CURRENT ONCOLOGY
A Canadian Cancer Research Journal

REVIEW ARTICLE

Treatment of peritoneal surface malignancies with hyperthermic intraperitoneal chemotherapy—current perspectives

J. Spiliotis MD PhD,* E. Halkia MD,† and E. de Bree MD PhD‡

ABSTRACT

Peritoneal carcinomatosis (PTC) represents advanced malignant disease and has generally been associated with a grim prognosis. Peritoneal surface malignancy is often the major source of morbidity and mortality; it is of major concern in cancer management. Although PTC is categorized as metastatic disease, it represents a special disease pattern considered to be a locoregional disease limited to the abdominal cavity. The combination of cytoreductive surgery (CRS) and intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) has successfully been used as locoregional treatment for selected patients with PTC from gastric, colorectal, and ovarian cancer; with mesothelioma; and with pseudomyxoma peritonei. In the prophylactic setting, HIPEC can also be used to prevent PTC in high-risk patients, and the first results of the "second-look" approach are promising. Patient selection—in which the risks of perioperative morbidity and mortality, which are analogous to those for any other major gastrointestinal surgery, are assessed—is of utmost importance. Those risks have to be weighed against the anticipated survival benefit, which depends mainly on tumour biology, extent of disease, and probability of achieving complete CRS. The present review discusses the principles of CRS and HIPEC, the most significant recent clinical data, and current perspectives concerning the application of this treatment modality in various malignancies. Ongoing trials and future directions are noted. It appears that the combination of CRS and HIPEC is an indispensable tool in the oncologist's armamentarium.

Key Words Peritoneal carcinomatosis, peritoneal mesothelioma, pseudomyxoma peritonei, cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, HIPEC

Curr Oncol. **2016 June;23(3):e266-e275** **www.current-oncology.com**

INTRODUCTION

Peritoneal carcinomatosis (PTC) represents advanced malignant disease and has generally been associated with a grim prognosis. Peritoneal surface malignancy is often the major source of morbidity and mortality; it is of major concern in cancer management. Although PTC is categorized as metastatic disease, it represents a special disease pattern considered to be locoregional disease limited to the abdominal cavity. Cytoreductive surgery (CRS) and intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) have been used as locoregional treatment for selected patients with PTC from gastric, colorectal, and ovarian cancers; with mesothelioma; and with pseudomyxoma peritonei (PMP)[1,2].

Annual publications about CRS and HIPEC have increased dramatically in number over the last few decades, and many novel data have consequently emerged. The aim of the present review was to use the U.S. Library of Medicine's PubMed database and the ClinicalTrials.gov registry to summarize the most significant recent clinical data and ongoing areas of research into the application of this treatment modality in various malignancies. To begin, however, the rationale and principles of CRS and HIPEC for peritoneal surface malignancies are briefly discussed.

CONTEXT

Conventional treatment of PTC includes (palliative) surgery and systemic chemotherapy. However, surgery leaves behind at least some microscopic disease, and systemic chemotherapy is generally not effective because of poor drug penetration[1]. Although usually considered to be a systemic disease, PTC can be better understood as regional dissemination. Many intra-abdominal malignancies with tumour implants on peritoneal surfaces can remain confined to the peritoneal cavity for a prolonged period of time. As a result, even though PTC is certainly considered

Correspondence to: Eelco de Bree, Department of Surgical Oncology, University Hospital, PO Box 1352, Heraklion 71110 Greece.
E-mail: debree@edu.uoc.gr **DOI:** http://dx.doi.org/10.3747/co.23.2831

a poor prognostic sign, it is not proof of distant metastasis, thus providing a rationale for regional cancer treatment[2].

Rationale for HIPEC

The main advantage of intraperitoneal (IP) chemotherapy is its ability to achieve a significantly higher concentration of the selected agent in the locoregional area, resulting in improved efficacy[3]. Administration of chemotherapy into the peritoneal cavity not only ensures better exposure of tumour tissue to the drug, but also less systemic toxicity, because only a limited portion of the drug is absorbed from the peritoneal cavity into the systemic vascular circulation[3,4]. Furthermore, the vascular drainage from a large portion of the peritoneum occurs through the portal venous system, allowing for early metabolism and inactivation of the drug in the liver[3].

Prerequisites

To be effective, IP chemotherapy has to fulfil certain prerequisites[3]. Because penetration of the intraperitoneally delivered drug into tumour deposits is limited, extensive CRS—leaving no, or very little, macroscopic disease behind—should always precede IP chemotherapy. Because the administered drug has to reach the entire serosal peritoneal surface, an adequate volume of the carrier solution must be maintained throughout the treatment time, and adhesions must be absent.

