Indian J Surg Oncol (June 2016) 7(2):188–197
DOI 10.1007/s13193-016-0501-9

REVIEW ARTICLE

# The role of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Ovarian Cancer: A Review

**Aditi Bhatt**[1] · **Olivier Glehen**[2,3]

Received: 7 January 2016 / Accepted: 28 January 2016 / Published online: 16 February 2016


**Abstract** Ovarian cancer is one of the leading causes of cancer related deaths in women worldwide. It is usually diagnosed in an advanced stage (Stages III and IV) when peritoneal cancer spread has already occurred. The standard treatment comprises of surgery to remove all macroscopic disease followed by systemic chemotherapy. Despite all efforts, it recurs in over 75 % of the cases, most of these recurrences being confined to the peritoneal cavity. Recurrent ovarian cancer has a poor long term outcome and is generally treated with multiple lines of systemic chemotherapy and targeted therapy. The propensity of ovarian cancer to remain confined to the peritoneal cavity warrants an aggressive locoregional approach. The combined treatment comprising of cytoreductive surgery (CRS) that removes all macroscopic disease and HIPEC (Hyperthermic Intraperitoneal Chemotherapy) has been effective in providing long term survival in selected patients with peritoneal metastases of gastrointestinal origin. Intraperitoneal chemotherapy used as adjuvant therapy has shown a survival benefit in ovarian cancer. This has prompted the use of CRS and HIPEC in the management of ovarian cancer as a part of first line therapy and second line therapy for recurrent disease. This article reviews the current literature and evidence for the use of HIPEC in ovarian cancer.

**Keywords** Ovarian cancer · Cytoreductive surgery · HIPEC · Recurrent ovarian cancer

## Introduction

Worldwide, ovarian cancer accounts for almost 200,000 cancer cases in women and is a leading cause of cancer related death, with over 100,000 deaths due to disease each year. [1] Majority of the patients are diagnosed in stages III and IV. In FIGO stage III and IV, the peritoneum is involved in at least 75 % of the patients. [2] The standard treatment of advanced ovarian cancer is cytoreductive surgery with the goal of removal of all macroscopic disease and systemic chemotherapy comprising of a platinum compound and a taxol. [3] With this treatment there is a complete remission in 60–80 % of the cases with a median survival of 35–38 months. Though there is a high initial response, most patients recur and majority of the recurrences are in the peritoneum. Even after recurrence, the disease remains confined to the peritoneal cavity for a long time making it an ideal target for loco regional therapy. [4] Thus an aggressive loco regional strategy is warranted in the management of both advanced and recurrent ovarian cancer.

## Rational for Complete Cytoreductive Surgery (CRS)

### For Stage III and IV Ovarian Cancer

Cytoreductive surgery (CRS), which comprises of removal of all macroscopic disease, is the current standard of care for surgery for ovarian cancer. The earliest evidence to support the benefit of cytoreductive surgery for ovarian cancer came from the retrospective review of 102 patients by Griffiths et al. in which they showed that the survival time was inversely

✉ Olivier Glehen
olivier.glehen@chu-lyon.fr

[1] Department of Surgical Oncology, Fortis Hospital, Bangalore, India

[2] Hospices Civils de Lyon, Department of Surgical Oncology, Centre Hospitalier Lyon-Sud, 69495 Pierre-Bénite, Cedex, France

[3] Université Lyon 1, EMR 3738, 69600 Oullins, France

proportional to residual mass size under 1.6 cm, and surgery improved survival relative to reduction in mass size below this limit. [5] In another study by Hoskins et al., of a subgroup of 294 patients from a GOG study, all of whom had residual disease >1 cm, patient with residual disease <2 cm survived longer than those with larger residual disease. Among those with larger residual disease, size does not affect prognosis appreciably. [6] This study forms the basis of the GOG recommendation of optimal debulking which as residual implants <1 cm. The same authors retrospectively reviewed 394 patients from a GOG study all of whom had residual disease <1 cm and concluded that apart from the size of residual disease, the other factors influencing survival are extent of disease, age, tumor grade and the number of residual lesions. [7] The Gynecologic Oncology Group (GOG) has defined optimal debulking as residual implants less than 1 cm. [8] However, Chi et al. pointed out, such measurements are subjectively determined at the completion of surgery and due to tissue induration or inadequate exploration, assessments of residual tumor size are often not entirely accurate. [9] A meta-analysis by Bristow et al. of data from 53 studies including 6885 patients with stage III-IV epithelial ovarian cancer who underwent CRS followed by cisplatin or carboplatin based chemotherapy showed that the percent maximal CRS was an independent prognostic variable for survival ($P < 0.001$). When patients with no residual tumor were compared to those with any size of residual tumor, there was a difference in median survival of 46.9 months between the 2 groups for stage IIIC and 30 months for stage IV favoring no residual disease. Similarly, when patients with residual tumor size of 1–10 mm were compared with those having residual disease >10 mm there was a difference in median survival in favor of the first group of 4.9 months for stage 3C and 2.3 months for stage 4. [10] This provides sufficient evidence to conclude that the goal of CRS for ovarian cancer should be to achieve complete tumor removal with no visible or palpable disease anywhere in the abdomen. When required, extensive upper abdominal surgery including diaphragm resection and splenectomy should be employed to achieve complete tumor removal. [11, 12] Though spread to these regions is considered indicative of aggressive tumor biology, complete cytoreduction in this area has shown to have a survival benefit as well. [7, 13, 14].

### For Recurrent Ovarian Cancer

Recurrent ovarian cancer is described as platinum sensitive if it recurs after 6 months of completion of initial therapy and platinum resistant if it recurs within 6 months. [15] The role of CRS for recurrent ovarian cancer has been evaluated by several studies. A retrospective review by Munkarah et al. showed that patients left with no gross residual disease after CRS for recurrent ovarian cancer had a survival of 44–60 months as compared to 35 months in those receiving chemotherapy alone. However the authors concluded that it was not clear whether surgery added to the benefit produced by chemotherapy alone in this group of patients [16]. Bristow et al. carried out a meta-analysis including 2019 patients to determine the relative effect of multiple prognostic variables on overall post-recurrence survival time among cohorts of patients with recurrent ovarian cancer undergoing CRS. The only statistically significant clinical variable independently associated with post-recurrence survival time was the proportion of patients undergoing complete CRS ($p = 0.019$). 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. [17].

