Controversies in surgery in ovarian cancer — what is its real role?

Ignace Vergote

University Hospitals Leuven, Dept. Gynaecological Oncology, Herestraat 49, 3000 Leuven, Belgium

Summary

Rupture of an ovarian malignant tumour should be avoided at the time of surgery for an early ovarian cancer. Laparoscopic removal of ovarian cysts should be restricted to patients with preoperative evidence that the cyst is benign. Degree of differentiation is the most important independent prognostic factor in stage I disease and should be used in decisions on therapy in clinical practice and the future FIGO (International Federation of Gynecology and Obstetrics) classification of stage I. In early ovarian cancer, staging adequacy and tumour grade were the only two statistically significant prognostic factors for survival in the multivariate analysis of the EORTC (European Organisation for Research and Treatment of Cancer) ACTION (Adjuvant ChemoTherapy In Ovarian Neoplasms) trial. According to the present data there is no scientific basis to rely *only* on adjuvant chemotherapy *or* on optimal staging procedure in medium and high risk stage I ovarian cancer.

Primary debulking surgery by a gynaecological oncologist remains the standard of care in advanced ovarian cancer. Optimal debulking surgery should be defined as no residual tumour load. Interval debulking is defined as an operation performed after a short course of induction chemotherapy, usually 2 or 3 cycles. Based on the randomised EORTC GCG (Gynaecological Cancer Group) trial, interval debulking by an experienced surgeon improves survival in some patients who did not undergo optimal primary debulking surgery. Based on the GOG (Gynecologic Oncology Group) 152 data, interval debulking surgery does not seem to be indicated in patients who underwent primarily a maximal surgical effort by a gynaecological oncologist. Open laparoscopy is probably the most valuable tool for evaluating the operability primarily or at the time of interval debulking surgery. In retrospective analyses, neoadjuvant chemotherapy followed by interval debulking surgery does not seem to worsen prognosis compared to primary debulking surgery followed by chemotherapy. However, we will have to wait for the results of the EORTC-GCG/NCI (National Cancer Institute) Canada randomised trial to know whether neoadjuvant chemotherapy followed by interval debulking surgery is as good as primary debulking surgery in some or all stage IIIc and IV patients.

The most suitable candidates for secondary debulking surgery are those who had an initial complete response to chemotherapy, a long treatment-free interval (e.g. more than 12 months), and resectable disease (without diffuse carcinomatosis).

Introduction

Surgery and platin-based chemotherapy are the corner stones of ovarian cancer treatment. In this chapter we will focus on the importance of cyst rupture during surgery and the role of surgery as a staging procedure in early ovarian cancer, the role of primary or interval debulking surgery in advanced ovarian cancer, and the value of secondary debulking surgery and palliative surgery.

Cyst rupture during surgery for early ovarian cancer

Five-year survival rates of 70% to 90% have been reported for invasive stage I ovarian carcinoma [1–10]. Classic clinical and pathological prognostic factors, such as degree of differentiation, FIGO stage, histological type, dense adhesions, large-volume ascites, rupture before surgery, extra-capsular growth, and age of the patient, have been identified by multivariate analyses as independent prognostic characteristics [2–10]. Other factors, such as rupture during surgery, bilaterality, and positive peritoneal cytology, were of prognostic significance in some univariate analyses. Degree of differentiation is the only factor with independent prognostic value in all published multivariate analyses.

In a study of 1545 patients [11] with invasive epithelial ovarian cancer FIGO stage I, we observed

that degree of differentiation was indeed the most powerful prognostic indicator in stage I ovarian cancer. In this study, multivariate analyses identified degree of differentiation as the most powerful prognostic indicator of disease-free survival, followed by rupture before surgery, rupture during surgery and bilaterality of the tumour and age. We concluded that degree of differentiation should be used in decisions on therapy in clinical practice and in the future FIGO classification of stage I ovarian cancer.

