably attributable to patient selection criteria employed, surgeon experience, extent of surgery required, surgical objective in terms of residual disease smaller than 1 cm versus no gross evidence of disease and institutional approach.

Prognostic factors to predict prolonged survival after secondary cytoreduction

Prognostic factors to predict prolonged survival after secondary cytoreduction are outlined in Box 2. The therapeutic value of surgery for recurrent ovarian cancer is widely debated, as it is difficult to quantify the impact of surgical cytoreduction in relation to other factors, including the biology of the disease and potential patient selection bias. In an effort to address some of these issues, Bristow *et al.* conducted a meta-analysis of 2019 patients from 40 study cohorts in order to determine the effect of multiple prognostic factors on overall survival among cohorts of patients undergoing surgical cytoreduction for recurrent ovarian cancer [35]. The only statistically significant clinical variable independently associated with survival was the proportion of patients undergoing complete surgical cytoreduction. This effect was quantified such that after controlling for all other factors, each 10% increase in the proportion of patients undergoing complete surgical cytoreduction was associated with a 3-month increase in median cohort survival time (Figure 1).

Box 2. Prognostic factors for survival after secondary surgical cytoreduction.

- Complete surgical cytoreduction.
- Longer disease-free interval.
- Absence of ascites greater than 500 ml.
- Absence of peritoneal carcinomatosis.
- Limited number of sites of recurrence.
- Size of largest recurrent tumor less than 10 cm.
- Absence of salvage chemotherapy.
- Platinum-based chemotherapy following secondary cytoreduction.

Although the role of DFI was not shown to be a reliable predictor of successfully performing secondary surgical cytoreduction in the DESKTOP trial [18], there is a significant body of evidence to support that a longer DFI is associated with an improved survival [17,21,26–28,36]. Most studies in the literature use a 6-month DFI as a cut-off in order for a patient to be a candidate for secondary surgical cytoreduction. Eisenkop *et al.* found that improved survival was associated with longer DFIs when comparing 6–12 versus 13–36 versus more than 36 months [17]. In a study cohort of 153 patients, Chi *et al.* used a statistical analysis termed smoothing techniques to demonstrate that survival was significantly improved after secondary surgical cytoreduction in longer DFI groups and identified cut-off points of 6–12, 13–30 and over 30 months [21]. Similar findings of significant survival impact associated with longer DFIs have been reported [26–28,36], although other data did not detect any impact on survival [7,30,37,38].

Multiple prognostic factors for prolonged survival that have been investigated refer to preoperative tumor burden and include absence of ascites, absence of peritoneal carcinomatosis, number of sites of recurrence and tumor diameter of recurrent disease. With regard to ascites, the DESKTOP trial found ascites less than 500 ml was a positive predictive factor of survival on both univariate and multivariate analyses [18]. Chi *et al.* reported ascites was significantly associated with survival on univariate but not multivariate analysis [21]. As discussed earlier, Harter *et al.* demonstrated that the presence of carcinomatosis is a reliable predictor for the inability to completely resect a patient, but if complete resection is achieved, the survival rate is similar to completely resected patients who did not have peritoneal carcinomatosis [24]. Thus, the presence of carcinomatosis does not directly impact survival as much as it impacts the ability to perform successful surgery. Similarly, having multiple sites of recurrence has been associated with a decreased rate of successful surgical cytoreduction and an associated negative impact on survival [20]. Several studies have reported a decreased survival with multiple sites of disease recurrence [8,21,36]. Chi *et al.* found that patients with a single site of recurrence had a median survival of 60 months compared with 42 months with multiple sites of recurrence and

28 months for patients with carcinomatosis [21]. Salani *et al.* demonstrated that patients with one or two radiographic recurrence sites had an improved median survival time of 50 months compared with patients with three to five sites, whose median survival time was 12 months [36]. Another potential prognostic factor reported by some studies to adversely affect survival is larger tumor diameter ranging from 5 to 10 cm [14,17,28], although the association of tumor size to survival is still controversial [8,31,33,34,38].

