Surgical Management of Recurrent Epithelial Ovarian Cancer

11

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11.1 Introduction

A large proportion of the patients with advanced ovarian cancer develop disease recurrence within few years [1, 2]. Most of the patients who recur die within 5 years since recurrent disease is usually incurable [3]. Second-line therapy includes either chemotherapy or surgery or both chemotherapy and surgery but the outcomes remain poor.

Although most of the initial recurrences are frequently platinum sensitive, patients eventually develop resistance to platinum-based chemotherapy [3]. Resistance to chemotherapy, which is either intrinsic (primary) or acquired (secondary), is a major problem in the treatment of ovarian cancer and the main contributing factor in cancer-associated mortality. An aggressive locoregional therapy comprising of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in addition to systemic chemotherapy has produced promising results. The optimal use of this combined modality treatment in addition to systemic therapy has the potential to provide a significant prolongation of the disease-free survival (DFS) and overall survival (OS) both in these patients.

11.2 Appropriate Terminology for Recurrent Disease

The time to recurrence after completion of first-line chemotherapy, i.e. the platinum-free interval (PFI), has been used to classify recurrent ovarian cancer into two broad groups—platinum sensitive or platinum resistant.

This division is arbitrary and was done for the purpose of study design and interpretation by the Gynecologic Oncology Group (GOG) [4]. The platinum-sensitive group comprises of patients who recur 6 months or more after cessation of platinum-based chemotherapy. The clinically resistant group consists of those patients who actually progress while receiving platinum-based therapy, whose best response to platinum-based therapy is stable disease, and who recur within 6 months of cessation of platinum-based treatment [5]. Within this group are patients who have progressed on chemotherapy or had a less than partial response (stable disease) and could be termed as 'platinum refractory'. This is seen in 20% of the cases, and these patients have the lowest probability of responding to second-line ther-

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apy. Among the other platinum-resistant patients are those that have a complete clinical response after surgery and chemotherapy and recur within 6 months of cessation of therapy. This would include patients who had optimal and suboptimal cytoreductive surgery (CRS) both [5]. Subsequent recurrences are classified according to the PFI from the last treatment.

The PFI has been widely used as a clinical surrogate for predicting the response to chemotherapy and determining the prognosis [6]. However, there are several caveats in using this division. There is a variability in the use and timing of investigations used to diagnose a recurrence. This influences the time at which the relapse is diagnosed and hence the categorization of the patients as platinum sensitive or platinum resistant. Moreover, in the platinum-sensitive group, the 'platinum-free interval' affects the response to further systemic therapy, with patients who are platinum-free for more than 12 months having better outcomes than those with a shorter PFI [6].

At the fourth Ovarian Cancer Consensus Conference (fourth OCCC) in Vancouver in 2010, there was an agreement that future clinical trials should evaluate outcomes based on four subsets of patients [7]. This division is also based on the PFI and is as shown in Table 11.1.

With the increasing use of non-platinum and biological agents like poly-ADP-ribose polymerase (PARP) inhibitors and angiogenesis inhibitors that may have an impact on disease biology and response to subsequent therapy, the PFI may not be the only prognostic factor affecting outcomes. At Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup, the PFI was replaced by a broader term, i.e. treatment-free interval (TFI), which was further divided into the TFI from last plati-

num dose (TFIp), the TFI from last non-platinum therapy (TFInp) as well as last biological agent (TFIb) [8]. These classifications are being used to stratify patients for clinical trials that evaluate various systemic therapies.

An additional prognostic factor that has been overlooked in these classifications is the completeness of the first surgery. Some patients who did not have an attempt at complete CRS by a surgical/gynecologic oncologist may or may not have a complete response after chemotherapy. They may be inappropriately classified as platinum resistant/platinum refractory. Classe et al. suggested that to distinguish patients with a true early relapse refractory to platinum, other criteria such as the completeness of primary surgery performed in an expert centre need to be added to the disease-free interval [9].

11.3 Pattern of Recurrence

The commonest site of recurrence in epithelial ovarian cancer is the peritoneum. Seventy five percent of recurrences occur in the peritoneum, and in almost 50% of these cases, the peritoneum is the only site of recurrence [10]. Nodal recurrence is the second most common and is usually associated with peritoneal disease. Distant metastases are a rare site of disease recurrence [10].

Disease can recur in both treated and non-treated areas of the peritoneum. Pelvic recurrences are more common than upper abdominal recurrences [11, 12].

A retrospective study of 104 patients showed that in comparison to patients receiving systemic chemotherapy alone, patients who received intraperitoneal chemotherapy were more likely to recur in the upper abdomen or in extra-abdominal nodes [13]. Most of the recurrences from ovarian cancer are diffuse. In a study of 270 patients, reported by Ferrandina et al., 'diffuse peritoneal carcinomatosis' was seen in 62.1% of cases, while recurrences presented as a single lesion or multiple nodules occurred in 9.9 and 26.7% of cases, respectively [14]. Peritoneal carcinomatosis was defined as 20 or more peritoneal nodules by Chi et al. [15]. Isolated recurrence has been

Table 11.1 Classification of recurrence according to the platinum-free interval

Platinum-free interval	Subgroup
<1 month	Platinum refractory
1–6 months	Platinum resistant
6–12 months	Partially platinum sensitive
>12 months	Fully platinum sensitive

reported in patients with platinum-resistant disease as well [16]. It has been shown that the pattern of recurrence is dependent neither on the initial stage nor the completeness of CRS. A complete CRS does not affect the timing or pattern of recurrence though it reduces the absolute number of recurrences [17]. However, most of these studies consider <1 cm residual disease as a cut-off for complete cytoreduction though current evidence has shown that outcomes are better in patients with no residual disease as compared to any size of visible residual tumour [18].

11.4   Treatment of Recurrence

The treatment of recurrence essentially depends on the prior course of disease. It is important to review the prior treatment that has been administered—the surgical details and its completeness, the chemotherapy regimen, the time interval to recurrence—if complete remission was achieved or not.

The cornerstone of second-line therapy has been chemotherapy, and surgery is conventionally reserved for isolated localized recurrences. However, despite subjective and objective responses to second-line therapy and a prolonged disease-free and overall survival that is obtained in certain patients who have platinum-sensitive disease, the outcome of these patients is poor and cure is almost impossible [5]. The intent of treatment needs to be defined before starting any kind of therapy.

The tendency of recurrent disease to remain confined to the peritoneal cavity for prolonged periods forms a strong rationale for an aggressive locoregional approach comprising of CRS with or without hyperthermic intraperitoneal chemotherapy (HIPEC).

11.4.1 Evidence for Cytoreductive Surgery for Recurrent Ovarian Cancer

CRS can be performed as a second look following previous suboptimal surgery (secondary CRS) or for disease recurrence after complete response to first-line therapy (salvage CRS). The term 'secondary CRS' is broadly used for both situations. The completeness of surgery is defined according to the maximum diameter of the residual disease nodules. Complete cytoreduction is generally used for cases where there is no visible residual disease according to the completeness of cytoreduction score (Table 11.2) by Sugarbaker et al. [19]. The other commonly used term is 'optimal cytoreduction' which as defined by the Gynecologic Oncologic Group (GOG) as residual disease measuring <1 cm in maximal diameter [20].

Most of the evidence to support the use of CRS for recurrent ovarian cancer comes from retrospective studies [21–24]. These studies had a complete cytoreduction rate ranging from 50 to 87%. The median overall survival (OS) in patients undergoing complete cytoreduction ranged from 29 to 60 months. The criteria for complete CRS varied from no visible macroscopic residual disease to residual disease measuring <2 cm. Most of these studies have a short follow-up (1–4 years) and do not stratify patients according to PCI.