Patient selection becomes important in CRS for recurrence since recurrent ovarian cancer is a very heterogeneous disease. In general better outcome is expected in patients with a limited disease extent or more localized relapse, a long disease-free interval after completion of primary therapy (i.e., more than 12 months), when the patient is in good general health, and complete resection or minimal residual disease is possible (Completeness of cytoreduction score of CC-0/CC-1). In contrast, women with symptomatic ascites, carcinomatosis, early relapse (i.e., less than 6 months), and poor general health are least likely to benefit. [18–20].

The retrospective AGO-DESKTOP study retrospectively analyzed 267 patients who had undergone CRS for recurrent ovarian cancer and found completeness of cytoreduction as the only factor leading to prolonged survival. A combination of PS, early FIGO stage initially or no residual tumor after first surgery, and absence of ascites could predict complete resection in 79 % of patients. [21] The DESKTOP 2 study prospectively analyzed the predictive value of 3 of these criteria (complete resection at first surgery, good performance status, and absence of ascites and found that when all 3 are met complete cytoreduction can be achieved in 79 % of the patients with a morbidity of 11 %. [22] These criteria exclude a subgroup of patients who never had surgery by a gynecologic oncologist/surgical oncologist and hence have had an incomplete CRS. These studies also do not evaluate patients in terms of extent of carcinomatosis as determined by the Peritoneal Cancer Index (PCI) which is an important prognostic factor (Bakrin et al. EJSO). Though there is sufficient evidence to support the use of cytoreductive surgery for recurrent ovarian cancer, the selection criteria still need to be defined.

## Rational for intraperitoneal chemotherapy for Ovarian Cancer

Since ovarian cancer tends to remain confined to the peritoneal cavity, there is a strong rationale for using intraperitoneal

chemotherapy. Intraperitoneal delivery of chemotherapy allows exposure of the poorly vascularized tumor tissue to high concentrations of cytotoxic agents. The blood-peritoneal barrier limits passage of these high doses into the plasma and reduces the risk of systemic toxicity [23]. Local chemotherapy is unable to penetrate deeply into tissues so it is only likely to be suitable for patients who have undergone optimal CRS with minimal residual disease. This form of intraperitoneal chemotherapy is delivered after surgery as multiple cycles through a port connected to a catheter placed intraperitoneally. There have been three large phase III trials comparing intraperitoneal (IP) chemotherapy with IV chemotherapy. The first study was carried out in the pre-taxane era and is of questionable significance now. [24] In the second study there was a high morbidity in the experimental arm and there was only a marginal benefit in the overall survival. [25] A third trial, GOG 172, randomized 415 patients with residual disease ≤1 cm to receive IV paclitaxel and cisplatin or IV paclitaxel followed by IP cisplatin (day 1) and paclitaxel (day 8). A significant improvement in OS was demonstrated: 65.6 months in the IP arm compared with 49.7 months in the IV arm ($P = 0.03$). This was despite only 42 % of patients completing six cycles of IP chemotherapy. Grade ¾ toxicity was significantly greater and quality of life scores significantly worse in the IP arm. [26] Elit et al. published a meta-analysis of 7 randomized controlled trials for adjuvant intraperitoneal chemotherapy. A pooled analysis from 6 of the 7 studies confirmed the survival benefit of IP chemotherapy compared with IV chemotherapy alone (Relative risk, 0.88; 95 % confidence interval, 0.81–0.95) Adverse events and catheter related problems were more common in the IP chemotherapy group and often led to discontinuation of therapy. This study concluded that where the institutional facilities are available, cisplatin based intraperitoneal chemotherapy should be offered to patient who had complete CRS. [27] However, there are several problems with intraperitoneal chemotherapy like non-optimal systemic regimens, toxicity leading to discontinuation of therapy and the complexity of the regimens.

## Rationale for Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

The survival benefit shown by the use of intraperitoneal chemotherapy in ovarian cancer has prompted the use of HIPEC for the same. HIPEC has the added advantage of using heat which has several theoretical benefits. Heat has a direct cytotoxic effect. It potentiates the action of certain chemotherapeautic agents (mitomycin C, cisplatin, oxaliplatin) and increases their penetration into tumor tissue. Hyperthermia also reduces the mechanisms of cellular resistance to cisplatin. [28–30] It has been demonstrated that heat increases cisplatin accumulation in platinum resistant cell lines. In both platinum sensitive and platinum resistant cell lines both, it sensitizes the cells for cisplatin by mechanisms like increase accumulation in the cells, increased cisplatin and DNA adduct formation and decreased removal of these adducts from the cells. This effect is seen at a depth of 3-5 mm.

Giving intraperitoneal chemotherapy immediately after tumor removal also has the benefit of reducing tumor cell entrapment that is common after surgery. Further evidence to support HIPEC for ovarian cancer comes from the benefit shown in the treatment of gastrointestinal peritoneal carcinomatosis. Cytoreductive surgery and HIPEC is now the standard of care of pseudomyxoma peritonei and peritoneal mesothelioma. [31, 32] It is considered the standard of care for colorectal peritoneal metastases with a limited peritoneal spread. [33, 34] It is also shown benefit for gastric cancer with limited peritoneal spread and has been the only modality that has the potential to prolong survival in this sub group of patients with a very poor prognosis otherwise. [35, 36].