Only a few studies have evaluated the association of chemotherapy with survival [17,18]. Eisenkop *et al.* noted a survival disadvantage for patients who received salvage chemotherapy before undergoing secondary cytoreductive surgery, with a median survival of 25 months for patients receiving salvage chemotherapy versus 48 months for patients not receiving salvage chemotherapy before secondary surgery [17]. The DESKTOP trial examined the type of postoperative chemotherapy given to patients following secondary surgical cytoreduction and reported that women who received platinum-based chemotherapy had a significantly improved survival over patients treated with other chemotherapy regimens [18]. This can be explained by the fact that most patients who are candidates for secondary cytoreduction have, by definition, platinum-sensitive disease.

Role of hyperthermic intraperitoneal chemotherapy in recurrent ovarian cancer

Hyperthermic intraperitoneal chemotherapy (HIPEC) is an aggressive locoregional treatment modality currently being investigated in the setting of advanced and recurrent ovarian cancer. The ability of hyperthermia to increase the response to cytotoxic agents has been shown in human cell lines and animal models [39,40]. Spratt *et al.* were the first to look at the feasibility of its clinical use for peritoneal carcinomatosis in a patient with pseudomyxoma peritonei [41].

The median overall postrecurrence survival in patients undergoing secondary cytoreductive surgery without HIPEC is approximately 30 months, ranging from 10 to 62 months [35]. In the largest series to date on HIPEC in ovarian cancer, Bereder *et al.* reported a median overall survival of 46 months in patients with their first episode of recurrence [42]. In a systematic review of cytoreductive surgery and HIPEC in primary and recurrent ovarian cancer Bijelic *et al.* reported a median overall survival ranging from 22 to 54 months. They reported that seven out of 14 studies analyzed showed that patients who underwent complete cytoreduction had the greatest benefit [43]. Mostly platinum compounds have been used in HIPEC for ovarian cancer, but de Bree *et al.* noted promising results for docetaxel HIPEC in the setting of recurrent disease [44]. Although the consensus statement by Helm *et al.* concluded that HIPEC at the time of surgery for ovarian cancer has potential, there is no randomized evidence to support any additional survival benefit with HIPEC compared with secondary cytoreductive surgery followed by standard intravenous chemotherapy in the recurrent ovarian cancer setting [45]. In addition, cytoreductive surgery in combination with HIPEC is associated with significant severe morbidity, with rates of up to 40%, and mortality, with rates of 0–10% [46]. Further research is needed to determine the role of HIPEC in recurrent ovarian cancer following secondary cytoreductive surgery. HIPEC in ovarian cancer is not recommended outside of prospective controlled trials.

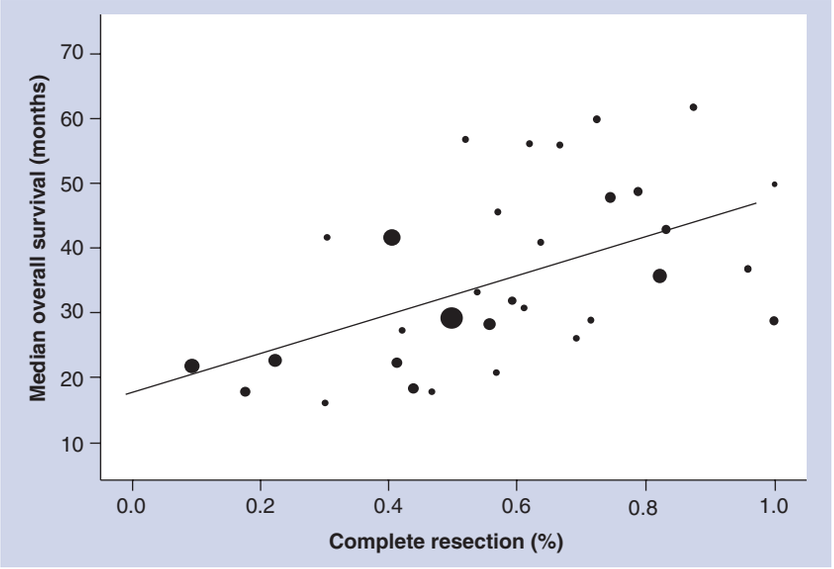

Figure 1. Simple linear regression analysis of median cohort overall survival versus proportion of patients in each cohort undergoing complete cytoreductive surgery for recurrent ovarian cancer. Circle size is proportional to the number of subjects in each study.
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Future perspective