Cyst rupture before surgery had been suggested as an independent prognostic factor in several studies [8–10,12], but rupture during surgery was significant only in univariate analyses [12–14,22]. Our study [11] confirmed that rupture before surgery was an important independent prognostic factor, but showed that rupture during surgery had an independent unfavourable impact on disease-free survival. This finding should stimulate surgeons to avoid rupture during surgery.

The unfavourable prognostic effect of rupture during surgery was observed in patients who underwent laparotomy. No firm conclusions can be made for the endoscopic removal of malignant tumours confined to the ovaries. In view of the reports on rapid peritoneal spread after laparoscopic removal of ovarian cancer and our findings [11], laparoscopic removal of ovarian cysts should be restricted to patients with preoperative evidence that the cyst is benign. Should an unexpected lesion be found at laparoscopy and documented by frozen section histopathological analysis, an immediate staging laparotomy is recommended [11,15–20].

Surgery as a staging procedure in early ovarian cancer

It has long been recognised that the standard surgery in early ovarian cancer consists of total hysterectomy, bilateral salpingo-oophorectomy, omentectomy and peritoneal cytology. Young et al. [21] were the first to show that extensive staging by an experienced gynaecological oncologist, performing a laparotomy via vertical incision exploring the entire upper abdomen and the pelvic and para-aortic lymphnode regions resulted in an upstaging of about 1/3 of the patients. In a later Italian study of 351 patients with early ovarian cancer, published by Zanetta et al. [22], it was shown that the extensiveness of the staging procedure was an independent prognostic factor in the multivariate analysis for survival and disease-free survival.

Based on these findings, the EORTC-GCG defined an optimal staging for early ovarian cancer as inspection and palpation of all peritoneal surfaces; biopsies of any suspect lesions for metastases; peritoneal washings; infra-colic omentectomy; blind biopsies of the right diaphragm and right and left para-colic gutter, pelvic side-walls of the ovarian fossa, of the bladder peritoneum and of the cul-de-sac and sampling of iliac and para-aortic lymph nodes.

In the EORTC–GCG trial, started in 1990 on adjuvant chemotherapy in ovarian neoplasms (ACTION), a new definition was proposed of optimal, modified, minimal and inadequate surgical staging in early ovarian cancer [23] (Table 1). In this study only, 1/3 of the patients were optimally staged according to these guidelines. This was substantially lower than in the Gynecologic Oncology Group (GOG) study randomising between 3 and 6 cycles of paclitaxel–carboplatin in which 76% of the patients were optimally staged according to similar guidelines [24]. In the EORTC study, staging adequacy and tumour grade were the only statistically significant prognostic factors for overall and recurrence-free survival, both in the univariate and the multivariate analyses. Adjuvant chemotherapy improved survival in the not-optimally staged patients, while this was not ob-

Table 1

Requirements for surgical staging following bilateral salpingo-oophorectomy and total abdominal hysterectomy[a] according to the EORTC-GCG ACTION-trial [23]

Surgical staging category	Staging guidelines
Optimal	Inspection and palpation of all peritoneal surfaces; biopsies of any suspect lesions for metastases; peritoneal washings; infra-colic omentectomy; blind biopsies of the right diaphragm and right and left para-colic gutter, pelvic side-walls of the ovarian fossa, of the bladder peritoneum and of the cul-de-sac and sampling of iliac and para-aortic lymph nodes
Modified	Everything between optimal and minimal staging
Minimal	Inspection and palpation of all peritoneal surfaces and the retroperitoneal area; biopsies of any suspect lesions for metastases; peritoneal washing; infracolic omentectomy
Inadequate	Less than minimal staging but at least careful inspection and palpation of all peritoneal surfaces and the retroperitoneal area; biopsies of any suspect lesions for metastases.

[a] Patients with stage Ia disease who wished to preserve fertility were permitted to have only a unilateral salpingo-oophorectomy.

served in the optimally staged patients [23]. However, the latter finding may be due to the low number of patients that were optimally staged ($n = 151$).