In a population-based study from the Netherlands, 408 patients who underwent secondary CRS at 38 centres experienced a median survival of 51 months [25]. Complete cytoreduction was achieved in 295 (72.3%) patients, with an OS of 57 months compared with 28 months in

Table 11.2 Scoring systems for completeness of cytoreductive surgery

Scores for completeness of cytoreductive surgery			
Completeness of cytoreduction (CC) score [19]		GOG criteria for 'optimal debulking' [20]	
CC-0	No visible residual disease	RD0	No visible residual disease (zero residual disease
CC-1	Residual disease 0–2.5 mm		
CC-2	Residual disease 2.5–2.5 cm	RD 1	Residual disease <1 cm (*optimal debulking*)
CC-3	Residual disease >2.5 cm	RD 2	Residual disease >1 cm (suboptimal debulking)

patients with incomplete cytoreduction (*p* = 0.001). Non-serous histology, a long progression-free interval (hazard ratio [HR], 0.29; 95% CI, 0.07–1.18), a good performance status (HR, 0.68; 95% CI, 0.49–0.94), secondary CRS without preoperative chemotherapy (HR, 0.72; 95% CI, 0.51–1.01) and complete CRS (HR, 0.46; 95% CI, 0.33–0.64) were prognostic factors for survival [25].

In a retrospective review of secondary CRS, Munkarah et al. found that patients with no gross residual disease after CRS had a survival of 44–60 months as compared to 35 months in those receiving chemotherapy alone [26]. Optimal cytoreduction was achievable in 38–87% of the study populations reviewed with acceptable perioperative complications and mortality. However, the impact of secondary CRS on survival could not be analysed due to (1) the inter-investigator differences in defining optimal cytoreduction, (2) the heterogeneity of the patients included (3) and the lack of information on postoperative therapy. Though most of these studies have drawbacks like small numbers, retrospective nature and lack of proper stratification based on prognostic variables, the survival reported is higher than that shown by modern multi-agent chemotherapy alone, especially in patients who had complete tumour removal (44–60 months) [26].

Bristow et al. published a meta-analysis of 40 studies, including 2019 patients, 13 studies were published between 1983 and 2000 and 27 (67.5%) were published between 2001 and 2007 [27]. Twelve of the 40 reports utilized prospective non-randomized data collection methodology; there were 27 retrospective analyses and one retrospective case-control study. The mean weighted median disease-free interval (DFS) prior to CRS for recurrent ovarian cancer was 20.2 months reflecting a tendency to select patients with platinum-sensitive disease for surgery. The parameter significantly associated with survival was the size of the residual disease. Each 10% increase in the proportion of patients left with optimal residual disease was associated with a 2.69-month increase in median survival time (95% CI 0.90 months to 4.49 months, *p* = 0.004). Similarly, each 10% increase in the proportion of

patients undergoing complete surgical resection was associated with an increase in median cohort survival time of 2.84 months (95% CI 1.29 months to 4.38 months, *p* = 0.0008). The various limitations of this study pointed out by the authors were selection bias in selecting studies for the meta-analysis as well as patient selection in each study, the data collection interval was 25 years leading to heterogeneity in the chemotherapy regimens and other prognostic factors like tumour size, the number of lesions and performance status were not analysed [27].

In a Cochrane Database review of nine studies comprising of 1194 patients, there was a prolongation in overall survival in women who had a complete cytoreduction (no visible residual disease) and optimal cytoreduction (<1 cm residual disease) compared to those who had suboptimal cytoreduction (>1 cm residual disease) [28]. This meta-analysis included only those studies that has >50 women and had compared outcomes between optimal and suboptimal cytoreduction. There were no randomized controlled trials in this study. The authors concluded that though suggestive, this could not be taken as conclusive evidence, and the survival benefit could be due to a more favourable disease biology rather than the surgical effort alone. According to them, a randomized controlled trial was needed to further define the role of secondary CRS [29].

Bickell et al. used the Surveillance, Epidemiology and End Results Medicare database to assess the benefit of CRS in women who developed recurrence after first-line therapy for ovarian cancer [29]. Women who developed recurrence within 6 months of completion of first-line therapy were excluded from the analysis. Of the 1635 (80%) women who experienced recurrence, 265 (16%) were treated with secondary CRS and chemotherapy, 1171 (72%) with chemotherapy alone and 199 (12%) received hospice care. Propensity score adjusted log-logistic analyses showed that women undergoing surgery with chemotherapy had significantly greater survival compared with those receiving chemotherapy alone (hazard ratio [HR] = 1.33; 95% confidence interval [CI], 1.20–1.47). The estimated median survival of women treated with

chemotherapy was 4.1 years from time of diagnosis; those treated with secondary surgery and chemotherapy survived a median of 5.4 years; 67% of those receiving hospice survived an average of 2.2 years. The 403 women who received no secondary treatments were classified as nonrecurrent and had a median survival of 9.3 years. The authors concluded that secondary CRS with chemotherapy to treat recurrent ovarian cancer increases survival by 1.3 years compared with chemotherapy alone and pending ongoing randomized trial results may be considered a standard of care [29].

There is a clear benefit of secondary CRS in selected patients with recurrent ovarian cancer who have a complete cytoreduction. They experience a significantly greater DFS and OS compared to patients undergoing chemotherapy alone. However, the chemotherapy group also comprises of patients with poor prognostic factors like platinum-resistant disease, extensive disease not amenable to complete cytoreduction and those with a poor performance status. Currently, three clinical trials are underway which will define the role of secondary CRS further.

The DESKTOP III is a phase 3 randomized controlled trial evaluating the role of cytoreductive surgery for first recurrence that has completed accrual. The results are expected in 2019. Patients with a positive AGO score (described below) are randomized to chemotherapy alone or CRS and chemotherapy (ClinicalTrials.gov identifier: NCT01166737).

Another randomized controlled multicentric trial is currently underway in the Netherlands (Netherlands Trial Register number: NTR3337; the Dutch SOCceR trial) that randomizes women with platinum-sensitive recurrence to undergo secondary CRS followed by platinum-based chemotherapy or platinum-based chemotherapy alone. Inclusion criteria are FIGO stage IC-IV (FIGO system 1988), first-line treatment consisted of complete or optimal ($\leq$ 1 cm) cytoreductive surgery and (neoadjuvant) platinum-taxol-based chemotherapy, ascites <500 mL (pocket <8 cm on ultrasound examination), complete resection seems possible (estimated by a gynaecologic oncologist), good

performance status (ECOG 0–1) and administration of platinum-based chemotherapy is possible [30].

The GOG 213 is a phase 3 randomized controlled trial that will determine the impact of secondary CRS in addition to chemotherapy in recurrent platinum-sensitive ovarian, fallopian tube and primary peritoneal cancer patients (NCT00565851).

The results of these trials will be available only after a few years. Meanwhile, CRS continues to be incorporated into second-line therapy as there is strong evidence showing a survival benefit.

The issues that need to be dealt with while incorporating CRS into second-line therapy are:

– Criteria for selecting patients
– Role of CRS in patients with platinum-resistant/platinum-refractory disease
– Sequencing systemic chemotherapy with CRS, before or after

11.4.1.1 Selection of Patients

Selection of patients is important for attaining optimal results. Most studies report a favourable outcome in patients who recur more than 12 months after completion of first-line therapy and those who have complete/optimal cytoreduction [21–24, 31].

Other factors like a solitary site or limited number of sites of recurrence, complete response to first-line therapy and small maximum tumour diameter have also been associated with better survival outcomes [21–24, 31]. Only patients with minimal (<500 cc) or no ascites are subjected to surgery [32]. Women with symptomatic ascites, carcinomatosis, early relapse (i.e. less than 6 months) and poor general health are not likely to benefit from secondary CRS [33–35].

The AGO-DESKTOP study retrospectively analysed 267 patients who had undergone CRS for recurrent ovarian cancer and concluded that only those patients who had a complete CRS experienced a prolonged survival. A combination of performance status, early FIGO stage at the first surgery or no residual tumour after first surgery and absence of ascites could predict complete resection in 79% of patients. However, in patients with a negative score, a complete cytoreduction was achieved

in 58%. The authors proposed a two-step model—patients with a negative score should undergo a laparoscopic evaluation and those without carcinomatosis be taken up for secondary CRS. With this strategy, a complete cytoreduction was possible in 63% of the patients with a negative score [36]. The DESKTOP II study prospectively analysed the predictive value of three of these criteria also known as the AGO score (complete resection at first surgery, good performance status and absence of ascites) and found that when all three are met with, a complete cytoreduction can be achieved in 76% of the patients with a morbidity of 11% [37]. This score is the first prospectively validated instrument to positively predict surgical outcome in recurrent ovarian cancer. It can aid in the selection of patients who might benefit from secondary cytoreductive surgery. However, in a retrospective study of 192 patients, a large proportion of patients with a negative AGO score also had complete removal of macroscopic disease at the time of secondary CRS, and the authors concluded that a refinement in the score was needed to exclude women who were unlikely to benefit from surgery [38].