At present, the use of secondary cytoreductive surgery for patients with recurrent ovarian cancer is not supported by level I or II evidence; nevertheless, the existing literature does show a consistent survival advantage in patients who undergo complete cytoreduction. Both AGO and the GOG are currently performing prospective randomized trials comparing surgery and chemotherapy with chemotherapy alone for patients with recurrent ovarian cancer. The results of these trials will be

critical in further evaluating and defining the role of secondary surgical cytoreduction in recurrent ovarian cancer. Hopefully, such information will help physicians to counsel their patients accordingly and to offer a secondary debulking procedure as appropriate. Determining accurate preoperative selection criteria continues to be a challenge and warrants further research. The role of heated intraperitoneal chemotherapy is still unknown and requires a prospective randomized trial.

For those patients who undergo successful secondary cytoreductive surgery and later experience disease recurrence, there is a small but growing body of literature proposing a role for tertiary cytoreduction in a highly select group of patients [47,48]. Similar to secondary cytoreduction, the amount of residual disease following tertiary cytoreductive surgery has demonstrated significant prognostic significance.

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Executive summary

Theoretical background for primary & secondary surgical cytoreduction

- The inverse relationship between postoperative residual tumor size and overall patient survival for primary ovarian cancer was reported in the landmark paper by Griffiths in 1975.
- Theories to help explain the benefit of tumor debulking include: reducing tumors from large slowly growing tumors to small rapidly dividing tumors more susceptible to the effects of chemotherapy, decreasing adverse metabolic events, enhancing perfusion and drug delivery, and decreasing the number of viable cells with potential for spontaneous mutations that can lead to drug resistance.
- Secondary cytoreductive surgery is defined as an operative procedure performed in patients after completion of primary treatment and a disease-free interval of at least 6 months with the goal of debulking as much tumor as possible.

Complete resection as the goal of secondary cytoreductive surgery

- 'Optimal debulking' refers to removal of tumor burden below a threshold above which there is no survival advantage.
- Maximal cytoreduction in primary ovarian cancer is being emphasized to provide the greatest survival advantage, although the concept of optimal debulking is well accepted in primary ovarian cancer as a maximum of 1 cm. The benefit of cytoreduction is still controversial in recurrent ovarian cancer.
- Based on the literature, the goal of secondary surgical cytoreduction should be complete gross resection of all visible disease.

Selection criteria to predict successful surgical outcome

- It is critical to be able to accurately predict preoperatively which patients will have the greatest probability of successful cytoreduction.
- Consensus statements giving preliminary selection criteria were published in 1999, largely based on expert opinion.
- The Descriptive Evaluation of preoperative Selection Kriteria for Operability in Recurrent Ovarian Cancer (DESKTOP) trial is the largest series to date on secondary cytoreductive surgery in ovarian cancer and reported the following factors to be predictive of successful cytoreduction: good performance status, no residual disease after primary surgery or International Federation of Gynecology and Obstetrics stage I/II disease, and absence of ascites greater than 500 ml.
- Other literature supports these additional selection criteria: longer disease-free interval, absence of carcinomatosis, small size of tumor and absence of preoperative salvage chemotherapy.

How frequently can successful surgery be performed?

- Careful selection of patients is the key to successful cytoreduction.
- Secondary surgery is challenging given the setting of re-exploration and the frequent need to perform many nongynecologic procedures, including bowel resection, diaphragm resection, liver resection and splenectomy.
- Most series report rates of 40–60% for optimal cytoreduction and 40% for complete cytoreduction, although some studies report rates as high as 80% for optimal or complete cytoreduction.