The combined analysis of the International Collaborative Ovarian Neoplasm Trial I (ICON-I) and the EORTC ACTION trial showed clearly that adjuvant platin-based chemotherapy improved survival and is indicated in all medium and high risk early ovarian cancer stage I patients [25]. On the other hand, the EORTC ACTION trial stressed the importance of adequate staging in these patients and questioned the value of adjuvant chemotherapy in optimally staged patients [26]. Based on these studies, we do believe that patients with medium or high risk stage I ovarian cancer should both be optimally staged (if the general condition of the patient allows this) and be treated with adjuvant carboplatin-based chemotherapy. According to the present data there is no scientific basis to rely *only* on adjuvant chemotherapy *or* on an optimal staging procedure in medium and high risk stage I patients.

Surgery in the primary management of advanced ovarian cancer

In the 1970s, Aure et al. [27] and Griffiths et al. [28] showed that the amount of residual tumour following primary surgery was an important prognostic factor in advanced ovarian carcinoma (Stages III and IV). Unfortunately, no prospective randomised controlled trials concerning the role of *primary* cytoreductive surgery in advanced ovarian carcinoma have been performed. Despite this lack of randomised controlled trials, primary cytoreductive surgery should be the standard of care in advanced ovarian cancer [29].

Interval debulking surgery is an operation performed in patients after a short course of induction chemotherapy, usually 2 or 3 cycles of chemotherapy, to remove as much primary and metastatic disease as possible in order to facilitate response to subsequent chemotherapy and to improve survival [29].

In the 1980s, the EORTC–GCG launched a randomised study to investigate the role of interval debulking in women who did not or could not have a successful primary debulking operation (reduction of disease to < 1 cm). During the same time period, several institutions started in patients with advanced ovarian cancer with neoadjuvant chemotherapy (without primary attempt at debulking) followed by an interval debulking surgery.

In this paper, we will try to define the present role of primary or interval debulking surgery in the primary management of advanced ovarian cancer.

Primary debulking surgery

It has become clear that primary debulking surgery is only advantageous to the patient if the primary cytoreductive surgery results in a minimal residual tumour load. In studies conducted in the 1970s, and in more recent multicentric trials investigating different chemotherapeutic regimens, the rates of optimal primary cytoreductive surgery were only 20% to 30% [27,30–34]. The meta-analysis of surgery in advanced ovarian cancer performed by Hunter et al. [34] has been criticised due to this low rate of optimal debulking and also because a lot of patients were not treated with optimal platinum-containing chemotherapy. More recently, Bristow et al. [35] performed a meta-analysis on the survival effect of maximal debulking surgery for advanced ovarian carcinoma during the platinum era. In this meta-analysis, 82 cohorts of patients with stage III or IV ovarian carcinoma were included (in total 6885 patients). In this study, there was a statistically significant positive correlation between percent maximal cytoreduction and median survival time, also after controlling for all other variables. In addition, each 10% increase in maximal cytoreduction was associated with a 5.5% increase in median survival time.

The definition of an optimal debulking has changed many times in the past 20 years, from a largest residual tumour mass of 2 cm to no residual tumour. Griffiths et al. [28] originally proposed that the residual tumour mass for an optimal debulking should be less than 1.5 cm. Later, many studies showed that patients without residual tumour had a better survival than those with less than 0.5 cm as the largest residual tumour mass, and the latter group had a better prognosis than patients with 0.5 to 1.5 cm residual tumour [36–42]. Vergote et al. [43] suggested that optimal cytoreductive surgery should be defined as no macroscopic residual tumour. Despite this clear evolution towards a more radical approach during primary debulking surgery, a questionnaire among US gynaecological oncologists showed that only 12% of the responders regarded optimal debulking surgery as no residual tumour, 30% as <0.5 cm, 61% as <1 cm and 13% as <1.5 cm [44].