Once again, these criteria exclude a subgroup of patients who never had surgery by a gynecologic oncologist/surgical oncologist leading to residual/recurrent disease and could benefit from secondary CRS.

It is prudent to undertake only those patients for surgery in whom there is probability of achieving a complete CRS. The survival in patients undergoing incomplete cytoreduction is similar to those receiving chemotherapy alone. This makes it important for such treatment to be carried out at expert centres by surgeons experienced in performing such procedures.

Despite the large body of evidence in favour of secondary CRS, the selection criteria need to be more clearly defined.

11.4.1.2 Platinum-Resistant Disease

The platinum-resistant group includes patients who are platinum refractory (progression on chemotherapy or stable disease after first-line therapy) and those who are platinum resistant (recurrence within 6 months of complete response to first-line therapy).

For patients with platinum-refractory disease who have had an attempt at complete cytoreduction at an expert centre, the treatment is chemotherapy. However, if the primary cytoreduction was not performed by an expert surgical/gynaecologic oncologist, a secondary CRS can be attempted.

Most studies use recurrence within 6 months as an exclusion criteria for secondary CRS; hence, evidence to support the use of surgery in these patients is scarce. Moreover, patients are not stratified as platinum refractory and platinum resistant which makes it difficult to determine the exact benefit or the selection criteria.

In a retrospective review of 18 patients by Musella et al., the 5-year overall survival was significantly longer in CRS group (57%) when compared with the control group of patients who received only systemic therapy (23.5%; $p = 0.035$). However, the peritoneum was the site of relapse in only 33% of these patients [39]. In another study of six patients with isolated peritoneal relapse and isolated lymph nodal recurrence treated with secondary cytoreductive surgery, secondary CRS significantly prolonged median time to first progression (12 vs 3 months; p-value = 0.016), median time to second progression (8 vs 3 months; p-value = 0.037) and post-relapse survival (PRS) (32 vs 8 months; p-value = 0.002). Residual tumour at the first surgery ($p = 0.017$), the PFI ($p = 0.020$) and complete cytoreduction ($p = 0.039$) were the independent prognostic factors on multivariate analysis [16]. In selected patients with platinum-resistant disease, secondary CRS could be attempted after second-line chemotherapy provided a complete cytoreduction can be attained. Such procedures are performed in patients with a good performance status and after controlling the disease with systemic chemotherapy.

11.4.2 Detection of Recurrence

In patients who have had a complete remission, an elevated CA 125 level is usually the first indication of disease recurrence. Some of these patients may have no clinical symptoms (pelvic pain, bloating, obstruction) or evidence of dis-

ease on imaging studies. The tumour marker elevation usually precedes the clinical manifestation of recurrence. A patient with platinum-refractory disease may have persistent marker elevation after completion of frontline therapy and/or radiological evidence of residual disease.

According to the Gynecologic Cancer InterGroup definition, CA 125 progression is defined by a progressive serial increase in serum CA 125 level as follows: patients with pretreatment CA 125 elevation normalizing during or after therapy or patients with pretreatment normal CA 125 who show a CA 125 value of at least two times the upper limit of the normal level on two measurements taken at least 1 week apart [40]. Patients with increased pretreatment CA 125 who never normalize must have a CA 125 value of at least two times the nadir value on two measurements at least 1 week apart [40]. This definition is now used in many clinical trials, together with Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

11.4.3 Early Versus Delayed Treatment of Recurrence

Since recurrent ovarian cancer is not curable in most cases, the role of early treatment based on tumour marker elevation alone has been questioned. In a randomized trial (MRC OV05/EORTC 55955), 529 of the 1442 registered patients were randomized to either receive immediate chemotherapy or chemotherapy at clinical progression following a rise in CA 125 levels [41].

In all, 94% of the patients randomized to immediate treatment received salvage therapy versus 88% of the patients in the delayed treatment arm. The median time to starting salvage therapy was significantly shorter in the immediate treatment arm (0.8 vs 5.6 months; HR: 0.29; $p < 0.00001$). At a median follow-up of 49 months, no differences in survival were observed between the two groups (HR: 1.0; $p = 0.98$). However, the evaluation of quality of life, which is of paramount importance given the palliative role of second-line therapy for the majority of relapsing patients, showed that it was significantly better in the delayed treatment arm. Median time spent with a good global health score was 7.2 months in the early versus 9.2 months in the delayed treatment arm, and time from randomization to first deterioration in global health score or death was shorter in the early compared with delayed group (3.2 vs 5.8 months; $p = 0.002$). The authors concluded that there was no role of starting second-line therapy in asymptomatic patients based on a rise in CA 125 alone [41]. The limitations of this trial which would preclude the use of such a strategy in clinical practice are the use of nonuniform salvage therapy across the participating centres, the diversity in the study population in terms of the PFI, the role of secondary CRS that was not explored and, in particular, the differences between optimal and suboptimal primary CRS in the two arms that were not evaluated [40]. Some of the patients who have resectable recurrences and could benefit from early treatment may be denied the benefit if such a strategy is applied uniformly.

Tanner et al. retrospectively evaluated outcomes in 121 patients who had a complete clinical response after first-line therapy and developed recurrent disease [42]. Twenty two (18.2%) were diagnosed with a symptomatic recurrence. Though the median time to first recurrence was similar for asymptomatic and symptomatic patients (24.8 vs 22.6 months, $p = 0.36$), the post-recurrence survival was significantly longer in asymptomatic patients (45.0 vs 29.4 months, $p = 0.006$). Though secondary CRS was attempted equally in both groups (41% vs 32%, $p = NS$), the rate of complete CRS (optimal residual disease (<or = 5 mm)) was higher in patients with asymptomatic disease (90 vs 57%, $p = 0.053$). On multivariate analysis, detection of asymptomatic recurrence was a significant and independent predictor of improved overall survival ($p = 0.001$). Median OS was significantly greater for asymptomatic patients (71.9 vs 50.7 months, $p = 0.004$). This difference did not appear to be attributable to a discrepancy in the timing of diagnosis as a lead time bias would suggest, but, rather, to the location of these recurrences, to their earlier amenability to salvage chemotherapy and to more successful secondary CRS due to decreased volume of disease [42].

The authors pointed out several limitations in the study—small size, retrospective nature, and exclusion of a large number of patients during the study period due to either inadequate follow-up information or transfer of the patient care to another provider.

In another retrospective review by Gadducci et al., no difference in survival was observed in asymptomatic patients versus symptomatic patients although the rate of attempted secondary CRS (15%) was significantly lower than the current series. However, patients undergoing secondary CRS and chemotherapy experienced a significantly better overall survival than those who did not undergo surgery [43].

Thus, there seems to be a clear benefit of detection and early treatment of asymptomatic recurrence though it may need further evaluation in randomized trials.

11.4.4 Investigations: Evaluation of Disease Extent

11.4.4.1 CT Scan

The most commonly performed investigation is a contrast enhanced CT scan of the thorax, abdomen and pelvis [44]. The typical CT findings in recurrent ovarian cancer are similar to that of peritoneal metastases arising from other primary sites:

– Thickened peritoneum
– Ascites
– Pelvic mass
– Pelvic/retroperitoneal lymphadenopathy
– Bowel surface/mesenteric deposits
– Omental involvement
– Pelvic sidewall involvement and/or hydroureter
– Diaphragmatic involvement

A CT scan determines not only the extent of the disease but also the involvement of certain areas that would preclude a complete CRS—like involvement of the porta hepatis, extensive involvement of the small bowel/mesentery, extensive diaphragmatic involvement and upper abdominal lymphadenopathy (suprarenal) [44]. Several CT-based scores and algorithms have been developed to predict the probability of complete CRS in advanced ovarian cancer, and the same can be used to predict the probability in case of recurrent disease [45–47]. The sensitivity of CT for peritoneal tumours less than 1 cm was found to be only 25–50% compared with 85–95% for larger tumour deposits [48]. A CT scan has been shown to underestimate the extent of carcinomatosis in 33% of patients [49].