Prognostic factors to predict prolonged survival after secondary cytoreduction

- The existing literature, although retrospective, consistently shows a survival advantage with complete resection of disease.
- Other prognostic factors include: longer disease-free interval, absence of ascites, absence of carcinomatosis, fewer and smaller lesions, absence of salvage chemotherapy and administration of platinum-based chemotherapy following secondary cytoreduction.

Role of hyperthermic intraperitoneal chemotherapy in recurrent ovarian cancer

- The role of hyperthermic intraperitoneal chemotherapy in recurrent ovarian cancer has not been determined.
- It is also important to keep in mind the reported severe morbidity rates of up to 40% and mortality rates of 0–10%.

Future perspective

- The results of ongoing prospective randomized trials comparing secondary surgery and chemotherapy to chemotherapy alone in recurrent ovarian cancer will help to more clearly define the role of secondary surgical cytoreduction.
- Further work is needed to determine accurate preoperative selection criteria that can help to predict which patients will be able to undergo successful complete cytoreduction.

Bibliography

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ: Cancer statistics, 2009. *CA Cancer J. Clin.* 59(4), 225–249 (2009).

2 du Bois A, Quinn M, Thigpen T *et al.*: 2004 consensus statements on the management of ovarian cancer: final document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIG OCCC 2004). *Ann. Oncol.* 16(Suppl. 8), viii7–viii12 (2005).

▪ **Consensus statements with recommendations for selection criteria for secondary cytoreductive surgery.**

3 Meigs JV: *Tumors of the Female Pelvic Organs*. MacMillan, NY, USA (1934).

4 Griffiths CT: Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. *Natl Cancer Inst. Monogr.* 42, 101–104 (1975).

▪ **Landmark study demonstrating inverse relationship of tumor size and overall survival in ovarian cancer.**

5 Hoskins WJ, Bundy BN, Thigpen JT, Omura GA: The influence of cytoreductive surgery on recurrence-free interval and survival in small-volume stage III epithelial ovarian cancer: a Gynecologic Oncology Group study. *Gynecol. Oncol.* 47(2), 159–166 (1992).

6 Hoskins WJ, McGuire WP, Brady MF *et al.*: The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. *Am. J. Obstet. Gynecol.* 170(4), 974–979 (1994).

7 Munkarah A, Levenback C, Wolf JK *et al.*: Secondary cytoreductive surgery for localized intra-abdominal recurrences in epithelial ovarian cancer. *Gynecol. Oncol.* 81(2), 237–241 (2001).

8 Gadducci A, Iacconi P, Cosio S *et al.*: Complete salvage surgical cytoreduction improves further survival of patients with late recurrent ovarian cancer. *Gynecol. Oncol.* 79(3), 344–349 (2000).

9 Eisenkop SM, Friedman RL, Wang HJ: Secondary cytoreductive surgery for recurrent ovarian cancer. A prospective study. *Cancer* 76(9), 1606–1614 (1995).

10 Norton L: Theoretical concepts and the emerging role of taxanes in adjuvant therapy. *Oncologist.* 6(Suppl. 3), 30–35 (2001).

11 Goldie JH, Coldman JA: A mathematical model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treat. Rep.* 63, 1727–1733 (1979).

12 Chi DS, Liao JB, Leon LF *et al.*: Identification of prognostic factors in advanced epithelial ovarian carcinoma. *Gynecol. Oncol.* 82, 532–537 (2001).

13 Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ: Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J. Clin. Oncol.* 20, 1248–1259 (2002).

14 Berek JS, Hacker NF, Lagasse LD, Nieberg RK, Elashoff RM: Survival of patients following secondary cytoreductive surgery in ovarian cancer. *Obstet. Gynecol.* 61, 189–193 (1983).

15 Morris M, Gershenson DM, Wharton JT: Secondary cytoreductive surgery in epithelial ovarian cancer: nonresponders to first-line therapy. *Gynecol. Oncol.* 33(1), 1–5 (1989).

