Chapter 14

Surgery for Recurrent Ovarian Cancer

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Additional information is available at the end of the chapter

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Abstract

Most patients with ovarian cancer (OC) have the epithelial subtype (EOC) and present with advanced stage disease. Despite improved surgical and medical management of primary disease, the majority of patients will develop recurrence and ultimately die of disease. The current surgical goal in primary EOC is complete surgical cytoreduction (CSC) as this significantly improves disease-specific survival and overall survival. CSC is a major independent prognostic factor in primary EOC. Recurrent ovarian cancer (ROC) can be diagnosed in the symptomatic or in the asymptomatic patient on clinical evidence, tumour marker results and/or imaging. There are data from cases series and retrospective series on the role of surgery in ROC but there is not yet level I evidence of secondary surgical cytoreduction improving overall survival. The published data emphasise that, as with primary disease, the surgical goal is CSC. In selecting patients for secondary cytoreductive surgery a number of predictive models have been proposed and tested. Patients with ROC who have undergone CSC have a better prognosis than those treated with chemotherapy alone or those in whom the surgical goal was not achieved. The counter-argument is that there is bias in the surgical reports—those patients not operated on chemotherapy alone, or who had incomplete cytoreduction and/or who had chemotherapy had less favourable disease-associated and patient-associated factors than those who had CSC. To address these concerns, there are currently three ongoing randomised controlled trials on surgery for ROC.

Keywords: ovarian cancer, recurrence, cytoreduction, surgery

1. Introduction

The hallmarks of cancer include (1) the potential for dissemination of cancer cells to adhere to distant sites and establish tumour growth—metastases and (2) the potential to recur following

primary or subsequent treatments. Frequently these develop together and herald relentless progression until the patient succumbs to disease. For all cancers, these processes show a greater propensity with higher stage (or TNM) of disease at presentation. Furthermore, it is known that certain types or subtypes of a given cancer have a greater or lesser tendency to metastasise and recur than others.

The typical clinical picture of ovarian cancer (OC) is presentation with advanced stage disease in the post menopausal woman and despite advances in medical and surgical treatments, most patients will die of disease. While arguably the goal of primary treatment is cure, this applies to those with early stage disease but not for all subtypes. Data from CRUK [1] show that there were 7378 new cases of OC and 4128 deaths from OC in 2014. These deaths were in most cases due to recurrent disease rather than primary disease. Survival is also associated with lower patient age and the overall 5-year survival is about 35%; the 5-year survival for stages III and IV disease is about 20 and <5%, respectively [1]. The majority of data on ovarian cancer is based on epithelial ovarian cancer (EOC) and this review predominantly deals with recurrent EOC.

2. Defining recurrent cancer

This is the detection of the cancer following a period of time after completion of primary treatment. The NCI Dictionary of Cancer terms [2], defines recurrent cancer as "Cancer that has recurred (come back) after a period of time during which the cancer could not be detected". This is vague and open to interpretation and in clinical practice requires more careful scrutiny:

1. How undetectable disease is defined at the end of primary treatment and how recurrence is defined?
2. How the recurrent disease is detected—clinically, by tumour marker(s), radiologically?
3. The time intervals in the follow-up of patients, the methods of surveillance and how often these are used.
4. Whether there is a clear distinction between persistence of disease following primary treatment and recurrence.

For example, a unit that regularly scans patients after primary treatment may detect evidence of recurrent disease sooner than a unit which relies on serial tumour markers. Indeed, 2 units may use imaging as part of surveillance but one unit may scan more often that another, or measure tumour markers more frequently than another. Complicating this further is that not all recurrences are associated with rising tumour markers and different modalities of imaging have differing sensitivities and specificities in detecting early or small volume recurrent disease. Compounding the understanding of the role of, and efficacy of, different managements for recurrent disease is tumour and patient heterogeneity [3]. As a consequence, caution needs to be given to the interpretation of data on the efficacy of different managements of recurrent cancer —including the role of surgery in recurrent ovarian cancer (ROC). Trial design and the endpoints of trials have important implications [3–5]. It is generally accepted though that overall survival (OS) is the most clinically relevant and the most clearly definable endpoint [3]. Modern imaging and tumour makers have replaced what was the common practice of second look laparotomy

(SLL) in OC, which is no longer recommended. Unlike most other recurrent gynaecological cancers where typically histologic confirmation of recurrence is required before treatment, this is the exception in cases of ROC.

Essentially all OC patients receive platinum-based chemotherapy as part of primary treatment and some concepts are used to help stratify and compare managements of recurrent cancer. These include (1) platinum-sensitive and platinum-resistant disease [6] and (2) platinum-free interval (the interval between date of last platinum dose and date of relapse, PFI) and (3) progression-free survival (PFS). The definition of platinum sensitive and platinum resistant is somewhat arbitrary, but clinically useful. There is an argument that surgical trials might instead focus on date of last treatment (treatment-free interval (TFI)), and date of last operation rather than response to platinum or PFI [7]. Platinum-sensitive OC is defined as disease that is undetected at completion of primary treatment with platinum and which is undetectable for at least 6 months after completion of platinum-based chemotherapy; platinum-resistant disease is ovarian cancer that is detected within 6 months of completion of platinum-based chemotherapy. Other terms used in reports on recurrent cancer are time to first subsequent treatment and intervention-free interval. It is not clear what impact the use of maintenance therapy as an extension of primary treatment will have on these definitions.