11.4.4.2 PET Scan/PET-CT Scan

Several studies demonstrated a benefit of fluorine-18-fluorodeoxyglucose positive emission tomography (FDG-PET) and FDG-PET/computed tomography (FDG-PET/CT) in the early detection of recurrent disease in ovarian cancer [50–53]. In a prospective multicentric study, Fulham et al. found a higher rate of detection of nodal, peritoneal and subcapsular liver disease as well as the total number of sites of disease with PET-CT as compared to CT [54]. They found that FDG-PET/CT altered the management in about 60% of the patients. In another study the accuracy of PET-CT for predicting optimal cytoreduction was found to be 78.6%. Like CT scan the main limitation is in the inability to detect small tumour nodules [55].

11.4.4.3 Staging Laparoscopy

Laparoscopy allows direct visualization of the peritoneal surfaces, the small bowel and its mesentery and can pick up small nodules that are missed on imaging. The disadvantages are its inability to evaluate retroperitoneal structures like the ureters and pancreas, the omental bursa near the celiac axis and the depth of involvement of the hepatic pedicle and the diaphragm [56]. Fagotti et al. evaluated the role of staging laparoscopy for selecting patients for secondary CRS. The negative predictive value, specificity, positive predictive value, sensitivity and accuracy rate of staging laparoscopy were 88.9, 64.0, 80.8, 95.0 and 83.1%, respectively [57]. A combined radiological (PET-CT) and laparoscopic evaluation showed a negative predictive value of 88.9%, a specificity of 59.3%, a positive predic-

tive value of 78.8%, a sensitivity of 95.3% and an accuracy rate of 81.4%. The authors suggested that a combination of these two modalities could optimize patient selection [57].

11.4.5 Surgical Strategies for Secondary Cytoreductive Surgery

The goal of secondary CRS should be to attain a complete/optimal cytoreduction. Many surgeons/institutions still use cut-offs of residual tumour measuring <0.5 or <1 cm as the criteria for optimal CRS though there is evidence that complete removal of macroscopic disease (completeness of cytoreduction score, 0, i.e. CC-0) results in superior outcomes as compared to leaving behind any amount of residual disease [15, 19, 27].

To attain a complete cytoreduction, a combination of peritonectomy procedures and visceral resections needs to be performed as for peritoneal metastases from other tumours [58]. The visceral resections include small and large bowel resection, cholecystectomy, partial gastrectomy, full-thickness diaphragm resection, splenectomy, distal pancreatectomy, partial ureteric resection, partial cystectomy and resection of pelvic sidewall [59–61]. A detailed description is provided elsewhere [62]. Such procedures have a survival benefit if complete CRS can be obtained [63]. Though the goal is complete removal of macroscopic disease, it should not impair the gastrointestinal and urinary function to the extent that the quality of life is significantly impaired. Extensive intestinal resections that impair digestion and nutrition and lead to dependence of parenteral nutrition (extensive small bowel resection with or without total gastrectomy or colectomy) should not be performed. Posterior pelvic exenteration is often necessary; however, the vesical trigone must be left intact because, in this context, a total cystectomy should never be performed [64].

If a pelvic and/or retroperitoneal lymphadenectomy was not performed during primary CRS, it should be performed irrespective of the presence or absence of nodal metastases in patients undergoing complete CRS. This is performed even in patients with no evidence of lymph node involvement on preoperative imaging. Nodal recurrence can be isolated or present with peritoneal disease [65, 66]. Retroperitoneal lymphadenectomy is performed till the level of the renal veins. There is a survival benefit of surgery for nodal recurrence even if it is bulky (>2 cm maximum diameter of the largest lymph node is considered bulky nodal disease) [67–69]. In case of disease involving the suprarenal nodes, lymphadenectomy can be performed in this region also if the disease is not bulky and limited [63].

Hepatic resection can be performed synchronously with secondary CRS for solitary or multiple parenchymal liver metastases. The goal of such resections should be to resect the liver lesions with a negative margin. Several retrospective studies have reported an acceptable morbidity and mortality for such combined resections [70]. The common prognostic factors reported in these studies were optimal CRS <1 cm residual disease, negative resection margins, disease-free interval >12 months, fewer number of liver metastases and fewer sites of disease. The surgical and oncological outcomes from various studies on resection of hepatic metastases in recurrent ovarian cancer are described in Table 11.3.

11.4.6 Minimally Invasive Secondary CRS

Several studies have reported the feasibility of a minimally invasive approach for secondary CRS [78–81]. These studies include patients with localized recurrence (1–3 nodules), good performance status and long platinum-free interval. The reported morbidity and mortality is similar to that of open surgery and conversion rates are low (Table 11.4). One series reported the use of loop electrosurgical excision and argon beam coagulator to ablate the metastases [79]. Such methods cannot replace a formal peritonectomy and/or resection of the viscera where indicated. Though there is no head to head comparison, it has been suggested that such an approach could shorten the postoperative recovery times, leading to a better psychological state and quality of life

Table 11.3 Surgical and oncological outcomes in patients undergoing secondary CRS with resection of liver metastases (adapted from reference [70])

Ref. no./year	No. of patients	Optimal CRS	Type of liver resection	Negative resection margins	OS (months)	Prognostic factors
[71] 2003	26	80.8%	Segmentectomy 69.2% Trisegmentectomy 3% Left hepatectomy 3.8% Right hepatectomy 15.4%	NA	26.3 optimal; CRS 27.3 suboptimal; CRS 8.6 ($p = 0.031$)	Residual disease, <1 vs >1 cm; DFI, <12 vs >12 months; distribution of disease, abdomen > pelvis or pelvis ≥ abdomen
[72] 2003	24	66.7	Wedge resection 12.5 Segmentectomy 70.9 Trisegmentectomy 8.3% Lobectomy 8.3%	54.1%	62 (95% CI, 41–83)	No significant prognostic factors found
[73] 2005	29	NA	NA	NA	Hepatic disease alone 25 (9–44); multi-organ recurrence 8 ($p = 0.033$)	Number of hepatic lesions; presence of other sites of disease; treatment with platinum-based chemotherapy
[74] 2008	10	100%	Bisegmentectomy 10% Trisegmentectomy 40% Lobectomy 50%	50%	33 (95% CI, 19–56)	Size of largest tumour ≥5 cm; negative resection margin ($p = 0.024$)
[75, 76] 2010	8	NA	Wedge resection 25% Segmentectomy 37.5% Sectorectomy 37.5%	NA	24	
[77] 2011	18	66.7%	Wedge resection 22.7% Segmentectomy 72.2% Bisegmentectomy 5.6%	66.7%	38 (3–78)	Distribution of disease: pelvis > abdomen or abdomen > pelvis; residual disease < or >1 cm; negative resection margins

[78]. The minimally invasive approach has an important limitation. A preoperative CT scan combined with a staging laparoscopy should be used to determine the extent of disease, though the extent of disease is usually underestimated. Moreover, the laparoscopic assessment is often limited by the presence of adhesions, and this should be kept in mind when taking up patients for such procedures.

11.4.7 Prognostic Factors

In a retrospective review of 153 patients with platinum-sensitive disease undergoing secondary cytoreductive surgery, Chi et al. reported that those with carcinomatosis had a poorer outcome compared to those patients with isolated disease or multiple nodules (<20) [15]. Similarly, patients recurring within 6–12

Table 11.4 Outcomes of minimally invasive surgical approach for secondary CRS (adapted from reference [78])

Ref. no./ year	No. of patients/ conversions	Recurrence	Surgical approach	Mean operating time (min)	Optimal CRS	Postoperative complications	Median disease-free survival (months)
[79] 2004	36 (2)	First	LPS	126	94%	2/34	13
[80] 2012	23 (1)	19 first	LPS	200	81.8%	1/22	71.9
		4 second					
[81] 2013	9 (0)	First	LPS robotic	177	88.9%	3/9	34.1
	10 (0)			220	70%	2/10	
[78] 2014	29 (2)	First	LPS	188	96.2%	1/27	14

LPS laparoscopic surgery, *CRS* cytoreductive surgery

months of completion of frontline therapy fared worse than those recurring from 13 to 30 months or >30 months [15]. It is important to have a reproducible quantification of the disease extent—the disease extent is one of the strongest prognostic factors determining the outcome of second-line surgical therapy—and having a uniform method of quantifying it enables comparison of treatment outcomes. The most commonly used score for this is the 'peritoneal cancer index' (PCI) developed by Paul Sugarbaker [19]. Other poor prognostic factors are mucinous or clear cell histology and more than one route of metastasis (e.g. peritoneal metastases with haematogenous or lymphatic spread) [15]. In a meta-analysis that included 2019 patients, Bristow et al. evaluated the impact of residual tumour size ranging from 0 to 2 cm on overall survival. The only statistically significant clinical variable independently associated with post-recurrence survival was the proportion of patients undergoing complete CRS ($p = 0.019$). When each study was analysed individually also, there was a survival benefit that was significant in patients who had complete CRS as compared to those who had any size of residual disease. The presence of any size of residual disease was associated with a greater risk of dying due to disease. After controlling for all other factors, each 10% increase in the proportion of patients undergoing complete CRS was associated with a 3.0-month increase in median cohort survival time [27].