Whether the observed survival benefits for optimally cytoreduced patients are a function of tumour biology or of surgical skill is a question that is still fiercely debated. Indeed, patients with good prognostic variables may be easier to debulk than patients with a poor prognosis. Indirect evidence is available that inherent tumour biology relates to resectability. For example, Heintz et al. [51] observed that cytoreduction was easier to achieve in young patients who had low-grade tumours, small metastases, and

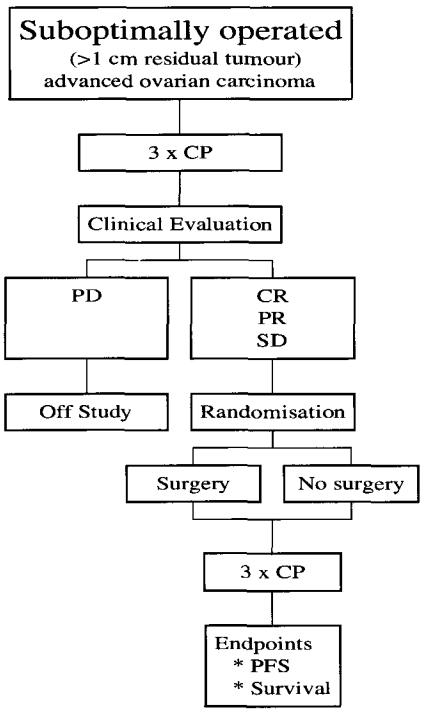
no ascites. Burghardt et al. [45] showed that women in whom optimal debulking was impossible had a higher number of positive pelvic and para-aortic lymph node metastases. In addition, Friedlander et al. [46] reported that the size of the largest residual tumour mass was not an independent factor when newer prognostic variables such as DNA ploidy were included in the multivariate analyses.

Not only the residual tumour load, but also the initial metastatic tumour load is of prognostic significance. In an analysis of the UCLA data, Hacker et al. [40] first observed that patients with extensive metastatic disease prior to cytoreduction (>10 cm in diameter) or with clinical ascites, had a poor prognosis even if the disease was cytoreduced to an optimal status. A later study from the same centre showed that the only prognostic factors influencing resectability to optimal status were metastatic disease larger than 5 cm and the presence of more than 1 litre of ascites [36]. Furthermore, in a study from the Netherlands, Heintz et al. [41] observed that the diameter of the largest metastasis before cytoreduction, and the presence of ascites or peritoneal carcinomatosis, influenced prognosis. Potter et al. [37] analysed 302 patients with ovarian carcinoma and concluded that the role of bowel resection should be questioned when residual disease remained at the completion of the operative procedure. In a study by the Gynecologic Oncology Group (GOG) of 349 patients with optimally resected (≤1 cm) disease, the multivariate analyses revealed that older age, poor degree of differentiation, and the presence of 20 or more residual lesions were independent, unfavourable prognostic variables [42]. Vergote et al. [43] reported that patients with stage IV disease, or more than 1000 g of total *metastatic* tumour load treated with primary debulking surgery, had a poor survival despite optimal surgery. Farias-Eisner et al. [47]. found that the number of residual peritoneal metastases was the most important prognostic factor in patients with less than 0.5 cm residual tumour. However, other studies suggest that the elimination of all peritoneal implants might improve survival [48,49].

The role of cytoreductive surgery in FIGO stage IV remains controversial. During the consensus meeting in 1998 it was agreed that patients with only a pleural effusion, or a supraclavicular node or a single cutaneous metastasis can be treated as stage III disease. However, extensive primary debulking in patients with liver or lung metastases was regarded as most likely of no benefit [50].

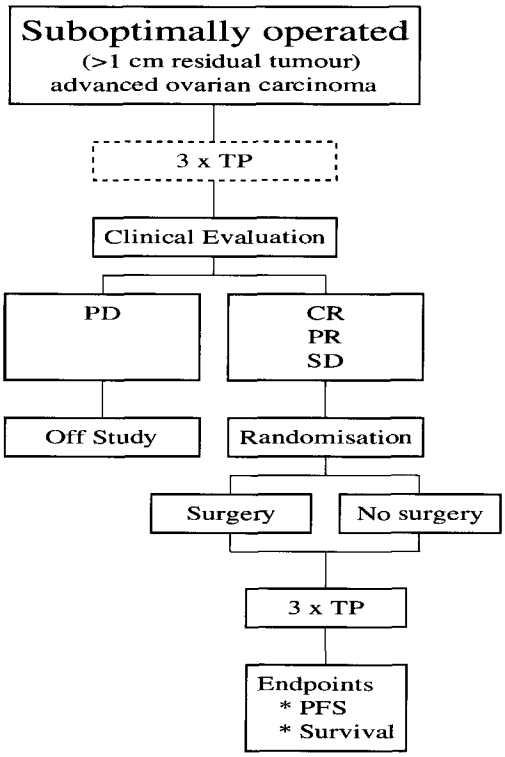
Interval debulking surgery after suboptimal primary debulking