3. Determination of recurrent ovarian cancer

Recurrence is documented clinically, and/or by tumour marker levels and/or radiologically and in different clinical units the policy of post-treatment surveillance is variable. The clinical determination of relapse may be in an asymptomatic or symptomatic patient, and rarely OC patients may present acutely, for example, with bowel obstruction. Indeed, previously treated OC patients who develop bowel obstruction almost always have (recurrent) disease as the cause, even if this is not suspected on tumour marker levels or on imaging.

3.1. Clinical features

Recurrence may be suspected from the patient's history—symptoms include weight loss, weight gain (e.g. from ascites), leg swelling (unilateral or bilateral), dyspnoea, pelvic pressure symptoms and loss of appetite. More unusual symptoms relate to the paraneoplastic syndrome including features associated with hypercalcaemia, myositis, erythema nodosum and herpes zoster. Less commonly patients have haematuria, vaginal or rectal bleeding. The patient may of course be asymptomatic.

The clinical examination, which should include assessment of the lymph nodes, abdominal and pelvic examination and recto-vaginal examination, may be normal. If the patient presents more acutely, for example with dyspnoea or evidence of bowel obstruction, there are usually concerning clinical findings.

3.2. Blood results

Unless clinically indicated, the usual test off treatment is to measure the serum tumour marker(s). The evidence that this is useful clinically and contributes to more efficacious treatment and

improved prognosis has been challenged [8, 9]. With regard to the common EOC, recurrent disease may not be associated with high levels of CA 125, it may be associated with a normal level or with a rise within the normal range, and there are other non-cancer explanations for a rising level post-treatment. In a recent trial, it was concluded that treating recurrences (early) with chemotherapy based on rising tumour marker(s) was not associated with increased survival but was associated with a reduced quality of life [8–10]. It is important to note, however, that secondary cytoreductive surgery was not a standard of care in this trial. On the other hand, there is some evidence that early surgical intervention in asymptomatic patients might increase the rate of complete secondary cytoreductive surgery [11, 12]. This then is an argument for post-treatment surveillance by serial tumour marker estimations. With a rise in CA125 noted, the median time to clinical evidence of relapse is 2–6 months. There are no national guidelines in the UK regarding the post-treatment use of serial assessment of serum markers which is often to allay patient anxiety or as part of a trial protocol. Likewise in the USA, the national society, Society of Gynecologic Oncologists (SGO) [13], has not unequivocally endorsed routine post-treatment surveillance using serum tumour marker(s).

3.3. Imaging

In 2000, a collaboration of major cancer groups published criteria to help standardise radiologic interpretation of response to treatment of disease (cancer), which are known as Response Evaluation Criteria in Solid Tumours (RECIST) [14]. In the non-acute routine clinical follow-up, there is variation in the use of imaging, the modality used and the frequency of imaging. Patients on clinical trials typically will have regular imaging as part of the trial. There are no national guidelines in the UK. The National Comprehensive Cancer Network (NCCN) does not stipulate or recommend routine imaging after primary treatment of OC [15]. In most centres, imaging will be performed if there are symptoms (e.g. weight loss, abdominal distension) or signs (palpable pelvic mass). In the UK, the usual imaging will be a CT scan of chest abdomen and pelvis; in other centres FDG-PET may be performed instead of, or in addition to, CT. Practices also vary in the timing of imaging in relation to rising serum tumour marker(s)—including rising levels within the normal range, and levels that exceed the normal range. However, as noted above, early treatment of recurrence with chemotherapy is reportedly not in the patient's best interest whereas earlier surgical intervention may be [8, 9, 11, 12]. In the symptomatic patient with, for example, suspected bowel obstruction, a number of imaging tests will be performed in an effort to confirm the diagnosis, to determine the cause, and to aid in the management decisions.

When deciding on the management of a patient with ROC whose initial management has been in another institution, in many cases it is recommended that there be a review of histology and relevant imaging, and details of the prior surgery. The operative reports should be obtained rather than reliance on a brief summary in patient correspondence.

4. Surgical considerations in the patient with ROC

A general impression is that secondary cytoreductive surgery for ROC is more commonly routine practice in the USA and parts of Europe, and less so in the UK. This is evidenced by the

fact that most reports on the role or impact of such surgery have come from non-UK centres. Almost all reports on surgery for ROC refer to recurrent EOC and not to the non-epithelial types or borderline cancers. Furthermore, the reports on surgical management mostly focus on the first recurrence after primary treatment, rather than the second or third recurrence. The NCCN Guidelines [15] state that secondary cytoreduction can be considered in patients with recurrent ovarian cancer (1) (detected at) more than 6–12 months after completion of initial chemotherapy, (2) who do not have ascites and (3) who have an isolated recurrence (or few foci) of disease which can be completely resected.

In clinical practice, there are different scenarios in which the surgical option for ROC needs to be considered.

Broadly these may be described as:

1. Recurrent ovarian cancer with pelvic and/or abdominal disease (including retroperitoneal lymph nodes); the patient may asymptomatic or symptomatic.
2. Surgery and intraperitoneal chemotherapy (IP) or heated intraperitoneal chemotherapy (HIPEC) for recurrent cancer.
3. Recurrent ovarian cancer outside the pelvis and abdomen.
4. Recurrent ovarian cancer and bowel obstruction.
5. Further recurrence in patients previously operated on or treated for recurrence.
6. Recurrent non-epithelial ovarian cancer (borderline tumours are discussed elsewhere).