11.4.8 Systemic Chemotherapy in Addition to Secondary Cytoreductive Surgery

The role of systemic chemotherapy in addition to secondary CRS has not been evaluated. Most studies have used systemic chemotherapy either before or after secondary CRS. All ongoing clinical trials have incorporated chemotherapy in the surgical arm as well. Though the best treatment strategy for such patients is not known, a logical approach is as follows. In patients with disease resectable upfront, secondary surgery could be performed first followed by chemotherapy. It is important in such cases that postoperative chemotherapy is not delayed due to complications. In patients who recur within 6 months of first-line therapy or have disease not amenable to a complete cytoreduction, second-line chemotherapy can be administered before secondary/salvage CRS.

11.5 Rational for Intraperitoneal Chemotherapy for Recurrent Ovarian Cancer

Recurrent ovarian cancer remains confined to the peritoneal cavity for prolonged periods which is the basis of using intraperitoneal chemotherapy as part of locoregional therapy. Intraperitoneal (IP) drug therapy offers the potential to increase the therapeutic index by enhanced local drug concentration and at the same time limiting systemic absorption and toxicity [82]. It exposes the

poorly vascularized tumour tissue to high concentrations of cytotoxic agents. The efficacy of IP drug therapy depends on the extent of drug penetration in tumour tissue, which is driven by diffusion and convection [82]. Obstacles to drug transport include elevated interstitial fluid pressure and the density of the interstitial matrix which are characteristic of tumour stroma [82]. In optimally resected stage III ovarian cancer, large randomized trials have shown that the addition of IP chemotherapy to adjuvant regimens significantly improved survival [83–86]. This type of chemotherapy is repeatedly administered through an implanted catheter and access port. Adverse events and catheter-related problems were more common in the IP chemotherapy group and often led to discontinuation of therapy [87, 88]. IP chemotherapy can be administered by direct abdominal wall puncture as well [89]. Benedetti-Panici reported the use of ultrasound-guided direct puncture and administration of chemotherapy in 38 patients with recurrent ovarian cancer. A total of 402 IP procedures were performed, with a mean of 10.5 procedures per patient. The feasibility rate was 97.4% [90]. In a retrospective study of 33 patients, Nicoletto et al. used IP chemotherapy administered in this manner for recurrent ovarian cancer [91]. This treatment was used as an alternative to systemic chemotherapy in patients who had received multiple lines of chemotherapy and no CRS was performed. IP cisplatin was administered on day 1 and paclitaxel on day 8 every 21–28 days for a total of 3–4 cycles. Twenty-seven patients had ascites and 14 patients had peritoneal carcinomatosis only. Fourteen (51.8%) out of 27 patients had a clinical response, with disappearance or significant reduction of ascites for more than 45 days after IP chemotherapy. These patients were compared to matched controls who received only systemic chemotherapy. In patients with less than three previous lines of treatment, IP chemotherapy conferred a survival advantage of about 2.2 months (IP = 10.0 vs IV = 7.8 months, $p = 0.011$). However, the survival advantage in heavily pretreated patients (with three or more previous treatments) was not significant [91]. There is not much evidence for this type of intra-peritoneal chemotherapy in recurrent ovarian cancer. Hyperthermic intraperitoneal chemotherapy (HIPEC) is more commonly used in combination with CRS for recurrent ovarian cancer.

11.6 Rationale for Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

The rationale for using HIPEC as part of second-line therapy for ovarian cancer is the same as that for CRS—recurrent ovarian cancer remains confined to the peritoneal cavity for a prolonged period. This is further supported by the benefit CRS and HIPEC have shown in the treatment of gastrointestinal peritoneal metastases. CRS and HIPEC are now the standard of care of pseudomyxoma peritonei and peritoneal mesothelioma and for colorectal peritoneal metastases with a limited peritoneal spread [92–95]. It is still the only treatment modality that has shown to prolong survival in patients with peritoneal metastases from gastric cancer [96, 97].

HIPEC is administered immediately after CRS which reduces tumour cell entrapment that is common after surgery. HIPEC has the added advantage of using heat which itself is cytotoxic to cancer cells and enhances the cytotoxicity of various chemotherapeutic drugs like platinum compounds, alkylating agents, mitomycin C and doxorubicin that is enhanced by hyperthermia [98–101]. Hyperthermia enhances tissue perfusion and oxygenation and may improve drug penetration [102].

11.7 HIPEC Methodology and Drugs

HIPEC can be performed by the open (coliseum) or closed technique maintaining an intra-abdominal temperature of 41–43° C throughout the procedure. HIPEC is performed only in those patients in whom complete cytoreduction is attained (CC-0 or CC-1) since the treatment is ineffective on residual disease more than 2–3 mm

in size [103]. Any drug that is used for HIPEC should be retained in the peritoneal cavity with a limited systemic absorption [104].

One of the most commonly used drugs in this setting is cisplatin. Cisplatin is a drug that is retained in the peritoneal cavity, and its penetration into the adjacent tissues is potentiated by heat in both platinum-sensitive and platinum-resistant cell lines [105].

Hyperthermia can modify the cellular resistance to cisplatin as demonstrated by Hettinga et al. [106]. Relatively high doses of heat 43° for 60 min can interfere with cisplatin resistance by several mechanisms like drug penetration, adduct formation and repair [105]. These are further elaborated in Table 11.5. Hyperthermia can increase the cytotoxicity of cisplatin in both platinum-sensitive and platinum-resistant cell lines [107].

Van de Vaart et al. showed that cisplatin in combination with hyperthermia in vitro leads to a higher cisplatin ± DNA adduct formation which was a good predictor of the cytotoxic effect. The level of cisplatin-DNA adduct formation which is needed for a cytotoxic effect was observed in tumour nodules up to a depth of 5 mm. Hence, the effect HIPEC is useful for patients who are cytoreduced to minimal residual disease (CC-0/1) [108].

The ideal dose of cisplatin has been evaluated in the CHIPASTIN trial. This phase 1–2 escalat-

ing dose trial established that 70 mg/m^2 of cisplatin for 1 h at 42 °C was the most appropriate protocol [109]. However, another phase 1 study concluded that a 100 mg/m^2 dose of cisplatin for HIPEC in recurrent platinum-sensitive ovarian cancer has an acceptable safety profile [110].

Oxaliplatin that is commonly used for HIPEC in colorectal and appendiceal tumours has been used in recurrent ovarian cancer as well [111–113]. There is no direct comparison of oxaliplatin with platinum agents or taxols though preclinical data have shown a role in recurrent and platinum-resistant ovarian cancer [114]. Oxaliplatin has only moderate cross-resistance with cisplatin or carboplatin [115].

Carboplatin has a favourable toxicity profile compared to cisplatin and has replaced it in many of the intravenous regimens [102]. When nephrotoxicity is a concern, it can be administered in full dose for HIPEC as opposed to cisplatin which requires a dose reduction [116]. When a high dose of carboplatin is used for HIPEC, the drug concentration achieved in the tumour tissue is similar or superior to that achieved by an equitoxic dose of cisplatin [117]. Carboplatin undergoes hyperthermic enhancement of cytotoxicity and has been shown to have a more homogenous distribution of platinum as compared to cisplatin [117, 118]. Phase 1 trials for HIPEC as first-line and second-line therapy found that carboplatin doses up to 800–1000 mg/m^2 were tolerable and did not preclude additional systemic therapy [119–121]. The duration of treatment is 90 min.