## HIPEC at various time points in the history of ovarian cancer

HIPEC can be used at various time points in the history of ovarian cancer as summarized by Mulier et al. [37] HIPEC can be used at the time of first line therapy i.e. at the time of primary CRS (upfront CRS and HIPEC), or at the time of interval CRS which is performed after neoadjuvant chemotherapy (Interval CRS and HIPEC) or as a consolidation therapy following completion of first line therapy along with second look surgery (Consolidation CRS and HIPEC). HIPEC can be used along with CRS performed as second line therapy, in patients who have had suboptimal surgery followed by chemotherapy and therefore have residual disease (secondary CRS and HIPEC) or in patients who have recurred after complete response to first line therapy (salvage CRS and HIPEC). [37] A recent meta-analysis which pooled 9 comparative studies and 28 examining CRS + HIPEC for primary and/or recurrent ovarian cancer showed that the addition of HIPEC to CRS and systemic chemotherapy improves survival for both primary and recurrent ovarian cancer. [38].

## HIPEC as First line therapy for Ovarian Cancer

There are many studies evaluating the role of HIPEC in first line therapy for ovarian cancer. Most of these studies are single institution studies with a limited number of patients. [39–46] and a few are multi institutional studies [47–49]. Most of the studies report results of HIPEC for first line and

second line therapy together. The details of the studies are provided in Table 1.

There is a lot of heterogeneity in the drugs, regimens and HIPEC methodology and patient selection thus making comparison and pooling of results extremely difficult.

The median disease free survival reported in these studies ranged from 11.8 to 41.2 months and the median overall survival ranged from 30.0 to 77.8 months. The 5 year overall survival ranged from 15 to 63 %. The most significant factors affecting outcome were the completeness of cytoreduction and the extent of disease evaluated by PCI (Peritoneal Carcinomatosis Index) [42, 43, 48, 49].

In comparison studies reporting the outcomes for frontline therapy for ovarian cancer that did not include HIPEC have reported a median disease free survival ranging from 12 to 33.2 months, median overall survival ranging from 26 to 58.2 months and 5 year overall survival ranging from 19.5 to 49 %. [13, 14, 25, 26, 51–57]. Thus, most of the results obtained with the addition of HIPEC to standard frontline therapy seem to be similar or inferior to the results obtained without the use of HIPEC. Only a few studies have reported a survival that is superior to that obtained without the use of HIPEC [43, 46], the patient numbers in these being small. Notably, one of the worst outcomes was reported by the French multicentric retrospective study [49] comprising of 92 patients treated with HIPEC in addition to standard frontline therapy. The authors mentioned that most of the patients in this series have stage IV or advanced ovarian cancer that cannot be completed resected initially, that are referred to tertiary centers and cannot be compared to patients whose outcomes are reported in other series.

Based on the above data it can be said that there is no substantial evidence to recommend HIPEC as part of first line therapy outside the setting of a clinical trial. Randomized controlled trials are underway to evaluate the role of HIPEC as a part of first line therapy for advanced epithelial ovarian cancer. A phase III randomized trial in the interval setting by the Netherlands Cancer Institute (OVHIPEC trial; Clinical Trials.gov identifier NCT00426257) has finished accrual in 2013. In this trial, patients not eligible for complete cytoreduction upfront are given 3 cycles of chemotherapy and then taken up for surgery. Patients with complete cytoreduction are then randomized to receive HIPEC or no HIPEC. A similar multicenter phase III randomized trial in the interval setting has just started in Italy (CHORINE: Cytoreduction and HIPEC in the treatment of OvaRIaN cancEr) [58].

## HIPEC as Second Line Therapy

CRS and HIPEC can be used as second line therapy after initial complete response, i.e. salvage CRS and HIPEC or in patients after incomplete CRS and chemotherapy leading to partial response or stable disease, secondary CRS and HIPEC. There is stronger evidence to support CRS and HIPEC as second line therapy as compared to first line therapy. Studies reporting the results of second line therapy are listed in Table 2. These studies have reported a median disease free survival ranging from 10 months to 26.2 months, median overall survival ranging from 24 to 45.7 months and a 5 year overall survival ranging from 15 % to 63 %. The largest series is the French retrospective study comprising of 474 patients. [49] The median overall survival was 45.7 months. Patients with platinum sensitive disease with a CCR score of CC-0 had a median OS of 47.2 months compared to that of 51.6 months for patients with platinum resistant disease. This difference was not statistically significant. This study showed that when treated with CRS and HIPEC patients with platinum resistant disease could also have a survival similar to those with platinum sensitive disease. A PCI of >8 was found to be a significant factor affecting both disease free and overall survival.

There are 5 case control studies that have compared CRS and HIPEC with CRS alone [67–71] and all but one have shown a statistically significant benefit of CRS and HIPEC over CRS alone. These studies are listed in Table 3. Thus CRS and HIPEC appears to be a beneficial option for patients with recurrent ovarian cancer where currently there is no standard therapy and though surgery has shown benefit over chemotherapy alone, most patients continue to be treated with multiple lines of chemotherapy. Selecting patients is the key, and as suggested by the French study, patients with a limited PCI derive the maximum benefit from this procedure. [49] Other important variable are the completeness of cytoreduction and time to recurrence.

Currently, trials are underway to further define the role of HIPEC in this setting. The CHIPOR trial is currently underway in France (NCT01376752) in which patients with recurrent ovarian cancer receive six cycles of chemotherapy followed by cytoreductive surgery if complete cytoreduction is deemed feasible. Patient who have had complete cytoreduction are then randomized to receive HIPEC or no HIPEC. Another trial for secondary CRS and HIPEC called the OVIHIPEC trial (NCT00426257) is currently underway in the Netherlands.