There are many published reports on the role and impact of secondary cytoreductive surgery in ROC. Many are from single institutions, often with small numbers, and with minimal quality of life data and, as yet, there are no published studies providing level I evidence on the impact of secondary cytoreductive surgery on overall survival in ROC. So although the best evidence at present is not yet confirmed in trials, there are three randomised controlled trials assessing the role of surgery in ROC, only one of which has just released preliminary data. These are DESKTOP III, SOCceR and GOG 213, in all of which an eligibility criterion is platinum-sensitive EOC [16–18].

a. DESKTOP III Trial: This follows on from the DESKTOP I and II trials and again the predictive model is the positive AGO score for complete secondary surgical cytoreduction. In this trial, two groups are compared—chemotherapy only group and cytoreductive surgery followed by chemotherapy group.
b. SOCceR Trial: This Dutch trial is of secondary CRS and chemotherapy compared to chemotherapy alone in recurrent disease. The primary endpoint is PFI.
c. GOG 213 Trial: In this trial after randomisation to cytoreductive surgery (CRS) patients are then randomised to one of four treatment arms, two of which contain bevacizumab.

Assessing surgery in ROC involves considering the can do/should do approaches and the best to worse scenario from surgery; allied considerations include the timing of surgery, the goal of surgery, morbidity and mortality from surgery and impact on quality of life issues (QoL). From

the patient's perspective when deciding on major surgery, the main considerations are whether there are symptoms or not, the impact of surgery on symptoms and on survival, morbidity and mortality from surgery, quality of life issues (QoL), and response to further chemotherapy or other agents. It is more often easy to decide who not to operate on electively for recurrent disease. This decision is based on disease-associated and patient-associated factors. The former include—disease-free interval, platinum-sensitive/platinum-resistant disease, histology, site or sites of recurrent disease, with and without ascites; the latter include whether the recurrence is symptomatic or asymptomatic, QoL and performance status. There are also surgeon-related factors which relate mostly to the surgical philosophy in the management of recurrent disease —in essence whether to operate on the asymptomatic patient or not, and whether to remove bulk disease only or to plan to achieve complete surgical cytoreduction (CSC) where at end of surgery there is no gross visible disease. As will be discussed, the evidence is very much in favour of CSC to maximise patient benefit as defined by overall survival. The surgeon and/or other members of the oncology team also need to discuss the treatment alternatives with the patient.

4.1. Patient selection criteria for secondary cytoreductive surgery

Major surgery for recurrent ovarian cancer is associated with morbidity and mortality—reportedly from minimal up to 88.8 and 5.5%, respectively [19]. Given the heterogeneity in the patient population and the variation in surgical practice, this perhaps is not surprising. However, it also attests to lack of appropriate reliable criteria for case selection. The goals for elective surgery for recurrent disease in the abdomen/pelvis are to (1) improve overall survival, (2) minimise surgical morbidity and (3) improve QoL. The data on QoL following secondary surgical cytoreduction are, however, sparse.

The rationale for surgery might be considered as an extension of the surgical philosophy in the management of primary ovarian cancer—that complete surgical cytoreduction and combination chemotherapy provides the best therapy to achieve increased overall survival. Furthermore, in the setting of recurrent disease and the known poorer response of ovarian cancer to second-line therapy compared to first-line therapy, one can argue that cytoreduction may have a more important role in recurrent cancer. Indeed, most of the evidence on clinical trials in the chemotherapy-only approach to ROC report median survival of about 18 months in platinum-sensitive disease and about 12 months in platinum-resistant disease [20]. Patients with ROC who undergo CSC have improved survival compared to those treated with chemotherapy alone, but selection bias is likely as those unfit for surgery, for example, will most often receive chemotherapy.

Repeatedly studies report that overall survival is improved with surgical cytoreduction in patients with platinum-sensitive disease but only in patients with CSC and in those with minimal residual disease. In essence the surgical goal in regard to cytoreduction for first recurrence is the same as for primary disease—complete resection. From these studies, a number of factors emerge which are associated with improved survival (**Table 1**). These factors are not dissimilar to those reported as important factors in improved outcome from chemotherapy for ROC [21, 22]. What is less clear from the reports is how much weight to

Primary disease
Initial FIGO stage (early versus late)
Residual disease after primary surgery (complete vs. incomplete)
Disease-free interval (platinum-sensitive, platinum-resistant)
Platinum-free interval
Recurrent disease
Performance status
Number of sites of recurrence
Ascites (present or absent (or <500 ml))
Serum CA 125
Tumour burden/largest tumour mass
Initial second-line chemotherapy before secondary surgery (yes/no)

Table 1. Prognostic factors for improved survival after cytoreductive surgery for ROC.

place on each factor in each individual case. Intuitively one would consider that long disease-free interval, good performance status (before elective surgery) and complete surgical cytoreduction would be favourable for improved survival. A number of predictive models been proposed to improve case selection for secondary complete cytoreductive surgery as these patients benefit most from surgery (**Tables 2** and **3**).