Paclitaxel (175 mg/m^2) alone or in combination with cisplatin (100 mg/m^2) at 41–43° C for 90 min has been used by some investigators for HIPEC in patients with platinum-sensitive recurrent ovarian cancer [122, 123]. The morbidity was acceptable and the drugs achieved high concentrations in the peritoneal tissue with low systemic absorption. The tissue penetration of paclitaxel was only 0.5 mm, compared to 2–3 mm for cisplatin [122, 124, 125]. The numbers in these studies are small, and further evaluation of toxicity and efficacy of such a regimen is needed. Unlike cisplatin, hyperthermia does not augment the cytotoxicity of paclitaxel [126].

Table 11.5 Cellular effect of hyperthermia related to cytotoxicity of cisplatin [107]

Effect of hyperthermia	Resistance mechanism that could be affected
Increase in membrane fluidity	Cisplatin accumulation
Membrane protein denaturation	Cisplatin accumulation
Cytoplasmic protein denaturation	Detoxification
Altered DNA conformation	DNA accessibility
Inhibition of DNA repair	Repair of cisplatin-DNA adducts
Disturbance of normal cellular functions	Altered signal transduction and others
Gene expression, signalling	Response of cells to cisplatin-DNA damage

Table 11.6 Various drug regimens for HIPEC in recurrent ovarian cancer

Regimen	IP drugs	IV drugs	Carrier solution	Duration
Sugarbaker regimen [136]	Cisplatin (50 mg/m^2)	Ifosfamide 1300 mg/m^2	Peritoneal dialysis solution	90 min
	Adriamycin (15 mg/m^2)	Mesna 260 mg/m^2		
National Cancer Institute Milan regimen [137]	Doxorubicin 15.25 mg/L, cisplatin 43 mg/L			90 min
Sugarbaker gemcitabine-based regimen for platinum-resistant ovarian cancer [138]	Gemcitabine 1000 mg/m^2		Peritoneal dialysis solution	90 min
Sugarbaker melphalan-based regimen for platinum-resistant ovarian cancer [127]	Melphalan 50–70 mg/m^2		Peritoneal dialysis solution	90 min
Sugarbaker liposomal doxorubicin-based regimen for platinum-resistant ovarian cancer	Liposomal doxorubicin 50–100 mg/m^2		Peritoneal dialysis solution	180 min

Melphalan has been used for HIPEC in patients with recurrent tumours arising from various primary sites including recurrent and platinum-resistant ovarian cancer [127, 128]. The use of melphalan has been prompted by responses produced in regional chemoperfusion in soft tissue sarcomas and extremity melanomas [129, 130]. Melphalan undergoes cytotoxic enhancement with hyperthermia and has a favourable peritoneal fluid to plasma ratio [131–134]. Bijelic et al. first reported the use of 50–70 mg/m^2 of melphalan at 41–43° C for 60–90 min in 34 patients [127]. The grade 3–4 morbidity was 43% and there was no mortality in this series. They recommended the use of 60 mg/m^2 for 60 min for future evaluation of the role of melphalan.

The other agents that have been used are mitomycin C, doxorubicin, gemcitabine and irinotecan.

There is no study that has performed a head to head comparison between various agents/regimens.

Helm et al. analysed the effect of chemotherapy agents on survival in relation to the time point at which they were used. In patients with platinum-sensitive recurrence, the OS was superior with carboplatin as compared to cisplatin ($p = 0.012$) and mitomycin ($p = 0.011$), but there was no significant difference between agents in platinum-resistant disease. However, the numbers in the carboplatin group were small [135].

Some of the common regimens for HIPEC are listed in Table 11.6.

11.8 Evidence for HIPEC in Recurrent Ovarian Cancer

Salvage CRS and HIPEC is performed in patients who have recurred after an initial complete response to first-line therapy, and secondary CRS and HIPEC is performed in patients who have had an incomplete CRS with chemotherapy resulting in a partial response or stable disease [139]. Investigators have compared outcomes in patients who received HIPEC during secondary CRS with those who only received SCS and postoperative chemotherapy and those who only received IV chemotherapy without SCS [140]. Most of the available evidence comes from retrospective single and multi-institutional studies (Table 11.7). These studies have reported a median DFS ranging from 10 to 7 months, median OS ranging from 24 to 51 months and a 5 year OS ranging from 15 to 63%.

Petrillo et al. in a study of 70 patients treated with secondary CRS and HIPEC reported a longer second remission than the first in 52% of the patients. This is higher than that reported by most chemotherapy trials in a similar patient population as the second and subsequent remissions are usually shorter than the first [159, 160]. In a French

Table 11.7 CRS and HIPEC as second-line therapy for ovarian cancer (Adapted from reference [141] with permission)

Ref no./year	Type of study	N	PS/PR	Method	Drug(s)	Median PCI	CC-0/1	Median DFS (months)	Median OS (months)	3-year OS	5-year OS
[142] 2000	Pilot	5	+/−		Cisplatin			3	16		
[143] 2004	SI Pros	30	+/−		Cisplatin		77%	17.1 [CC-0: 24.4]	28.1 [CC-0: 37.8]		
[144] 2004	SI Pros	11	+/−		Cisplatin/mitoxantrone		50%		30 ± 6		15%
[145] 2006	SI Pros	14	+/−		Paclitaxel						63%
[146] 2007	SI Pros	81	+/+	Closed	Cisplatin		55.5%	19.2 [CC-0: 26.9]	28.4 [CC-0: 54.9]		
[147] 2008	SI Pro	18	+/−	Closed	Cisplatin	14.9	87.3		24		16.7%
[148] 2009	SI Pros	25	+/−		Doxorubicin	13.4	92.8%	26.2	40		
[112] 2009	SI Pros	42	+/−		Cisplatin		77%	13	37		
					Oxaliplatin						
[149] 2010	SI Pros	10	+/−		Oxaliplatin	6	100%	10		83%	
[150] 2010	SI Pros	8	+/−	Closed	Cisplatin and mitomycin		70%				55%
[135] 2010	MI Pros	83	+/+	Open/closed	Platinum/mitomycin/combination				30.43		25.4%
[151] 2011	SI Pros	31	+/−				65%	13.3			
[113] 2011	Pilot	12	+/−		Oxaliplatin		100%	14.3			

(continued)

Table 11.7 (continued)

Ref no./year	Type of study	N	PS/PR	Method	Drug(s)	Median PCI	CC-0/1	Median DFS (months)	Median OS (months)	3-year OS	5-year OS
[152] 2012	MI Retro	474	+/+	Open/closed	Cisplatin Oxaliplatin Mitomycin Doxorubicin Cisplatin+ Doxorubicin Cisplatin+ Mitomycin	10.6	92.1%		45.7	59%	37%
[153] 2014	SI Retro	90	+/+	Open	Cisplatin		69%		35.0		
[154] 2014	SI Retro	25	+/−	Closed	Cisplatin + lipodox Paclitaxel + lipodox	12.63	88%	27	11.9		
[155] 2015	SI Pros	54	+/+	Open/closed	Cisplatin+ Paclitaxel	10	100%	12.4	32.9		
[156] 2015	SI Pros	23	+/−	Closed	Mitomycin Cisplatin Oxaliplatin Carboplatin		76%				
[157] 2015	MI Retro	70	+/−	Closed	Cisplatin Oxaliplatin	7	88%	27			52.8% 44.7% (7 years)
[9] 2015	MI Retro	314	+/+	Open/closed	Cisplatin [114] Other agents	7	79% (CC-0)	13 (PS) 14 (PR)	42 (PS) 51 (PR)		38%
[158] 2016	MI Retro	24	+/−	Closed	Cisplatin, carboplatin, oxaliplatin, doxorubicin, combination						

SI single institution, *MI* multi-institutional, *Pros* prospective, *Retro* retrospective, *PS* platinum sensitive, *PR* platinum resistant, *DFS* disease-free survival, *OS* overall survival

retrospective multicentric study of 474 patients, the median OS was 45.7 months, and in patients who had complete CRS, it was 47.2 months in patients with platinum-sensitive disease and 51.6 months in those with platinum-resistant disease [152]. This difference was not statistically significant and showed that patients with platinum-resistant disease could have a survival similar to those with platinum-sensitive disease (Fig. 11.1).