16 du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J: Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized Phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). *Cancer* 115(6), 1234–1244 (2009).

17 Eisenkop SM, Friedman RL, Spirtos NM: The role of secondary cytoreductive surgery in the treatment of patients with recurrent epithelial ovarian carcinoma. *Cancer* 88(1), 144–153 (2000).

18 Harter P, du Bois A, Hahmann M *et al.*: Surgery in recurrent ovarian cancer: the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR trial. *Ann. Surg. Oncol.* 13, 1702–1710 (2006).

▪▪ **Largest series looking at surgical cytoreduction in recurrent ovarian cancer using the Arbeitsgemeinschaft Gynaekologische Onkologie score to predict the likelihood of successful tumor debulking.**

19 Scarabelli C, Gallo A, Carbone A: Secondary cytoreductive surgery for patients with recurrent epithelial ovarian carcinoma. *Gynecol. Oncol.* 83, 504–512 (2001).

20 Zang Ry, Li ZT, Tang J *et al.*: Secondary cytoreductive surgery for patients with relapsed epithelial ovarian carcinoma: who benefits? *Cancer* 100, 1152–1161 (2004).

21 Chi DS, McCaughty K, Diaz JP *et al.*: Guidelines and selection criteria for secondary cytoreductive surgery in patients with recurrent, platinum-sensitive epithelial ovarian carcinoma. *Cancer* 106, 1933–1939 (2006).

22 Berek JS, Bertelsen K, du Bois A *et al.*: Advanced epithelial ovarian cancer: 1998 consensus statements. *Ann. Oncol.* 10(Suppl. 1), S87–S92 (1999).

23 Harter P, Sehouli J, Reuss A *et al.*: Predictive factors for resection in recurrent ovarian cancer. Intergroup study of AGO Kommission Ovar, Ago-OVAR, AGO Austria, MITO and NOGGO. Presented at: *The 12th Biennial Meeting International of the Gynecologic Cancer Society.* Bangkok, Thailand, 25–28 October 2008 (Abstract 38).

24 Harter P, Hahmann M, Lueck HJ *et al.*: Surgery for recurrent ovarian cancer: role of peritoneal carcinomatosis: exploratory analysis of the DESKTOP I trial about risk factors, surgical implications, and prognostic value of peritoneal carcinomatosis. *Ann. Surg. Oncol.* 16(5), 1324–1330 (2009).

25 Gronlund B, Lundvall L, Christensen IJ, Knudsen JB, Høgdall C: Surgical cytoreduction in recurrent ovarian carcinoma in patients with complete response to paclitaxel-platinum. *Eur. J. Surg. Oncol.* 31(1), 67–73 (2005).

26 Tay EH, Grant PT, Gebski V, Hacker NF: Secondary cytoreductive surgery for recurrent epithelial ovarian cancer. *Obstet. Gynecol.* 99, 1008–1013, (2002).

27 Leitao MM, Kardos S, Barakat RR, Chi DS: Tertiary cytoreduction in patients with recurrent ovarian cancer. *Gynecol. Oncol.* 95, 181–185 (2004).

28 Onda T, Yoshikawa H, Yasugi T, Yamada M, Matsumoto K, Taketani Y: Secondary cytoreductive surgery for recurrent epithelial ovarian carcinoma: proposal for patients selection. *Br. J. Cancer* 92, 1026–1032 (2005).

29 Segna R, Dottino PR, Mandeli JPP *et al.*: Secondary cytoreduction for ovarian cancer following cisplatin therapy. *J. Clin. Oncol.* 11, 434–439 (1993).

30 Janicke F, Holscher M, Kuhn W *et al.*: Radical surgery procedure improves survival time in patients with recurrent ovarian cancer. *Cancer* 70, 2129–2136 (1992).

31 Gungor M, Ortac F, Arvas M, Kosebay D, Sonmezer M, Kose K: The role of secondary cytoreductive surgery for recurrent ovarian cancer. *Gynecol. Oncol.* 97, 74–79 (2005).