The original DESKTOP OVAR I trial which involved 25 institutions (Arbeitsgemeinschaft Gynaekologische Onkologie [AGO] Descriptive Evaluation of preoperative Selection (K) Criteria for Operability in recurrent ovarian cancer trial) reported that the main predictor for overall survival was complete surgical resection, which was achieved in 49.8% of patients [23]. Patients with non-epithelial ovarian cancer, those with low malignant potential tumours, and those undergoing palliative surgery (as opposed to cytoreductive surgery) were excluded [23]. In the subsequent DESKTOP I Trial [24], in patients with platinum-sensitive disease, the authors reported a median survival of 45 months compared to 19 months in those with complete and incomplete surgical resection, and those (in other studies) treated with chemotherapy alone. Of interest, they also reported that peritoneal carcinomatosis was not a negative factor if complete resection was achieved emphasising that carcinomatosis was not a contraindication to surgery and that complete resection despite the presence of carcinomatosis improved survival [24]. From this study, three prognostic factors for complete resection were identified: (1) good performance status (defined as) on the ECOG criteria [25] (European Cooperative Oncology Group), (2) complete resection at first surgery for primary disease and (3) ascites volume less than 500 ml. These were grouped as the AGO score and defined as positive if all three were present. These were subsequently validated in the DESKTOP II study [26]. It is of interest that imaging was relevant to their predictive model only for measuring volume of ascites and not for the number, size or anatomic location of tumour recurrences. Intuitively it might be considered that carcinomatosis in the setting of recurrent disease would be a contra-indication to secondary surgery and that resection of such disease would not improve overall survival. Laparoscopic assessment was not

AGO Score [23, 24]

1. Complete surgical cytoreduction at primary surgery
2. Absence of ascites at recurrence (<500 ml)
3. ECOG performance status ≤1

Tian Scoring System [33]

1. Initial stage
2. Residual disease after primary cytoreductive surgery
3. Progression-free interval
4. CA 125 at recurrence
5. Presence of ascites at recurrence
6. Performance status

SeC-Score [34]

1. CA 125 at recurrence
2. HE4 at recurrence
3. Presence of ascites
4. Residual tumour volume at completion of primary surgery

Minaguchi Proposal [37]

1. TFI >12 m (versus < 12 m)
2. No distant metastases (versus distant metastasis)
3. Single versus more than one site of recurrence
4. PS 0

Memorial Sloan Kettering Proposal [40, 41]

1. Time to recurrence (DFI)
2. Single or more than one site of recurrence
3. Presence or absence of carcinomatosis
    - DFI 6–12 m surgery for single site recurrence, possibly if more than one site
    - DFI 12–30 m surgery for one or more sites of disease; possible surgery if carcinomatosis
    - DFI > 30 m surgery for single site, multiple sites, and carcinomatosis

Table 2. Predictive models for complete surgical Cytoreduction in recurrent ovarian cancer (based on platinum-sensitive disease).

part of the protocol. There is some suggestion that open laparoscopy may help in case selection —Plotti et al. [27] reported 34 of 38 patients who had a laparoscopy suggesting suitability for surgery subsequently underwent complete secondary cytoreduction. Although there are some randomised data on the use of laparoscopy to determine complete surgical cytoreduction in primary EOC, there are no such data for recurrent disease [28, 29].

A subsequent analysis based on pooled data from an international collaborative cohort [30] reported a scoring system ranging from 0 to 8: progression-free interval < 23.1 months (2), ascites (1), multiple sites of recurrence (1), residual disease after secondary cytoreductive surgery

Primary disease
Early FIGO stage
Complete cytoreduction at primary surgery
Long DFI/PFI
Recurrent disease
Good performance status
No ascites
Number of sites of recurrence**
Maximum tumour dimension
CA125***

*Based on data from platinum-sensitive epithelial ovarian cancer.
**The fewer the better the outcome.
***Normal versus abnormal level.

Table 3. Predictive factors for complete surgical cytoreduction (CSC) in ROC*.

[none, 0.1–1 cm (2): >1 cm (4)]. Low and high-risk models were defined. The difference in median survival between the two groups (63.0 and 19.1 months) was highly significant, and they reported that complete surgical resection was the goal if survival gain was to be maximised. Their model, however, is arguably not straightforward. Note is made that the results of imaging had more influence on decision making (ascites and number of sites of disease) than in the AGO predictive model. In contrast, other studies have reported an improved outcome with single site versus multiple site recurrence [31] and with a DFI of 24 months or more [32].

Tian et al. [33] reported on another model in an attempt to better define those patients with recurrent disease most likely to benefit from cytoreductive surgery. Six criteria were identified—initial FIGO stage, residual disease after primary cytoreduction, progression-free interval, ECOG performance status, CA125 and ascites. They categorised patients into low and high-risk groups based on the score. Compared to other models they reported lower complete cytoreduction rates (53.4% in the low risk group and 20.1% in the high-risk group) than in DESKTOP I. Another group proposed another model which they defined as the SeC-score using four criteria [34]: pre-operative CA 125, pre-operative HE4, ascites and residual disease at primary surgery. They reported a sensitivity and specificity of 82 and 83%. This is one of the few reports to comment on the potential value of CA125, and in a previous study an elevated CA 125 was reported as a negative prognostic factor [35]. Angioloi et al. were the only group reporting on the newer tumour marker, HE4, and the only one in which performance status was not considered. Again in this model, as in the AGO model, the role of pre-operative imaging was essentially only to measure the volume of ascites. Frederick et al. [36] reported in a study on 62 patients with prior complete cytoreduction and platinum-sensitive disease that the only pre-operative factor predicting prolonged survival was a CA125 of less than 250 U/ml which was associated with complete surgical cytoreduction. A Japanese group proposed another model using four criteria [37]—treatment-free interval > 12 months, single site disease, absence of distant metastasis(es) and performance status of 0. Depending on the number of favourable factors, the outcome in terms of complete resection, and overall survival were significantly different.