A PCI of >8 was found to be a significant factor affecting both disease-free and overall survival. The patients in this series included those with second and third recurrences as well. In 2015, the same group published the outcomes of secondary CRS and HIPEC in patients with first recurrence comprising of 314 patients from 13 institutions [9]. The CRS performed during first-line therapy was complete in 33.8% (101/314) patients, there was macroscopic residual disease in 66.2% (98/314) patients and this information was unknown for 15 patients. Treatment strategy was secondary chemotherapy followed by secondary surgery and HIPEC for 85.6% (269/314) of patients; the remaining patients were treated with secondary surgery and HIPEC before secondary chemotherapy. At a median follow-up of 50 months, the 5-year overall survival was 38.0%, with no difference between platinum-sensitive

($n = 148$) and platinum-resistant ($n = 161$) patients, and 5-year disease-free survival was 14%. Considering patients treated with second-line chemotherapy followed by secondary surgery and HIPEC, patients who had a pathological complete response to chemotherapy experienced a better DFS and OS both (Fig. 11.2). Median OS was not
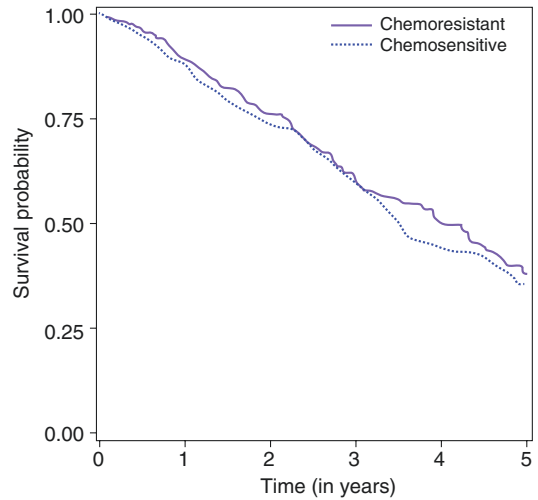

Fig. 11.1 Overall survival in platinum-sensitive (chemosensitive) and platinum-resistant (chemoresistant) recurrent epithelial ovarian cancer treated with cytoreductive surgery and HIPEC (log rank p-value = 0.799) (From ref. [152] with permission)
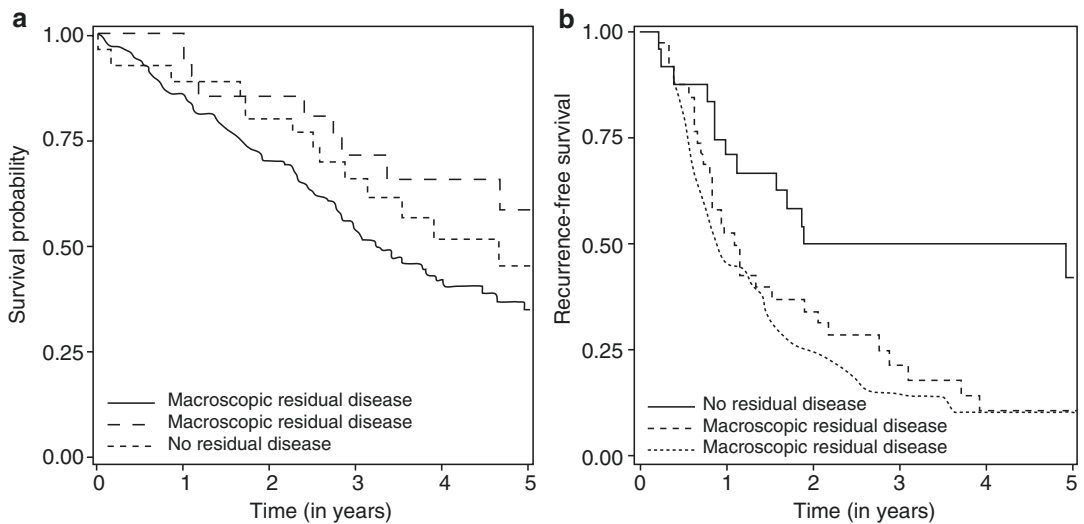

Fig. 11.2 Overall (**a**) and disease-free survival (**b**) according to pathological residual disease at the time of secondary CRS and HIPEC (From ref. [9] with permission)

reached for patients with no pathological residual disease, while for patients with microscopic residual disease it was 56 months and for patients with a macroscopic residual disease 39 months ($p = 0.073$). The median DFS was 41 months for patients with no pathological residual disease, 13 months for patients with microscopic residual disease and 10 months for those with a macroscopic residual disease ($p = 0.0019$). The residual disease distribution was similar in the platinum-sensitive and platinum-resistant cases [9].

Four other studies treated patients with platinum-resistant disease with CRS and HIPEC, two of these did not report the outcomes in patients with platinum-resistant disease separately. In a single institution series of 81 patients, the OS and DFS in patients with platinum-sensitive and platinum-resistant disease were similar. However, 58% of the patients had more than two disease recurrences and more than two surgical explorations leading to an inaccurate assessment of the PFI [146]. In another multi-institutional series of 83 patients, those with platinum-sensitive recurrence experienced a significantly better OS compared to patients with platinum-resistant disease [135]. However, patients with advanced and recurrent ovarian cancer were pooled together in this analysis due to which the impact of secondary CRS and HIPEC in platinum-resistant disease cannot be determined from this series.

In a meta-analysis of 9 comparative and 28 other studies evaluating the role of CRS and HIPEC in advanced and recurrent ovarian cancer, CRS and HIPEC with systemic chemotherapy appeared to significantly improve 1- and 3-year overall survival compared with CRS + chemotherapy alone (OR 3.48, 95% CI 1.44–8.44, $p = 0.006$; OR 7.39, 95% CI 2.29–23.86, $p < 0.001$, respectively). However, the 2-, 4- and 5-year overall survival benefit was not statistically significant (OR 2.84, 95% CI 1.01–7.89, $p = 0.05$; OR 2.82, 95% CI 0.71–11.2, $p = 0.14$; OR 2.37, 95% CI 0.4–14.12, $p = 0.34$, respectively) [161]. The first published randomized controlled trial for HIPEC in recurrent ovarian cancer randomized 120 women undergoing secondary CRS to receive HIPEC or not. They included both platinum-sensitive and platinum-resistant cases, using cisplatin and paclitaxel for the platinum-sensitive patients and a doxorubicin/paclitaxel regimen for the platinum-resistant cohort. The OS for the HIPEC group was significantly longer than that of the control group (26.7 vs 13.4 months). Patients with a complete cytoreduction experienced a better survival compared to those with residual disease, and a PCI > 15 had a negative impact on survival. There was no difference in the OS in patients with platinum-sensitive and platinum-resistant disease. Chi et al. pointed out several weaknesses in the reporting of this trial—lack of information on the DFS, median follow-up, postoperative first-line treatment and complication rates [140].

Several case-control studies have compared secondary CRS and HIPEC with CRS alone [123, 162–166]. In four of these, there was a statistically significant benefit of CRS and HIPEC over CRS alone. These studies are listed in Table 11.8. One case-control study showed a sur-

Table 11.8 Case-control studies comparing CRS and HIPEC with CRS alone as second-line therapy

Ref. no.	Year of publication	Type of recurrence	N	CRS+ HIPEC	CRS	Survival for CRS+ HIPEC	Survival for CRS alone	p Value
[162]	2009		26	14	12	58% (5 yrs OS)	17 (5 yrs OS)	0.011
[163]	2011		48	24	24	50% (3 yrs OS)	18% (3 yrs OS)	<0.01
[164]	2012	PS	67	30	37	68% (5 yrs OS)	42% (5 yrs OS)	0.017
[167]	2014	PS	111	27	81	79 M (median OS)	45 M (median OS)	0.016
[123]	2014	PS	54	32	22	45 (3 yrs DFS)	23 (3 yrs DFS)	0.078
[165]	2014	PS	42	23	19	75.6% (4 yr OS)	19.4% (4 yr OS)	0.013
[166]	2016	PS	79	29	50	59.3 M (median OS)	58.3 M (median OS)	0.95

PS platinum sensitive, *DFS* disease-free survival, *OS* overall survival, *M* months, *yrs* years

vival benefit of secondary CRS and HIPEC over systemic chemotherapy alone in patients with platinum-sensitive recurrence [167]. Most of these studies have a small number of patients.