## Morbidity and Mortality of CRS and HIPEC in Ovarian Cancer

The greatest criticism of HIPEC has been the morbidity and mortality of the procedure. HIPEC has a well demonstrated learning curve. [72] Over the years, the morbidity and mortality of this procedure has declined and is comparable to that of CRS alone. Table 4 lists that morbidity and mortality rates reported in various studies with HIPEC for ovarian cancer. Reported morbidity rates range from 0 % to

**Table 1** HIPEC as part of first line therapy for treatment of advanced ovarian cancer

| Ref no | Type of study | Year of Publication | No of Pts | Indication | HIPEC | Open/closed | Drug/s | Median DFS (months) | Median OS (months) | 3 Yr OS | 5 yr. OS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| [39] | SI Prospective | 2004 | 8 | Primary | + | Open | Cisplatin + Mitomycin | | 33 ± 6 | | 15 % |
| [40] | SI Prospective | 2005 | 10 | Primary Interval 2nd Look | + | Open | Cisplatin + Mitomycin + Etoposide | 41.2 | 70.2 | | |
| [41] | SI Prospective | 2006 | 19 | Primary | + | | Paclitaxel | | | | 63 % |
| [42] | SI Prospective | 2009 | 31 | Primary | + | | Doxorubicin | 26.2 | 34.1 | | |
| [43] | Multi-institutional, prospective | 2010 | 31 | Second look | + | Open | Oxaliplatin | | | 67 % (2 yrs) | |
| [44] | SI Prospective | 2010 | 45 | Primary | + | Closed | Cisplatin + Mitomycin | | | | 55 % (70 % for CC-0) |
| [50] | Case Control study | 2005 | 29 + 19 | Second look | + | Open | Cisplatin | | 64.4 | | |
| [47] | Prospective, Multi-institutional registry | 2010 | 57 | Primary Interval Second Look | + | Open/Closed | Platinum/Mitomycin/ Combination | | 30.0 | | |
| [48] | Multi-institutional Phase 2 study | 2011 | 26 | Primary | + | Closed | Cisplatin + Mitomycin | 30 | | | 60.7 % |
| [45] | Single Institution Retrospective study | | 51 | Primary | + | Closed | Carboplatin or Mitomycin | | 28.5 | | 28 ± 7 % |
| [46] | Single Institution Retrospective | 2013 | 15 | Primary | + | | | 21.1 | 77.8 | | 72 % |
| [49] | Multi- institutional Retrospective | 2013 | 92 | Primary | + | Open/Closed | Cisplatin<br>Oxaliplatin<br>Mitomycin<br>Doxorubicin<br>Cisplatin + Doxorubicin<br>Cisplatin + Mitomycin | 11.8 | 35.4 | 47 % | 17 % |

Abbreviations: SI: Single Institution; DFS: Disease Free Survival; OS: Overall Survival

**Table 2** CRS and HIPEC as second line therapy for ovarian cancer

| Ref no | Type of Study | N | Year of Publication | HIPEC | Method | Drug/s | Median PCI | CC-0/1 | Median DFS (months) | Median OS (months) | 3 Year OS | 5 Year OS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [58] | Pilot | 5 | 2000 | + | | Cisplatin | | | 3 | 16 | | |
| [59] | SI Prospective | 30 | 2004 | + | | Cisplatin | | 77 % | 17.1 [CC-0: 24.4] | 28.1 [CC-0:37.8] | | |
| [39] | SI Prospective | 11 | 2004 | + | | Cisplatin/Mitoxantrone | | 50 % | | 30 ± 6 | | 15 % |
| [41] | SI Prospective | 14 | 2006 | + | | Paclitaxel | | | | | | 63 % |
| [60] | SI Prospective | 81 | 2007 | + | Closed | Cisplatin | | 55.5 % | 19.2 [CC-0: 26.9] | 28.4 [CC-0: 54.9] | | |
| [61] | SI Prospective | 18 | 2008 | + | Closed | Cisplatin | 14.9 | 87.3 | | 24 | | 16.7 % |
| [42] | SI Prospective | 25 | 2009 | + | | Doxorubicin | 13.4 | 92.8 % | 26.2 | 40 | | |
| [62] | SI Prospective | 10 | 2010 | + | | Oxaliplatin | 6 | 100 % | 10 | | 83 % | |
| [44] | SI Prospective | 8 | 2010 | + | Closed | Cisplatin and Mitomycin | | 70 % | | | | 55 % |
| [47] | Multi institutional Prospective | 83 | 2010 | + | Open/ Closed | Platinum/Mitomycin/ Combination | | | | 30.43 | | 25.4 % |
| [63] | SI Prospective | 31 | 2011 | + | | | | 65 % | 13.3 | | | |
| [64] | Pilot | 12 | 2011 | + | | Oxaliplatin | | 100 % | 14.3 | | | |
| [65] | SI Prospective | 42 | 2012 | + | | Cisplatin Oxaliplatin | | 77 % | 13 | 37 | | |
| [49] | Multi-institutional Retrospective | 474 | 2013 | + | Open/ Closed | Cisplatin Oxaliplatin | 10.6 | 92.1 % | | 45.7 | 59 % | 37 % |
| | | | | | | Mitomycin | | | | | | |
| | | | | | | Doxorubicin | | | | | | |
| | | | | | | Cisplatin + Doxorubicin | | | | | | |
| | | | | | | Cisplatin + Mitomycin | | | | | | |
| [66] | SI Prospective | 54 | 2015 | + | | Cisplatin + Paclitaxel | 10 | 100 % | 12.4 | 32.9 | | |

Abbreviations: *SI* Single Institution, *DFS* Disease Free Survival, *OS* Overall Survival

**Table 3** Case control studies comparing CRS and HIPEC with CRS alone as 2nd line therapy

| Ref No | Year of Publication | N | CRS+ HIPEC | CRS | Survival for CRS+ HIPEC | Survival for CRS alone | *p* Value |
|---|---|---|---|---|---|---|---|
| [67] | 2009 | 26 | 14 | 12 | 58 % (5 yrs. OS) | 17 (5 yrs. OS) | 0.011 |
| [68] | 2011 | 48 | 24 | 24 | 50 % (3 yrs. OS) | 18 % (3 yrs. OS) | <0.01 |
| [69] | 2012 | 67 | 30 | 37 | 68 % (5 yrs. OS) | 42 % (5 yrs. OS) | 0.017 |
| [70] | 2014 | 111 | 27 | 81 | 79 M (Median OS) | 45 M (Median OS) | 0.016 |
| [71] | 2015 | 54 | 32 | 22 | 23 (3 yrs. DFS) | 45 (3 yrs. DFS) | 0.078 |

Abbreviations: *SI* Single Institution, *DFS* Disease Free Survival, *OS* Overall Survival, *M* Months; *yrs*. years

31.3 % (Grade 3 and 4 morbidity according to the Clavien-Dindo classification) and mortality rates from 0 to 4.2 % which are similar to those reported by Bristow et al. in their meta-analysis of patients undergoing CRS alone [17].