A number of studies have assessed the two most used predictive models—that proposed by Harter (AGO) and that proposed by Tian [23, 33]. Janco et al. [38] reported that although a positive AGO score was predictive of complete SCR in 79% of patients, in 64.4% of AGO negative cases complete SCR could also be achieved—and as such the AGO score was not an independent factor associated with improved survival. Similar findings of complete cytoreduction—high positive predictive value and high false negative rates—were reported for both models in a population based study on Dutch patients [39]. In this study, 48% of patients had had chemotherapy before surgical cytoreduction but this did not impact on their results. Following on from an earlier proposal for surgical resection in ROC [40], the Memorial Sloan Kettering group compared their scoring system to the AGO and the Tian models in identifying those patients likely to benefit from secondary cytoreductive surgery—that is, those patients in whom complete surgical resection is more likely to be achieved. They proposed to offer secondary cytoreductive surgery to those with: (1) a disease-free interval of less than 6 months, if there was single site disease, (2) disease-free interval of 12–30 months, even if multiple sites of disease provided there was no carcinomatosis and (3) those with carcinomatosis, if the disease-free interval was more than 30 months. These selection criteria might be considered to be counter-intuitive and are different to those of previous reports, but their assessment of the impact of carcinomatosis, is similar to that of the DESKTOP I study, albeit in the context of a longer DFI. They reported [41] that their model was more predictive of complete resection than either the AGO or Tain model. A study from two French centres [42], where initial laparoscopic assessment was common, both the AGO and Tian models were used to evaluate patients; they reported high positive predictive values for complete cytoreduction (80.6 and 74%, respectively, for each model) yet high false negative values (65.4 and 71.4%, respectively).

It can been seen than that although various models have been proposed with some common criteria, the more commonly used AGO and Tian models are associated with significant false negative predictions. It is of no surprise that the factors associated with improved survival in ROC and factors associated with increased rate of CSC in ROC, are similar (**Tables 1** and **3**). Perhaps surprising is that in most series pre-operative CA125 is not considered relevant. Most studies do not report on or recommend an initial laparoscopic assessment, a procedure not without risks, limitations and the associated logistic problems of planning operating lists. Other than Eisenkop's early reports [43, 44], it is also surprising that in most other later models determining and evaluating criteria for surgery of ROC, tumour volume or size of recurrence were not considered relevant. An exception is the report by Onda et al. [45] in which size of recurrent disease or tumour burden was an important factor in case selection. While much emphasis has been given to the importance of complete resection in primary EOC and the positive impact on survival, some reports have emphasised that initial tumour burden in primary disease limits the gains from such surgery—the argument again about surgical skill and tumour biology [46–48]. If indeed tumour burden is important in primary disease, arguably it should be of similar if not more importance in recurrent disease, where chemotherapy is less effective. Furthermore, it is quite clear that patients treated for primary EOC by gynaecological oncologists who achieve CSC have an improved outcome when the cancer recurs, compared to patients in whom primary surgery was incomplete. The positive effects of optimum treatment of primary EOC, continue through recurrent disease. Quite evidently, the characteristics of primary

disease and its management (e.g. complete versus incomplete surgical cytoreduction) have a major impact on the surgical decision making for recurrent disease.

Most recently the preliminary results of one of the RCTs on secondary cytoreductive surgery for recurrent ovarian cancer, DESKTOP III, have been reported in an abstract at the 2017 meeting of ASCO [49]. These were that (1) complete resection was achieved in 67% of patients, (2) there was an increase in PFI (14 months versus 19.6 months), (3) an increase in time to first subsequent treatment (TFST) (13.9 months and 21 months) and (4) data on OS are immature.

5. SCS in platinum-sensitive recurrent ovarian cancer

There are now numerous reports on secondary cytoreductive surgery (SCS) for recurrent ovarian cancer, with the focus on the epithelial subtype. They consistently show a benefit in overall survival—that is in ROC, complete surgical cytoreduction (with or without subsequent chemotherapy) is superior to chemotherapy only in these patients. The counter-argument is that the cases selected for surgery have more favourable features than those treated with chemotherapy alone. But as with primary disease, there is a subgroup who will not undergo surgery and be treated with chemotherapy alone, or rarely palliative care only. These treatment options should not be seen as competing for patients or as an either/or dilemma but as part of the multi-disciplinary team decision as to what is the best management for a particular patient.

The initial report by Berek et al. [50] on ROC showed a survival benefit where the surgical result was optimal (<1.5 cm residual) compared to suboptimal. In a later small study on 36 patients Eisenkop, and a subsequent study by the same authors on 106 patients [43, 44] reported a survival benefit from cytoreduction which was compromised by prior second-line chemotherapy before secondary cytoreductive surgery and where the tumour burden (maximum tumour diameter) was large (>10 cm). Their reports are unusual in that most other reports do not consider either factor as important in case selection for SCS. They also reported that the key surgical factor improving overall survival was complete cytoreduction. Other reports have found the same association and reported [51] that chemotherapy before surgical cytoreduction had a negative impact on surgery.

A common intraoperative finding in recurrent disease is carcinomatosis, which is most problematic where there is extensive involvement of the small bowel serosa and/or mesentery and often results in incomplete surgical cytoreduction. However, the DESKTOP I and II trials reported that even with carcinomatosis, if complete surgical clearance is achieved, carcinomatosis is not a negative prognostic factor in recurrent disease. Indeed, Chi et al. also consider that carcinomatosis is not a contra-indication to secondary cytoreductive surgery if the disease-free interval is 30 months or more as there is patient benefit if CSC is achieved [40, 41]. In a retrospective review of patients with ROC treated in the CALYPSO trial [52], complete surgical cytoreduction was associated with improved survival compared to patients treated with chemotherapy alone; however, as patients who had less favourable features and who did not have complete cytoreduction derived notably less benefit from surgery, then, as noted by the authors,

there is likely to be a significant selection bias in the surgical studies on ROC [52]. Most reports have not addressed quality of life (QoL) issues, but in one report [27], no difference was found to be in QoL in patients with ROC who had chemotherapy alone and those who had surgery and chemotherapy.