32 Zang RY, Zhang ZY, Li ZT *et al.*: Effect of cytoreductive surgery on survival of patients with recurrent epithelial ovarian cancer. *J. Surg. Oncol.* 75, 24–30 (2000).

33 Tebes SJ, Sayer RA, Palmer JM *et al.*: Cytoreductive surgery for patients with recurrent epithelial ovarian carcinoma. *Gynecol. Oncol.* 106, 482–487 (2007).

34 Ayhan A, Gultekin M, Taskiran C *et al.*: The role of secondary cytoreduction in the treatment of ovarian cancer: Hacettepe University experience. *Am. J. Obstet. Gynecol.* 194, 49–56 (2006).

35 Bristow RE, Puri I, Chi DS: Cytoreductive surgery for recurrent ovarian cancer: a meta-analysis. *Gynecol. Oncol.* 112(1), 265–274 (2009).

▪▪ **Meta-analysis demonstrating the survival advantage of complete cytoreduction in recurrent ovarian cancer.**

36 Salani R, Santillan A, Zahurak ML *et al.*: Secondary cytoreductive surgery for localized, recurrent epithelial ovarian cancer: analysis of prognostic factors and survival outcome. *Cancer* 109, 685–691 (2007).

37 Cormio G, di Vagno G, Cazzolla A *et al.*: Surgical treatment of recurrent ovarian cancer: report of 21 cases and a review of the literature. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 86, 185–188 (1999).

38 Vaccarello L, Rubin SC, Vlamis V *et al.*: Cytoreductive surgery in ovarian carcinoma patients with a documented previously complete surgical response. *Gynecol. Oncol.* 57, 61–65 (1995).

39 Meyn RE, Corry PM, Fletcher SE *et al.*: Thermal enhancement of DNA damage in mammalian cells treated with *cis*-diamminechloroplatinum(II). *Cancer Res.* 40, 1136–1139 (1980).

40 Alberts DS, Peng YM, Chen HS *et al.*: Therapeutic synergism of hyperthermia-*cis*-platinum in a mouse tumor model. *J. Natl Cancer Inst.* 65, 455–461 (1980).

41 Spratt JS, Adcock RA, Muskovin M, Sherrill W, McKeown J: Clinical delivery system for intraperitoneal hyperthermic chemotherapy. *Cancer Res.* 40(2), 256–260 (1980).

42 Bereder J, Glehen O, Habre J *et al.*: Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from ovarian cancer: a multiinstitutional study of 246 patients. *J. Clin. Oncol.* 27(Suppl. 15), (2009) (Abstract 5542).

43 Bijelic L, Jonson A, Sugarbaker PH: Systematic review of cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis in primary and recurrent ovarian cancer. *Ann. Oncol.* 18(12), 1943–1950 (2007).

44 de Bree E, Theodoropoulos PA, Rosing H *et al.*: Treatment of ovarian cancer using intraperitoneal chemotherapy with taxanes: from laboratory bench to bedside. *Cancer Treat. Rev.* 32(6), 471–482 (2006).

45 Helm CW, Bristow RE, Kusamura S, Baratti D, Deraco M: Hyperthermic intraperitoneal chemotherapy with and without cytoreductive surgery for epithelial ovarian cancer. *J. Surg. Oncol.* 98(4), 283–290 (2008).

46 Chua TC, Robertson G, Liauw W, Farrell R, Yan TD, Morris DL: Intraoperative hyperthermic intraperitoneal chemotherapy after cytoreductive surgery in ovarian cancer peritoneal carcinomatosis: systematic review of current results. *J. Cancer Res. Clin. Oncol.* 135(12), 1637–1645 (2009).

47 Leitao MM Jr, Kardos S, Barakat RR, Chi DS: Tertiary cytoreduction in patients with recurrent ovarian carcinoma. *Gynecol. Oncol.* 95(1), 181–188 (2004).

48 Shih KK, Chi DS, Barakat RR, Leitao MM Jr: Tertiary cytoreduction in patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer: an updated series. *Gynecol. Oncol.* 117(2), 330–335 (2010).