Major complications include anastomotic leakage, bowel perforation, intraperitoneal hemorrhage and wound dehiscence. Complications specific to the administration of chemotherapy are neutropenia which is caused by systemic absorption of the drug. Grade 3–4 toxicity has been reported in 8 to 31 % of the patients. In the CHIPOVAC study which used intraperitoneal oxaliplatin, the authors reported a high morbidity of 29 % due to which the study had to be closed prematurely. [43] Most of complications were hemorrhages that may be due to the drug used. However, other studies using oxaliplatin have not found a similar morbidity. [64, 65] In the French retrospective study, 8 % of the patients had acute renal insufficiency out of which 2 % developed chronic renal disease and 1 % required long term dialysis. The risk factors for major morbidity on multivariate analysis were PCI, CCR score, duration of surgery and the number of anastomoses [49, 75, 76].

Morris et al. reviewed 24 studies for the morbidity and mortality rates (including patients undergoing CRS and HIPEC for non-ovarian primary tumors) and found a mean major or grade III/IV morbidity of 28.8 % (range 0 % to 52 %); in high-volume centers it ranged from 12 % to 52 %. Re-operation rates following treatment that occurred in the perioperative period ranged from 0 % to 23 %. Overall, mean mortality rate was 2.9 % (range 0 % to 17 %); in high-volume centers it ranged from 0.9 % to 5.8 %. The authors concluded that morbidity and mortality rates following CRS and HIPEC are not different from those caused by major gastrointestinal

**Table 4** Morbidity and mortality of CRS and HIPEC for ovarian cancer

| Ref No | Year of Publication | No of patients | Indication | Drug/s | Morbidity | 30-day Mortality |
|---|---|---|---|---|---|---|
| [59] | 2004 | 30 | Second line | Cisplatin | 16.7 % | 3.3 % |
| [41] | 2006 | 33 | First line Second line | Paclitaxel | 6 % | 0 % |
| [73] | 2006 | 40 | First line Second line | | 0 % | 0 % |
| [60] | 2007 | 81 | Second line | Cisplatin | 13.6 % | |
| [61] | 2008 | 47 | First line Second line | Cisplatin | 21.3 % | 4.2 % |
| [42] | 2009 | 56 | First line Second line | Doxorubicin | 17.8 % | 1.8 % |
| [43] | 2010 | 31 | First line | Oxaliplatin | 29 % | 0 % |
| [44] | 2010 | 53 | First line Second line | Cisplatin + Mitomycin | 23 % | 0 % |
| [47] | 2010 | 141 | First line Second line | Platinum/Mitomycin/Both | | 0.5 % |
| [74] | 2010 | 19 | First line | Paclitaxel | 7 % | 3.5 % |
| [48] | 2011 | 26 | First line | Cisplatin + Doxorubicin | 15.3 % | 3.9 % |
| [64] | 2011 | 31 | First line Second line | Oxaliplatin | 29.03 % | 0 % |
| [65] | 2012 | 42 | Second line | Cisplatin/Oxaliplatin | 21 % | 0 % |
| [49] | 2013 | 566 | First line Second line | Cisplatin<br>Oxaliplatin<br>Mitomycin<br>Doxorubicin<br>Cisplatin + Doxorubicin<br>Cisplatin + Mitomycin | 31.3 % | 0.8 % |

surgeries. [75] The same conclusion was reached in the French study of 1290 patients that included patients with non-gynecologic primaries [76] Thus, it can be concluded that HIPEC does not add to the morbidity and mortality of CRS alone.

## HIPEC methodology and drugs

HIPEC is performed by the open and closed techniques. Till date no study has shown benefit of one technique over the other. The intraperitoneal temperature is maintained between 41 and 43 degrees Celsius. 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. [77] Commonly used drugs are cisplatin, oxaliplatin, mitomycin, doxorubicin, carboplatin and paclitaxel. [41–43, 50, 57, 60, 61] Other drugs like gemcitabine and irinotecan have also been used. [76] The choice of drug depends on its pharmacokinetic properties. The drug should be retained in the peritoneal cavity with limited systemic absorption. [23] 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 cells lines. [78] The ideal dose of cisplatin has being evaluated in the CHIPASTIN trial. This phase I-II escalating dose trial established that the use of 70 mg/m2 of cisplatin for one hour at 42 °C was the most appropriate protocol (Clinical Trials identifier: NCT02217956).

## Conclusions

Thus, there is a strong rationale for using CRS and HIPEC in the treatment of ovarian cancer. This form of aggressive loco regional therapy has the potential to cure patients as shown in patients with peritoneal metastases of gastrointestinal origin. HIPEC do not increase significantly mortality and morbidity of CRS alone. PCI should be used as a tool to select patients and also as a prognostic marker. Currently, there is insufficient evidence to recommend its routine use as part of first line therapy outside the setting of a clinical trial. However, there is sufficient evidence in the form of large retrospective studies, case control studies, and recent meta-analysis demonstrating its benefit as second line therapy, where it can be used in both platinum resistant and platinum sensitive cases. Its role in this setting also needs to be evaluated in randomized controlled trials. Patient selection is very important and such treatment should be offered at experienced centers after meticulous patient selection.