Interval debulking surgery after suboptimal primary debulking followed by 3 courses of platinum-based chemotherapy has been investigated in 2 prospective randomised trials [51,52]. The EORTC study design is summarised in Fig. 1. In this study patients with epithelial ovarian carcinoma with a FIGO stage IIb–IV and suboptimal residual disease (>1 cm) were included. In the group of patients randomised in the interval debulking surgery arm there was an observed reduction in the risk of death of 49%. At the time of an update of the study in 2001, after a median follow-up of 6.3 years, the survival remained improved up to 9 years after randomisation ($P = 0.0032$). It is important to know that in this study, the overall survival of patients with less than 1 cm tumour at the time of opening the abdomen is exactly the same as for those patients who were debulked at the time of interval debulking surgery to less than 1 cm. Furthermore, no subgroups of patients could be identified (stage, age, grading, or peritoneal



Legend :
- CP : Cyclophosphamide 750 mg/m^2, Cisplatin 75 mg/m^2, q. day 21.
- PD : progressive disease
- CR : complete remission
- PR : partial remission
- SD : stable disease
- PFS : progression free survival

Fig. 1. Study design EORTC Interval Debulking Surgery [25].



Legend :

- TP : Paclitaxel 135 mg/m^2/24 hrs, Cisplatin 75 mg/m^2, q. day 21.
- PD : progressive disease
- CR : complete remission
- PR : partial remission
- SD : stable disease
- PFS : progression free survival

Fig. 2. Outline GOG 152 Secondary Interval Debulking Trial [26].

carcinomatosis, number of lesions, tumour size at the time of interval debulking surgery) who did not show an improved survival.

The outline of the GOG 152 is summarised in Fig. 2. Also in this trial patients with suboptimal (residual tumour >1 cm) stage III and IV ovarian carcinoma were included. One of the important differences with the EORTC trial is that in the GOG-trial, one of the eligibility criteria was that at the time of primary surgery the patient should have had appropriate ovarian cancer surgery, defined as a laparotomy with an adequate excision to explore the entire abdominal cavity, with a *maximal effort* to resect uterus, tubes, ovaries, omentum and all gross residual ovarian cancer. The main differences between the two trials are summarised in Table 2.

In the EORTC study there were more patients with stage IV disease, poor WHO (World Health Organization) performance status and a higher residual tumour load after primary surgery. It can be concluded from both studies that based on the EORTC trial, interval debulking surgery by an experienced gynaecological oncologist improves survival in some patients who have not been optimally operated upon primarily (poor medical condition, inexperienced surgeon). On the other hand, based on the GOG 152 trial, interval debulking surgery does not seem to be indicated in patients who underwent primarily a *maximal surgical effort* by a gynaecological oncologist.

Table 2

Patient characteristics of the randomised GOG-152 and EORTC trials on interval debulking surgery after 3 courses of first-line chemotherapy in ovarian cancer

	GOG 152	EORTC IDS
Chemotherapy	TP	CP
Stage IV	6%	21%
Performance status 2	7%	17%
Residual tumour after primary surgery:		
1–2 cm	12%	6%
2–5 cm	56%	30%
5–10 cm	23%	38%
>10 cm	9%	26%

TP: Paclitaxel 135 mg/m^2/24 h + Cisplatin 75 mg/m^2.
CP: Cyclophosphamide 750 mg/m^2, Cisplatin 75 mg/m^2, q. day 21.
IDS: Interval Debulking Surgery.