Thus, CRS and HIPEC appear to be a beneficial option for patients with recurrent ovarian cancer where currently there is no standard therapy. Though there are case-control studies demonstrating its benefit over CRS alone, the numbers in these studies are small, and further evaluation is needed in randomized controlled trials. Selecting patients is the key—patients with a limited PCI derive the maximum benefit from this procedure [152]. Other important variables are the completeness of cytoreduction and time to recurrence.

11.9 Clinical Trials Evaluating the Role of HIPEC in Recurrent Ovarian Cancer

Four clinical trials are underway to evaluate the role of HIPEC in recurrent ovarian cancer (Table 11.9). The HORSE trial (NCT01539785)—CRS with or without HIPEC in Ovarian cancer recurrence—is underway in Italy and is expected to complete accrual in 2018. Patients with platinum-sensitive ovarian cancer (PFI > 6 months) are randomized to secondary CRS with or without HIPEC followed by systemic chemotherapy in both arms. The primary end point is progression-free survival, and the secondary end points are post-recurrence overall survival, quality of life, morbidity and mortality and pattern of recurrence. Patients will be stratified according to PCI and PFI. HIPEC is expected to result in a >6 months benefit in the PFI. A similar trial CHIPOR (NCT01376752) is underway in Europe. At the first recurrence (PFI > 6 months), all patient receive three cycles of second-line chemotherapy followed by CRS with or without HIPEC. HIPEC is performed by the open or closed method using 75 mg/m^2 of cisplatin for 60 min. The primary end point is overall survival (HIPEC should provide a 12-month benefit in overall survival), and the secondary objectives are improvement in DFS post-recurrence, morbidity and mortality, quality of life and cost-effectiveness. In addition, the pathological response to chemotherapy will be assessed, and a pharmacokinetic study comparing the open and closed methods will be performed. A similar phase 2 multi-institutional trial is being carried out in the United States using HIPEC with carboplatin for 90 min. The primary end point is progression-free survival. The fourth trial is being carried out at the Loma Linda University in the United States (NCT02672098). This is a phase 1 prospective study with the primary objective of comparing the efficacy and safety of CRS and HIPEC in treatment of recurrent ovarian, primary peritoneal or fallopian tube cancers. All patients with residual disease ≤2.5 mm after CRS will receive HIPEC for 90 min with carboplatin (800 mg/m^2) using the closed abdomen technique. The primary objective is progression-free survival. Historical controls will be used for comparison.

Table 11.9 Ongoing clinical trials evaluating the role of HIPEC in recurrent ovarian, fallopian tube and primary peritoneal cancer

ClinicalTrials.gov ID	Phase	Type of recurrence	Primary Institution/Group	HIPEC drugs	Control arm	Experimental arm
NCT01539785 (HORSE/ MITO 18)	3	PS	Catholic University of the Sacred Heart, Italy	Cisplatin	CRS+ SC	CRS+ HIPEC+ SC
NCT01376752 (CHIPOR)	3	PS	UNICANCER Europe	Cisplatin	SC+CRS	SC+CRS+HIPEC
NCT02672098	1	PS	Loma Linda University Cancer Center, US	Carboplatin		CRS+ HIPEC+ SC
NCT01767675	2	PS	Memorial Sloan Kettering Cancer Centre + others, US	Carboplatin	CRS+ SC	CRS+ HIPEC+ SC

PS platinum sensitive, *SC* systemic chemotherapy

Most of these trials are lagging behind in recruiting the expected number of patients over a given time period. The probable reasons for this as mentioned by the investigators are patients wanting treatment with HIPEC and to not undergo randomization and physician preference for newer systemic therapies instead of HIPEC. None of these trials evaluate the role of CRS and HIPEC in platinum-resistant patients.

These trials will help in clarifying the role of HIPEC in recurrent ovarian cancer. The drug regimens used have been validated in phase 1–2 trials [109, 110, 168]. However, given the multitude of regimens in use in clinical practice and in absence of a head to head comparison, future evaluation will continue to determine the best drugs and protocols.

Preclinical studies provide a strong basis for applying this therapy in clinical practice [169]. HIPEC in addition to secondary CRS has shown promising results in the data available so far. The challenge is to optimize HIPEC methodology and drug regimens and integrate CRS and HIPEC with systemic therapies to provide a meaningful benefit of this treatment to patients—in terms of survival, cost-effectiveness and quality of life.

11.10 Morbidity and Mortality

Reported mortality rates of secondary CRS and HIPEC range from 0 to 4.2%. Large series have reported a major morbidity (grade 3–4 complications) in 30–34.8% and a reoperation rate of 8% [9, 152, 157]. The meta-analysis by Huo et al. reported a pooled median 30-day post-HIPEC mortality rate in 1.8% (range, 0–13.6%) and major (grade 3–4) morbidities in 26.2% (1.8–55.6%) of the patients. The pooled rate of minor (grade 1–2) morbidities was 27.5% (16–60.2%) [161]. These reports are similar to the morbidity and mortality rates reported in patients undergoing CRS alone for advanced ovarian cancer [18, 170]. Major complications include anastomotic leakage, bowel perforation, intraperitoneal haemorrhage, acute renal failure and wound dehiscence. Complication specific to the administration of chemotherapy is neutropenia which is caused by systemic absorption of the drug. Over the years there has been a

decline in the morbidity and mortality from this procedure which is due to the increase in experience of high volume centres [171]. In these expert centres, the reduction in mortality is not just due to lower complication rates but also due to their ability to rescue patients with complications [172]. Morbidity and mortality should no longer preclude the use of this treatment where it is indicated.

11.11 Management of Subsequent Recurrences

Recurrent ovarian cancer that has been rendered disease-free after second-line therapy will recur in almost all cases. Ovarian cancer can be considered a chronic disease with majority of the patients developing multiple recurrences that can be induced into a remission with surgery and or chemotherapy [173]. The second, third and subsequent recurrences have been treated with a combination of CRS with or without HIPEC and systemic chemotherapy. In one of the first reports on tertiary CRS, Leitao et al. reported a median disease-specific survival (DSS) of 34.4 months (range 20.4–46.4 months) in 26 patients. The outcome was better in patients who had optimal cytoreduction (residual disease <0.5 cm) and a long disease-free interval >12 months (median DSS-60 months). Patients with platinum-resistant disease also experience a prolonged survival after optimal CRS [173]. In another series of 77 patients, the same authors reported a median DSS of 47.7 months [174]. Residual disease after surgery remained the only independent prognostic factor. The survival in both these series was similar to that reported for secondary CRS and was superior to that reported with chemotherapy alone [173, 174]. Similar results have been reported by other investigators [175, 176]. In another series of 159 patients, the platinum-free interval after second-line therapy, presence of mesenteric lymph node metastases at secondary CRS and tertiary CRS (as opposed to systemic chemotherapy) were predictors of survival [177]. However, the strongest predictor of survival was complete tumour removal, and patients with residual disease had a survival similar to those receiving chemotherapy alone. Patients with

ascites and disease and recurrence outside the pelvis have a poor outcome [177, 178].

HIPEC has been used along with tertiary and subsequent cytoreductive procedures. Most of these studies have a mixture of patients with first, second and subsequent relapses, and its role in third- and fourth-line therapy has not been evaluated separately [112, 146, 152].

Cytoreductive surgery with or without HIPEC can provide a survival benefit in selected patients with recurrence after second-line therapy. There are no randomized trials comparing surgical treatment with chemotherapy.

Conclusion

Recurrent ovarian cancer is a chronic disease. Secondary/salvage cytoreductive surgery can be considered the standard of care for first recurrence in platinum-sensitive disease though the results of randomized controlled trials are awaited. Early detection and treatment of recurrence has a survival benefit. HIPEC in addition to CRS and systemic chemotherapy has shown promising results in retrospective and case-control studies in both platinum-sensitive and platinum-resistant disease and has acceptable rates of morbidity and mortality. The results of randomized controlled trials are awaited which will clarify its role in this situation. The patient selection for CRS and HIPEC, drugs and protocols need standardization. An optimization of clinical strategies is needed to provide the maximal benefit of CRS and HIPEC to patients—in terms of survival, cost-effectiveness and quality of life. Such treatment requires multidisciplinary management and should be carried out at expert centres.

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