## References


1. Primary Cytoreductive Surgery for Advanced Stage Ovarian Cancer: indications for Radical Resection; Bristow R. Cancerología 2; Suplemento 1 (2007): s31-s36
2. Sehouli J, Senyuva F, Fotopoulou C, Neumann U, Denkert C, Werner L (2009) Gülten O; Intra-abdominal tumor dissemination pattern and surgical outcome in 214 patients with primary ovarian cancer. J Surg Oncol 99(7):424–427
3. Hennessy BT, Coleman RL, Markman M (2009) Ovarian cancer. Lancet 374:1371–1382
4. Bakrin N, Classe JM, Pomel C, Gouy S, Chene G, Glehen O (2014) Hyperthermic intraperitoneal chemotherapy (HIPEC) in ovarian cancer. J Visc Surg 151:347–353
5. Griffiths CT (1975) Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. Natl Cancer Inst Monogr 42: 101–104
6. Hoskins WJ, McGuire WP, Brady MF, Homesley HD, Creasman WT, Berman M, Berek JS (1994) The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. Am J Obstet Gynecol 170:974–979
7. Hoskins WJ, Bundy BN, Thigpen JT, Omura GA (1992) The influence of cytoreductive surgery on recurrence-free interval and survival in small-volume stage III epithelial ovarian cancer: a Gynecologic Oncology Group study. Gynecol Oncol 47:159–166
8. Whitney CW, Spirtos N (2009) Gynecologic oncology group surgical procedures manual. Philadelphia Gynecologic Oncology Group
9. Chi DS, Ramirez PT, Teitcher JB, et al. (2007) Prospective study of the correlation between postoperative computed tomography scan and primary surgeon assessment in patients with advanced ovarian, tubal, and peritoneal carcinoma reported to have undergone primary surgical cytoreduction to residual disease 1 cm or less. J Clin Oncol 25:4946–4951
10. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ (2002) Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 20(5):1248–1259
11. Aletti GD, Dowdy SC, Podratz KC, Cliby WA (2006) Surgical treatment of diaphragm disease correlates with improved survival in optimally debulked advanced stage ovarian cancer. Gynecol Oncol 100:283–287
12. Eisenhauer EL, Abu-Rustum NR, Sonoda Y, et al. (2006) The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients with stages IIIC-IV epithelial ovarian cancer. Gynecol Oncol 103:1083–1090
13. Eisenkop SM, Spirtos NM, Friedman RL, et al. (2003) Relative influences of tumor volume before surgery and the cytoreductive outcome on survival for patients with advanced ovarian cancer: A prospective study. Gynecol Oncol 90:390–396
14. Chi DS, Eisenhauer EL, Zivanovic O, et al. (2009) Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. Gynecol Oncol 114: 26–31
15. Bukowski RM, Ozols RF, Markman M (2007) The management of recurrent ovarian cancer. Semin Oncol 34:S1–15
16. Makara AR, Coleman RL (2004) Critical evaluation of secondary cytoreduction in recurrent ovarian cancer. Gynecol Oncol 95: 273–280
17. Schorge J, McCann C, Del Carmen M (2010) Surgical Debulking of Ovarian Cancer: What Difference Does It Make? Rev Obstet Gynecol 3(3):111–117
18. Bristow RE, Puri I, Chi DS (2009) Cytoreductive surgery for recurrent ovarian cancer: a meta-analysis. Gynecol Oncol 112:265–274