Neoadjuvant chemotherapy followed by interval debulking surgery

An alternative to the performance of primary debulking surgery is to start neoadjuvant chemotherapy. This approach has been advocated by some authors, especially for the treatment of stage IV ovarian cancer or for patients with a very high metastatic tumour load (e.g. more than 1 kg) or for patients with poor general conditions. These phase II retrospective reports have suggested that the outcome of these women, treated with neoadjuvant chemotherapy followed by interval debulking surgery, is essentially the same as for patients treated with primary debulking surgery followed by chemotherapy. These studies are summarised in Table 3.

Most studies have performed the interval debulking surgery after 3 or 4 courses of neoadjuvant chemotherapy. The arguments for this timing of the interval surgery are: firstly that chemotherapy-induced fibrosis is less extensive after 3 than after 6 courses, secondly that more patients might be chemoresistant after 6 courses than after 3 courses, and lastly that earlier studies investigating the role of debulking surgery at the time of second-look surgery after 6 courses of chemotherapy did not improve survival.

Although the survival results for these 648 patients with stage III and/or stage IV ovarian cancer treated

Table 3
Retrospective studies in which patients with advanced ovarian cancer were treated with neoadjuvant chemotherapy followed by interval debulking surgery

Author [Ref. no.]	*n*	Main conclusions
Lawton FG [52]	36	78% IDS of which 89% <2 cm
Jacob JH [53]	22	Same survival as 18 matched controls
Lim JT [54]	30	NAC can make patients operable
Shimizu Y [55]	74	46% IDS to <2 cm
Onnis A [56]	88	42% IDS to <2 cm
Surwit E [57]	29	Median survival = 22 months (= primary debulking)
Vergote I [42]	75	Crude survival higher when selecting about half the patients for NAC
Schwartz PE [58]	59	Similar survival compared with those treated during the same time period with primary debulking
Ansquer Y [59]	54	Better survival for patients treated with NAC compared with non-debulked tumours
Kuhn W [60]	37	Better median survival in the group treated with NAC compared with primary debulked group
Recchi F [61]	34	Only stage IV, median survival 28 months
Kayikcioglu F [62]	45	NAC followed by IDS does not appear to worsen prognosis
Ushijima K [63]	65	Similar survival in NAC group compared with primary debulking group
Total	648	

IDS: Interval Debulking Surgery; NAC: Neoadjuvant chemotherapy.

with neoadjuvant chemotherapy (usually followed by interval debulking surgery) are similar or better than those treated with primary debulking surgery, no firm conclusions can be drawn because all these studies were retrospective. As an example, we [43] observed in our series a better survival when selecting 45% of our patients for neoadjuvant chemotherapy and 55% for primary debulking surgery compared with a historical series with very aggressive debulking (82% < 0.5 cm residual tumour). However, in the historical series, only 76% of the patients were treated with platinum and none with paclitaxel, while in the group treated with neoadjuvant chemotherapy 94% was treated with platinum (and 30% also platin and paclitaxel).

Laparoscopy as a technique to select patients for neoadjuvant chemotherapy

Nelson et al. [65] proposed computerised tomographic (CT) criteria to predict operability in patients with suspect ovarian masses. Attachment of tumour to the spleen or tumours larger than 2 cm on the diaphragm, liver surface, mesentery, gall bladder on CT were regarded as inoperable. However, 6 out of 18 patients judged to be inoperable based on these criteria were optimally debulked. Therefore, we do not believe that operability can be judged based on CT findings. Later we [66] found that CT with peritoneography was superior to standard CT but still less sensitive than laparoscopy to evaluate operability. In our institution between 1995 and 2002, we performed an open laparoscopy in 173 patients to establish the diagnosis of stage III or IV ovarian carcinoma and found that open laparoscopy was the best technique to evaluate the operability and to exclude other primary tumours metastatic to the pelvis. In the last 71 cases, all port sites were completely excised at the time of primary debulking surgery or interval debulking surgery. Twenty-two of these contained malignant cells. The total number of port site metastases in the whole series of 173 patients was 30 (17%). It should be noted that in this series all port site metastases disappeared during the neoadjuvant chemotherapy or were excised at the time of surgery. None of the patients recurred later during the follow-up in the port sites and none of the patients had a port site metastasis at the time of death. Therefore, we believe that port site metastases in advanced ovarian cancer are frequent but not of prognostic significance.