6. SCS in platinum-resistant recurrent ovarian cancer

This subgroup of patients has a poor prognosis and more recently bevacizumab has been used as part of second-line treatment. With the associated operative morbidity and possible negative impact on QoL of major surgery in these patients, there has been understandable reluctance both from surgeons and patients to undertake surgery. Where there has been initial suboptimal cytoreduction the surgical goal of complete CSC is rarely achieved, if one extrapolates from the results of Rose et al. [53] in primary disease. A key finding in that study was the training and skill of the surgeon who performed the primary surgery—a gynaecological oncologist whose goal was complete cytoreduction, or a non-specialist surgeon. Case selection for surgery in ROC is also influenced by the patient's performance status, the number of and sites of metastasis and in these cases obtaining the operative report from the initial surgery is often instructive. The practice in the UK is more towards non-surgical management of recurrent disease in platinum-resistant cases. A more common clinical situation is the patient with persistent but stable disease after primary treatment, in whom the disease progresses. In these patients, elective surgery with the goal of achieving complete clearance of disease is most unlikely to be achieved if the original surgery by a gynaecological oncologist was suboptimal and in such cases the recommended treatment is second-line chemotherapy.

Nevertheless, there are some patients who were disease free at completion of treatment for primary disease and have recurrent disease at one or a few sites within 6 months of completing treatment and in whom secondary cytoreductive surgery may be an option [41, 54, 55] and may enhance the otherwise limited response to chemotherapy. Whether or not there is a role for initial laparoscopic assessment is unclear and practices vary. Treatment alternatives must be discussed including palliative care [15]. In other clinical situations, a decision may be made to operate on a patient to remove a large mass that is symptomatic even if CSC cannot be achieved or warranted.

A less common EOC is the low grade serous carcinoma, which typically is less chemosensitive and runs a more indolent course than the high grade serous carcinoma. Often in recurrent disease, there is calcification which can render surgical resection more difficult. Given these usual clinical features there more often is recourse to secondary cytoreductive surgery [56]. This is an individual decision and the pace of growth of the tumour site(s) and whether or not the patient is symptomatic are important considerations.

7. Chemotherapy or surgery as initial treatment for ROC

In an early study [43], a less favourable outcome from secondary surgical cytoreduction was reported if this was preceded by second-line chemotherapy. This was not found in a later

study [56] on a small number of patients. However, if second-line chemotherapy has been given and there has been disease progression, in general there would be a greater reluctance to operate. This sequence of management of initial chemotherapy has been proposed as a means to case select for secondary cytoreduction as only those showing a response should undergone surgery. Bulky disease has been considered an adverse factor in those undergoing surgery for ROC, but only in a few reports; Eisenkop et al. [43, 44] reported on patients with tumour mass more than and less than 10 cm and Onda et al. reported [45] a poorer outcome from surgery with tumour masses greater than 6 cm. Perhaps not surprising that amongst all patients treated initially with chemotherapy for ROC, those who do better are those who also have more favourable factors for surgery—such as longer DFI, good performance status and small volume disease. As with surgery, predictive models for response and outcome for patients treated with chemotherapy for ROC have been described. In the model proposed by Lee et al. [22], CA125 level (≤ 100 IU/l or > 100 IU/l) was assessed as was largest tumour size (<5 cm or >5 cm) but the role of secondary cytoreductive surgery was not assessed. Different managements of ROC may be appropriate in a particular patient but in patients with favourable factors, secondary cytoreductive surgery (with or without chemotherapy) results in a better outcome (overall survival) than chemotherapy alone [24, 30, 33], although level I evidence on overall survival benefit is awaited [49]. In a large retrospective study on ROC in which patients were treated with chemotherapy alone or with cytoreductive surgery and chemotherapy, the latter group had improved overall survival, but only in those with no residual disease or smaller volume residual disease [57].

8. Surgery and IP/HIPEC chemotherapy for recurrent ovarian cancer

The Cochrane review on the use of intraperitoneal (ip) chemotherapy for primary OC [58] concluded that this treatment prolonged PFS and OS. While there is evidence of a survival benefit for IP chemotherapy/HIPEC after cytoreductive surgery in primary disease, there are fewer reports on its use and efficacy in recurrent disease [59]. No mention was made of this type of treatment in the Cochrane review on recurrent ovarian cancer [60] nor in the review by the Fifth Ovarian cancer Consensus Conference of the Gynecologic Cancer InterGroup [7].

Boisen et al. [61] reported on a retrospective study of 25 patients treated with iv/ip chemotherapy but without secondary cytoreductive surgery. The study period was over 6 years on a selected group of patients and 10 of 25 had an improved treatment-free interval. In a feasibility study of ip chemotherapy in 56 patients with platinum-sensitive recurrent disease all of whom had had prior secondary cytoreductive surgery (67.9% to <1 cm), 79% tolerated 6 cycles of ip platinum. No difference in outcome was noted related to the completeness of secondary surgery and the median overall survival was 51 months; no clinical factors associated with improved PFS or OS were identified [62]. The data from other studies report that the main indicators for response to ip chemotherapy are (1) volume of residual disease and (2) platinum-sensitive disease [63, 64]. Fujiwara, in contrast reported responses in patients with suboptimal surgical resection [65].