19. Fotiou S, Aliki T, Petros Z, et al. (2009) Secondary cytoreductive surgery in patients presenting with isolated nodal recurrence of epithelial ovarian cancer. Gynecol Oncol 114:178–182
20. Schorge JO, Wingo SN, Bhore R, et al. (2010) Secondary cytoreductive surgery for recurrent platinum-sensitive ovarian cancer. Int J Gynaecol Obstet 108:123–127
21. Harter P, du Bois A, Hahmann M, et al. (2006) Surgery in recurrent ovarian cancer: the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR trial. Ann Surg Oncol 13:1702–1710
22. Harter P, Sehouli J, Reuss A, Hasenburg A, Scambia G, Cibula D, Mahner S, Vergote I, Reinthaller A, Burges A, Hanker L, Pölcher M, Kurzeder C, Canzler U, Petry KU, Obermair A, Petru E, Schmalfeldt B, Lorusso D, du Bois A (2011) Prospective validation study of a predictive score for operability of recurrent ovarian cancer: the Multicenter Intergroup Study DESKTOP II. A project of the AGO Kommission OVAR, AGO Study Group, NOGGO, AGO-Austria, and MITO. Int J Gynecol Cancer 21(2):289–295
23. Cotte E, Colomban O, Guitton J, et al. (2011) Population pharmacokinetics and pharmacodynamics of cisplatinum during hyperthermic intraperitoneal chemotherapy using a closed abdominal procedure. J Clin Pharmacol 51(1):9–18
24. Alberts DS, Liu PY, Hannigan EV, et al. (1996) Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med 335:1950–1955
25. Markman M, Bundy BN, Alberts DS, et al. (2001) Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the gynecologic oncology group, southwestern oncology group, and eastern cooperative oncology group. J Clin Oncol 19:1001–1007
26. Armstrong DK, Bundy B, Wenzel L, et al. (2006) Intraperitoneal cisplatin and paclitaxel in Ovarian cancer. N Engl J Med 354:34–43
27. Elit L, Oliver TK, Covens A, Kwon J, Fung MK, Hirte HW, Oza AM (2007) Intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer: a systematic review with meta- analysis. Cancer 109:692–702
28. Glehen O, Gilly FN (2004) Peritoneal carcinomatosis from digestive tract cancer: new management by cytoreductive surgery and intraperitoneal chemo hyperthermia. Lancet Oncol 5:219–228
29. Hettinga JV, Konings AW, Kampinga HH (1997) Reduction of cellular cisplatin resistance by hyperthermia — a review. Int J Hyperth 13:439–457
30. van de Vaart PJ, van der Vange N, Zoetmulder FA, van Goethem AR, van Tellingen O, ten Bokkel Huinink WW, Beijnen JH, Bartelink H, Begg AC (1998) Intraperitoneal cisplatin with regional hyperthermia in advanced ovarian cancer: pharmacokinetics and cisplatin-DNA adduct formation in patients and ovarian cancer cell lines. Eur J Cancer 34(1):148–154
31. Chua TC, Moran BJ, Sugarbaker PH, et al. (2012) Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Clin Oncol 30: 2449–2456
32. Yan TD, Deraco M, Baratti D, et al. (2009) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. J Clin Oncol 27:6237–6242
33. Elias D, Gilly F, Boutitie F, et al. (2010) Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol 28:63–68
34. Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H (2008) 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol 15:2426–2432
35. Glehen O, Gilly FN, Arvieux C, et al. (2010) Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. Ann Surg Oncol 17(9):2370–2377
36. Glehen O, Passot G, Villeneuve L, et al. (2014) GASTRICHIP: D2resection and hyperthermic intraperitoneal chemotherapy in locally advanced gastric carcinoma: a randomized and multi-center phase III study. BMC Cancer 14:183
37. Mulier S, Claes JP, Dierieck V, Amiel JO, Pahaut JP, Marcelis L, Bastin F (2012) Survival Benefit of Adding Hyperthermic IntraPEritoneal Chemotherapy (HIPEC) at the Different Timepoints of Treatment of Ovarian Cancer: Review of Evidence. Curr Pharm Des 18:3793–3803
38. Huo YR, Richards A, Liauw W, Morris DL (2015) Hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery (CRS) in ovarian cancer: A systematic review and meta-analysis. Eur J Surg Oncol 41(12):1578–1589. doi:10.1016/j.ejso.2015.08.172
39. Piso P, Dahlke MH, Loss M, Schlitt HJ (2004) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in peritoneal carcinomatosis from ovarian cancer. World J Surg Oncol 2:21
40. Yoshida Y, Sasaki H, Kurokawa T, et al. (2005) Efficacy of intraperitoneal continuous hyperthermic chemotherapy as consolidation therapy in patients with advanced epithelial ovarian cancer: a long-term follow-up. Oncol Rep 13(1):121–125
41. Rufián S, Muñoz-Casares FC, Briceño J, et al. (2006) Radical surgery peritonectomy and intraoperative intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis in recurrent or primary ovarian cancer. J Surg Oncol 94:316–324
42. Pavlov MJ, Kovacevic PA, Ceranic MS, Stamenkovic AB, Ivanovic AM, Kecmanovic DM (2009) Cytoreductive surgery and modified heated intraoperative intraperitoneal chemotherapy (HIPEC) for advanced and recurrent ovarian cancer - 12-year single center experience. Eur J Surg Oncol 35(11):1186–1191
43. Pomel C, Ferron G, Lorimier G, et al. (2010) Hyperthermic intraperitoneal chemotherapy using oxaliplatin as consolidation therapy for advanced epithelial ovarian carcinoma. Results of a phase II prospective multicentre trial. CHIPOVAC study. Eur J Surg Oncol 36(6):589–593
44. Roviello F, Pinto E, Corso G, et al. (2010) Safety and potential benefit of hyperthermic intraperitoneal chemotherapy (HIPEC) in peritoneal carcinomatosis from primary or recurrent ovarian cancer. J Surg Oncol 102(6):663–670
45. Parson EN, Lentz S, Russell G, et al. (2011) Outcomes after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal surface dissemination from ovarian neoplasms. Am J Surg 202(4):481–486
46. Gonzalez Bayon L, Steiner MA, Vasquez Jimenez W, et al. (2013) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for the treatment of advanced epithelial ovarian carcinoma: upfront therapy, at first recurrence, or later? Eur J Surg Oncol 39:1109–1115
47. Helm CW, Richard SD, Pan J, et al. (2010) Hyperthermic intraperitoneal chemotherapy in ovarian cancer: first report of the HYPER-O registry. Int J Gynecol Cancer 20(1):61–69
48. Deraco M, Kusamura S, Virzì S, et al. (2011) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy as upfront therapy for advanced epithelial ovarian cancer: multi-institutional phase-II trial. Gynecol Oncol 122(2):215–220
49. Bakrin N, Bereder JM, Decullier E, et al. (2013) Peritoneal carcinomatosis treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for advanced ovarian carcinoma: a French multicentre retrospective cohort study of566 patients. Eur J Surg Oncol 39:1435–1443