Secondary cytoreductive surgery

Berek at al. [67] initially defined secondary cytoreductive surgery and implied that these operations were performed in patients who had persistent or recurrent disease at the completion of a full planned course of chemotherapy. This excludes a set of patients who develop progressive disease during their initial therapy. Many studies suggested that secondary cytoreductive surgery at the time of the completion of the primary chemotherapy had little influence on the survival.

In our experience and that of other researchers, patients with advanced ovarian cancer considered to

Table 4

Retrospective studies on secondary debulking surgery in patients relapsing after a long treatment-free interval

Author [Ref. no.]	*n*	Optimal debulking [a]	Median survival (months)
Janicke [68]	30	14/30 (47%) (NoR)	18
Munkarah [69]	25	18/25 (72%) (<2 cm)	25
Segna [70]	100	61/100 (61%) (<2 cm)	17
Morris [71]	30	17/30 (57%) (<2 cm)	16
Pecorelli [72]	22	8/22 (36%) (NoR)	20
Meier [73]	93	38/93 (41%) (NoR)	24
Tay [74]	46	19/46 (41%) (NoR)	23
Zang [75]	106	46/106 (43%) (<1 cm)	20
Scarabelli [76]	149	104/149 (70%) (<1 cm)	24
Eisenkop [77]	106	87/106 (82%) (NoR)	35
TOTAL	707	412/707 (58%)	16–35

[a] According to the authors' definition.
NoR = No residual disease.

be the most suitable candidates for a secondary debulking operation are those who had an initial complete response to chemotherapy, a long treatment-free interval (i.e. longer than 12 months) before the development of clinically recurrent disease and resectable disease without peritoneal carcinomatosis (Table 4). We restrict the discussion in this paper on secondary patients to this group of patients with relapse after a long treatment-free interval. In this type of patients (see Table 4) [68–77], an optimal debulking, defined as no residual tumour, was achieved in 166 out of 297 (56%) patients resulting in a median survival ranging from 18–35 months.

Generally, the key findings of these reports substantiate that the longer the interval from completion of chemotherapy to clinical relapse, the more likely that a secondary resection will be associated with prolonged survival. Another important feature is the complete resectability of the residual disease in the peritoneal cavity and whether the disease has metastasised to the parenchyma of the abdominal viscera (e.g. the liver). Patients with resectable disease limited to the pelvis are more likely to have benefit from a secondary debulking surgery than those with diffuse carcinomatosis [78]. Patients with progressive disease at chemotherapy are not likely to derive much benefit from surgery. Good performance status and younger patients age correlate with a positive outcome.

The variables making a patient an optimal candidate for secondary cytoreductive surgery are summarised in Table 5.

The possibility of complete resection can in our experience best be evaluated prior to the laparotomy using an open laparoscopy.

Table 5

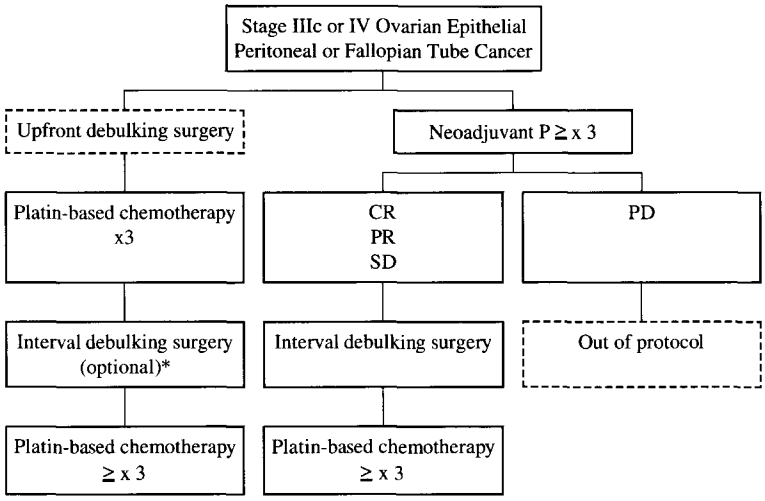
The variables making a patient an optimal candidate for secondary cytoreductive surgery