Ansaloni et al. [66] provided one of the first reports on HIPEC following cytoreductive surgery in 30 patients with recurrent disease. In this small study, HIPEC was considered safe and there

was a trend to improved survival with complete cytoreduction and HIPEC. A more recent study [67] reported a survival benefit in what they described as randomised trial on the use of HIPEC in recurrent ovarian cancer. However, there were a number of deficiencies in study design and questions were raised about the validity of the results and the efficacy of HIPEC as reported in that study [68]. In another retrospective review [69], Cripe et al. reported on 32 patients that CRS and HIPEC were feasible. However, they also noted 65.6% grade 3 or 4 toxicity (morbidity) and that troublesome pleural effusions were associated with diaphragmatic stripping and/or resection. As a number of chemotherapeutic agents were used with varying dwell times and temperatures, it is unclear what regimen to recommend. As with primary disease, a key component in the use of HIPEC is complete cytoreduction or minimal residual disease (<5 mm deposits). A recent report on a retrospective cases series from China on 46 patients with advanced (n = 16) or recurrent (n = 30) ovarian cancer reported a survival benefit with HIPEC but only when there was complete surgical cytoreduction [70]. However, the adjuvant treatment included iv/ip chemotherapy and it is not clear what contribution HIPEC and ip chemotherapy made to improved survival. In contrast, in a study on secondary cytoreductive surgery in EOC, 50 patients underwent surgery only and 29 also had HIPEC, although there were no deaths in the latter group and two in the former group, the addition on HIPEC did not confer an advantage on median disease-free survival [71]. Data were not presented, however, on overall survival or disease-specific survival. In a larger retrospective multi-centre Italian study on 226 patients with primary ovarian cancer and 285 with ROC treated over 16 years, HIPEC was of benefit in patients with ROC who had had complete surgical resection and platinum-sensitive disease [72]. In a large French study of HIPEC in primary and recurrent ovarian cancer, no difference was noted in overall survival between patients with platinum-sensitive and platinum-resistant disease and the main prognostic factor for survival and DFI was the extent of disease, or tumour burden, as measured on the peritoneal cancer index [73]. In the studies showing benefit of CSC and HIPEC, it is still unclear what, if any, additional benefit HIPEC can achieve over CSC. There is still ongoing debate about the role of HIPEC, with the view that HIPEC should be offered only in clinical trials [74]. In fact a number of trials of ip chemo and HIPEC in recurrent ovarian cancer are recruiting [75].

9. Recurrent ovarian cancer outside the abdomen and pelvis

With the improvement in overall survival in ovarian cancer, and better understanding of cancer genetics, targeted therapies and improved surgery, it is now more common to see patients with unusual or atypical sites of recurrent disease [76]. Sites include breast, brain, bone (including vertebral spine), chest wall, skin (other than port site metastasis) and lymph nodes such as the axillary nodes [77–79]. Given the unusual location of metastasis it is important to exclude other sites of disease and commonly PET-CT is used. Biopsy is often necessary to exclude another cancer. In contrast, histologic confirmation of recurrent OC in the pelvis and/or abdomen is not usual clinical practice. Management of the recurrence will include general supportive measures such as pain relief, radiotherapy (e.g. with vertebral metastasis) and chemotherapy, trial drugs and specialised surgery, for example, neurosurgery. The surgery may be indicated for symptom relief and may be considered necessary, even life-saving, in the

presence of metastatic disease at other sites. In assessing the role of specialised surgery for recurrent metastatic ovarian cancer, factors to be considered include—morbidity of surgery, likelihood of resecting disease, likelihood of palliating symptoms by surgical resection, and the patient's prognosis, with and without surgery. There is also some evidence that patients treated with IP chemotherapy and then subsequently with bevacizumab have a greater propensity to develop unusual sites of metastastic recurrence [80]. Patients with a BRCA mutation compared to those who do not have a BRCA mutation more often develop unusual sites of recurrence.

10. Recurrent ovarian cancer and bowel obstruction

Most patients with EOC present with advanced stage disease and most will develop recurrence. A common presentation of recurrent disease is relapsing and remitting bowel obstruction, the course of which is more often chronic than acute [81, 82]. Invariably the development of bowel obstruction indicates recurrent (or progressive) disease, even if the tumour markers are not elevated and there is no radiological evidence of disease. The management is conservative, at least initially with fasting, intravenous fluids and pharmacological manipulation [81, 82]. Involvement of the palliative care team is important. Surgical intervention is associated with significant morbidity and mortality and not all patients, perhaps only about two-thirds benefit from surgery in terms of resumption of adequate oral intake. Despite this common problem in recurrent ovarian cancer, QoL data on surgical and non-surgical intervention are notably absent from most reports.

Surgical intervention includes—placement of a gastrostomy tube [83], by pass procedures, but most often formation of a diverting stoma. As the disease is often more extensive in the pelvis with serosal and mesenteric disease, more often an ileostomy is raised rather than a colostomy, although often when a loop ileostomy is performed it is necessary to defunction the large bowel by raising a mucous fistula. If a recto-vaginal fistula develops from extensive pelvic disease, a colostomy may provide successful palliation but typically to a limited extent. That is, the patient will continue to have other problems related to the pelvic disease—including pelvic pain, discharge and vaginal or rectal bleeding. It is important to discuss with the patient the likely palliative benefit of surgery, as it is to discuss the outcomes from the surgical and non-surgical management of bowel obstruction.