50. Gori J, Castaño R, Toziano M, et al. (2005) Intraperitoneal hyperthermic chemotherapy in ovarian cancer. Int J Gynecol Cancer 15: 233–239
51. Vergote I, Tropé CG, Amant F, et al. (2010) Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 363(10):943–953
52. Kumar L, Hariprasad R, Kumar S, *et al*. (2010) Upfront surgery vs neoadjuvant, chemotherapy in advanced epithelial ovarian carcinoma (EOC): a randomized, study. IGCS 13. Prague (A824)
53. Chi DS, Musa F, Dao F, et al. (2011) An analysis of patients with bulky advanced stage ovarian, tubal, and peritoneal carcinoma treated with primary debulking surgery (PDS) during an identical time period as the randomized EORTC-NCIC trial of PDS vs neoadjuvant chemotherapy (NACT). Gynecol Oncol 124(1):10–14
54. Sehouli J, Savvatis K, Braicu EI, Schmidt SC, Lichtenegger W, Fotopoulou C (2010) Primary versus interval debulking surgery in advanced ovarian cancer: results from a systematic single-center analysis. Int J Gynecol Cancer 20(8):1331–1340
55. Morice P, Brehier-Ollive D, Rey A, et al. (2003) Results of interval debulking surgery in advanced stage ovarian cancer: an exposed-nonexposed study. Ann Oncol 14(1):74–77
56. Onda T, Kobayashi H, Nakanishi T, et al. (2009) Feasibility study of neoadjuvant chemotherapy followed by interval debulking surgery for stage III/IV ovarian, tubal, and peritoneal cancers: Japan Clinical Oncology Group Study JCOG0206. Gynecol Oncol 113(1):57–62
57. Lee SJ, Kim BG, Lee JW, Park CS, Lee JH, Bae DS (2006) Preliminary results of neoadjuvant chemotherapy with paclitaxel and cisplatin in patients with advanced epithelial ovarian cancer who are inadequate for optimum primary surgery. J Obstet Gynaecol Res 32(1):99–10
58. van der Vange N, van Goethem AR, Zoetmulder FAN, et al. (2000) Extensive cytoreductive surgery combined with cisplatin under hyperthermic conditions (OVHIPEC) in patients with recurrent ovarian cancer: a feasibility pilot. Eur J Surg Oncol 26:663–668
59. Zanon C, Clara R, Chiappino I, et al. (2004) Cytoreductive surgery and intraperitoneal chemohyperthermia for recurrent peritoneal carcinomatosis from ovarian cancer. World J Surg 28:1040–1045
60. Cotte E, Glehen O, Mohamed F, et al. (2007) Cytoreductive surgery and intraperitoneal chemohyperthermia for chemoresistant and recurrent advanced epithelial ovarian cancer: prospective study of 81 patients. World J Surg 31:1813–1820
61. Di Giorgio A, Naticchioni E, Biacchi D, et al. (2008) Cytoreductive surgery (peritonectomy procedures) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of diffuse peritoneal carcinomatosis from ovarian cancer. Cancer 113(2): 315–325
62. Carrabin N, Mithieux F, Meeus P, et al. (2010) Hyperthermic intraperitoneal chemotherapy with oxaliplatin and without adjuvant chemotherapy in stage IIIC ovarian cancer. Bull Cancer 97(4):E23–E32
63. Königsrainer I, Beckert S, Becker S, et al. (2011) Cytoreductive surgery and HIPEC in peritoneal recurrent ovarian cancer: experience and lessons learned. Langenbeck's Arch Surg 396(7): 1077–1081
64. Frenel JS, Leux C, Pouplin L, et al. (2011) Oxaliplatin-based hyperthermic intraperitoneal chemotherapy in primary or recurrent epithelial ovarian cancer: A pilot study of 31 patients. J Surg Oncol 103(1):10–16
65. Ceelen WP, Van Nieuwenhove Y, Van Belle S, Denys H, Pattyn P (2009) Cytoreduction and hyperthermic intraperitoneal chemoperfusion in women with heavily pretreated recurrent ovarian cancer. Ann Surg Oncol 19(7):2352–2359
66. Coccolini F, Campanati L, Catena F, Ceni V, Ceresoli M, Jimenez Cruz J, Lotti M, Magnone S, Napoli J, Rossetti D, De Iaco P, Frigerio L, Pinna A, Runnebaum I, Ansaloni L (2015) Hyperthermic intraperitoneal chemotherapy with cisplatin and paclitaxel in advanced ovarian cancer: a multicenter prospective observational study. J Gynecol Oncol 1:54–61. doi:10.3802/jgo.2015.26.1.54
67. Munoz-Casares FC, Rufian S, Rubio MJ, et al. (2009) The role of hyper-thermic intraoperative intraperitoneal chemotherapy (HIPEC) in the treatment of peritoneal carcinomatosis in recurrent ovarian cancer. Clin Transl Oncol 11:753–759
68. Spiliotis J, Vaxevanidou A, Sergouniotis F, Lambropoulou E, Datsis A, Christopoulou A (2011) The role of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of recurrent advanced ovarian cancer: a prospective study. J BUON 16:74–79
69. Fagotti A, Costantini B, Petrillo M, et al. (2012) Cytoreductive surgery plus HIPEC in platinum-sensitive recurrent ovarian cancer patients: a case-control study on survival in patients with two-year follow-up. Gynecol Oncol 127:502–505
70. Safra T, Grisaru D, Inbar M, Abu-Abeid S, Dayan D, Matceyevsky D, Weizman A, Klausner JM (2014) Cytoreduction surgery with hyperthermic intraperitoneal chemotherapy in recurrent ovarian cancer improvesprogression-free survival, especially in BRCA-positive patients- a case-control study. J Surg Oncol 110(6):661–665. doi:10.1002/jso.23688
71. Cascales-Campos PA, Gil J, Feliciangeli E, Gil E, González-Gil A, López V, Ruiz-Pardo J, Nieto A, Parrilla JJ (2015) Parrilla The role of hyperthermic intraperitoneal chemotherapy using paclitaxel in platinum-sensitive recurrentepithelial ovarian cancer patients with microscopic residual disease after cytoreduction. Ann Surg Oncol 22(3):987–993. doi:10.1245/s10434-014-4049-z
72. Smeenk RM, Verwaal VJ, Zoetmulder FA (2007) Learning curve of combined modality treatment in peritoneal surface disease. Br J Surg 94(11):1408–1414
73. Raspagliesi F, Kusamura S, Campos Torres JC, et al. (2006) Cytoreduction combined with intraperitoneal hyperthermic perfusion chemotherapy in advanced/recurrent ovarian cancer patients: the experience of National Cancer Institute of Milan. Eur J Surg Oncol 32:671–675
74. Kim JH, Lee JM, Ryu KS, et al. (2010) Consolidation hyperthermic intraperitoneal chemotherapy using paclitaxel in patients with epithelial ovarian cancer. J Surg Oncol 101(2):149–155
75. Chua TC, Yan TD, Saxena A, Morris DL (2009) Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure? A systematic review of morbidity and mortality. Ann Surg 249:900–907
76. Glehen O, Gilly FN, Boutitie F, et al. (2010) Toward curative treatment of peritoneal carcinomatosis from non- ovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. Cancer 116:5608–5618
77. Elias DM, Ouellet JF (2001) Intraperitoneal chemohyperthermia: rationale, technique, indications, and results. Surg Oncol Clin N Am 10:915–933
78. Hettinga JV, Lemstra W, Meijer C, Dam WA, Uges DR, Konings AW, De Vries EG, Kampinga HH (1997) Mechanism of hyperthermic potentiation of cisplatin action in cisplatin-sensitive and -resistant tumor cells. Br J Cancer 75:1735–1743