1. Long interval from time after complete remission (12 months or longer)
2. Potential for complete resection
3. High-performance status
4. Young age
5. No metastasis to the parenchyma of the abdominal viscera nor extra-abdominal metastases

Palliative secondary surgery

Patients who have failed two or more chemotherapy regimens frequently develop gastro-intestinal obstruction. Selection of candidates for surgery to relieve intestinal obstruction is often difficult and challenging for both the clinician and the patient. Several guidelines have been proposed to select patients for palliative surgery. These reports attempt to categorise the presumptive estimate of duration of survival as a relative indication or contra-indication for surgery to correct intestinal obstruction [79]. However, estimates of duration of surgery in terminal patients with ovarian cancer are often inaccurate, so the surgeon must be quite careful and take care not to overuse these prognostic factors. Selection criteria which might be used for palliative surgery in patients with an intestinal obstruction could be those who have an overall good medical status with a good performance status, limited or no ascites, the will to live, prior laparotomy tended to have more focal disease, and a suspicion of local obstruction where a bypass or local resection might be feasible.

However, in our experience, the number of patients requiring laparotomy for relieve of intestinal obstruction has decreased substantially based on two new developments. First, the use of second-, third- or fourth-line chemotherapy, such as liposomal doxorubicin (Doxil or Caelyx), Topotecan, Gemcitabine, Hexamethylmelamine, with often relief of the intestinal obstruction in up to 40% of the cases [80]. Secondly, the use of conservative treatment such as the placement of a gastrostomy tube, either endoscopically or by cut-down to the stomach with direct insertion [81] or the use of octreotide. Another approach is to give minimal intravenous fluids and frequent small feedings, with avoidance of nasogastric suctioning [82]. In these patients, who are otherwise terminally ill, this can be a compassionate means of managing terminal and intestinal obstruction.



Legend :

- P: Platin-based chemotherapy (carboplatin or cisplatin) – other drugs allowed.
- PD : progressive disease
- CR : complete remission
- PR : partial remission
- SD : stable disease

* In patients not optimally debulked during primary debulking and showing response or stable disease after 3 courses of chemotherapy.

Fig. 3. Study design ongoing EORTC 55971 trial comparing neoadjuvant chemotherapy with primary debulking surgery.

Future directions

It has been shown that rupture during or before surgery of an stage I ovarian cancer decreases disease-free survival. Future research should focus on the impact of a laparoscopy on the development of peritoneal implants. Furthermore, it has been shown in early ovarian cancer that optimal staging procedures result in a better selection of patients with a very good prognosis, making adjuvant chemotherapy possibly unnecessary. A combination of optimal staging procedures and new biological markers, such as DNA-ploidy, might enable better patient selection for adjuvant therapy. The EORTC is considering a randomised trial comparing relaparotomy with optimal staging versus adjuvant chemotherapy in medium and high-risk non-optimally staged early ovarian cancer.

Although there is evidence from retrospective studies that neoadjuvant chemotherapy followed by interval debulking surgery is a valid alternative in a selected group of patients with stage III or IV ovarian carcinoma, this must be confirmed in a prospective randomised trial. Therefore, the EORTC–GCG, in cooperation with the NCI Canada, launched a prospective randomised trial to compare primary debulking surgery with neoadjuvant chemotherapy (Fig. 3). To be eligible, the patients should have biopsy-proven stage IIIc or IV epithelial ovarian cancer or peritoneal or fallopian tube carcinoma. The study is expected to close in 2005 with a target accrual of 704 patients.

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