11. Surgery for second recurrence and beyond

There are fewer reports on the role of surgery for second, third, etc. relapse of EOC. Intuitively the factors that are important in surgical decision making for first recurrence should also be important in surgical decision making in patients with second and subsequent recurrence. It is clear too that if surgery is contemplated for such relapses the patients are highly selected and more often than not surgical intervention will be for palliation (e.g. bowel obstruction) rather than for complete cytoreduction. More usually in clinical practice patients with second and

subsequent relapse will be treated with chemotherapy or other drug therapy. The paucity of cases and reports on tertiary cytoreduction emphasises the uncommon clinical scenario of a patient with second relapse of EOC undergoing surgery. In a multi-centre retrospective review of 406 patients [84], based over a 16-year period, it was reported that residual tumour after secondary and tertiary surgery was an important prognostic factor and surgical outcome was compromised by ascites and upper abdominal disease. Avras et al. [85] reported that the surgical goal, as with first recurrence, should be complete cytoreduction as this improved overall survival. The usual factors to be considered for surgery in recurrent disease with the goal of complete cytoreduction, such as disease-free interval, were reported but they also found an association with increased size of recurrent disease and reduced benefit from surgery. Another report highlighted the importance of case selection and maximixing cytoreduction [86]. No QoL data were presented in these papers.

12. Recurrent non-epithelial ovarian cancer

Most reports on ROC almost exclusively deal with epithelial ovarian cancer. Even with the EOC, the subgroup of mucinous cancers, which are less chemosensitive than their serous counterparts, arguably should more often be treated with surgery for first recurrence than with chemotherapy. The recent Gynecologic Cancer Intergroup (GCIG) report provided little guidance [87]. Two reports describe a very poor outcome when mucinous ovarian cancers relapse and caution about surgical intervention [88, 89]. It remains unclear whether recurrent mucinous cancer should be managed as recurrent pseudomyxoma peritoneii with extensive peritoneal resection and HIPEC.

There are fewer reports on the less common OC subtypes. Granulosa cell tumours, which have limited chemosensitivity compared to EOC typically have an indolent course. Whereas primary disease is often of low stage, recurrent disease is characterised by multi-site relapse which presents different surgical challenges if complete cytoreduction is the goal [90]. Given their more indolent behaviour there may be an argument for targeting symptomatic masses rather than CSC. For germ cell tumours, most of the information is extrapolated from data on male patients. Germ cell tumours are rare in females and the immature teratoma, defined by the presence of immature cancerous tissue, most often immature neural tissue, typically is managed by chemotherapy after initial surgery. Two conditions described in the literature on germ cell tumours are the “growing teratoma syndrome” and “chemotherapeutic retroconversion” are generally considered to be the same as histologically the tissue found is mature teratoma [91]. In the former, after successful chemotherapy, there is recurrent disease but of mature not immature teratoma; in the latter, chemotherapy given to immature teratoma resulted in subsequent mature elements only. This is important to recognise as otherwise disease-progression or recurrence (of original immature disease) is diagnosed. If further immature teratoma is diagnosed after primary treatment this is associated with a less favourable prognosis and pathological confirmation of recurrence as mature or immature is necessary to appropriately manage. Typically treatment of recurrent disease is conservative surgery and further chemotherapy [92]. The specific considerations are the young age of patients and fertility preservation, chemosensitivity and the growing

teratoma syndrome. The more usual indication for surgery is to remove a symptomatic mass or a growing mass that is causing pressure symptoms (the growing teratoma syndrome). In such cases, the focus of surgery in the typical young patient, with fertility preservation necessary, is not complete cytoreduction but resection of the symptomatic mass. A less common clinical problem is of peritoneal disease with mature glial tissue—gliomatosis peritoneii, which most often has a very indolent course. Typically the initial primary surgery has been fertility preserving. With relapsed disease, which may be in the pelvis or disseminated, including involvement of the retroperitoneal lymph nodes, it is important to determine whether the relapsed disease is mature or immature teratoma, and although both pathologies may be present the more common is mature teratoma [93]. For gliomatosis peritoneii, which is of different grades, surgery should be in symptomatic patients only, the goal is palliation and not complete cytoreduction, which is most often not feasible. When secondary surgery is undertaken for recurrent disease the reproductive organs should be preserved if possible (including the uterus). The surgical goal is cytoreduction with fertility preservation, and it is reasonable to leave small volume disease on the one remaining ovary.

13. Conclusion

Most patients with OC present with late stage disease and most are destined to develop recurrence and to die of disease. Consideration needs to be given as to how recurrence is diagnosed and whether the patient is asymptomatic or symptomatic. The majority of data on ROC is from studies on EOC, but the role of secondary surgery is influenced by the histologic subtypes of OC. Patients treated with second-line chemotherapy tend to have less favourable features than those treated initially with surgery. In non-randomised studies, where there is likely selection bias, usually showed a benefit in overall survival from secondary cytoreductive surgery compared to chemotherapy alone. Consistently non-randomised studies report that the benefit of surgery in terms of DFI and survival is seen only in patients with complete surgical cytoreduction. Only one of three current randomised trials has reported preliminary data which show a benefit from surgery and data on overall survival are awaited. As complete surgical cytoreduction at primary surgery is an important factor in improved outcome from primary treatment and from secondary treatment, patients with primary OC should be managed in specialist units where complete cytoreduction is achieved in the majority of patients. There may be a benefit from ip chemotherapy or HIPEC following cytoreductive surgery for ROC but level one evidence is needed.

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