The choice of the chemotherapeutic drug to be used during HIPEC is very important. The aspects that must be taken into account are described in detail elsewhere[5,6]. In short, the agent should not cause local toxicity and should not require metabolization into its active form (usually in the liver). It should also be directly cytotoxic, have well-established activity against the malignancy being treated, and demonstrate a pharmacokinetic advantage after IP administration, with high locoregional drug exposure and limited systemic toxicity. A synergistic effect with heat is preferred, because increased temperature can enhance the responsiveness of tumour cells to cytotoxic agents[7]. The drug of choice for intravenous (IV) administration is not necessarily the one that is optimal for IP chemotherapy. More favourable pharmacokinetics and thermic enhancement can make a systemically less-effective drug highly advantageous for IP chemotherapy.

The intraoperative application of HIPEC immediately after CRS aims to treat microscopic and minimal macroscopic peritoneal disease before the formation of early postoperative adhesions. When adhesions form, the IP chemotherapy might not reach the tumour cells in some areas of the peritoneal cavity[8].

The abdominal wall can be open or closed during the HIPEC treatment period. A roller pump is used to perfuse the drug solution throughout the peritoneal cavity, usually for 30–90 minutes, at an intra-abdominal temperature of approximately 40°C to 42°C.

Cytoreductive Surgery

As already mentioned, effective complete or optimal CRS, leaving behind no macroscopic disease or tumour nodule of less than a few millimetres, should precede HIPEC. Cytoreductive surgery should not be confused with debulking surgery, which is surgery aimed at reducing gross tumour burden. The ultimate goal of CRS is to remove all macroscopic peritoneal disease. The peritonectomy procedures have been well described by Sugarbaker[9] and can be categorized into right subdiaphragmatic and parietal peritonectomy, left subdiaphragmatic and parietal peritonectomy, greater omentectomy and splenectomy, lesser omentectomy and stripping of the omental bursa, and pelvic peritonectomy with salpingo-oophorectomy in women. Additionally, resection of other involved organs such as the uterus, gallbladder, stomach, distal pancreas, colon, and small bowel are performed. The extended and multi-visceral resections should be performed only if an optimal or complete CRS can be achieved[10]. Morbidity from such surgery is discussed later in this review.

Patient Selection

It is of utmost importance to carefully select patients who could benefit from this major procedure and to avoid the attendant morbidity and mortality in patients who are not expected to benefit.

When evaluating a patient for CRS and HIPEC, the surgeon should take into account tumour biology, the extent of disease, and the patient's age and comorbidities, which could compromise the intraoperative and postoperative courses[11]. The patient should be adequately fit to undergo this major multimodality treatment. Most importantly, preoperative evaluation should assess whether optimal or complete CRS is feasible in the individual patient. Widespread and high-volume peritoneal disease, extensive involvement of small bowel or mesenterium, more than 1 bowel stenosis, large tumour masses in the lesser omentum, extensive disease in the hepatoduodenal ligament, biliary or uretal obstruction because of penetration through the peritoneum (and not because of external compression), and para-aortic lymph node metastases are usually considered to be contraindications because they are suggestive of aggressive biologic behaviour, lower probability of optimal or complete CRS, and poor outcome. A CRS and HIPEC approach also usually seems to be contraindicated when extra-abdominal metastases and liver metastases are present, because the biology of those tumour locations will not be influenced by locoregional treatment. However, because the prognosis for colorectal cancer patients with limited resectable liver metastases after hepatic surgery and current chemotherapeutic regimens is reasonable, some centres will use liver surgery, CRS, HIPEC, and systemic chemotherapy to treat patients with up to 3 peripherally localized and resectable liver metastases and limited PTC. The morbidity and long-term results in such patients are not different from those of colorectal PTC patients without liver metastases (to be discussed shortly)[12–14]. Infiltration of the liver capsule by peritoneal tumour should be differentiated from parenchymal liver metastases.

Radiologic investigations such as computed tomography (CT), magnetic resonance imaging, and position-emission tomography have been used to assess the foregoing criteria, with the aim of improved preoperative patient selection[15]. Although CT was not, in the past, very accurate in depicting peritoneal tumour deposits[16], modern contrast-enhanced multislice CT is regarded as the fundamental imaging

modality, and magnetic resonance imaging, position-emission tomography, laparoscopy, and serum tumour markers can be taken into consideration but are not considered essential[17]. Computed tomography enteroclysis provides information about small-bowel and mesenterium involvement[18].

Most recently, to improve patient selection, various prognostic scoring systems have been introduced to preoperatively evaluate patients for CRS and HIPEC[19–21]. The preoperative parameters used in those scoring systems include histopathology, blood tests (especially serum tumour markers), symptoms, and tumour burden (as evaluated by imaging studies). In colorectal PTC, the COREP score—which consists of one histopathologic variable, hemoglobin, white cell count, and four serum tumour markers and their preoperative changes over time—was able to accurately predict open–close surgery in 87% of subjects, complete CRS in 81%, and survival of less than12 months in 83%[19]. In a multicentre retrospective study[20], colorectal cancer patients with PTC who had no or just mild symptoms, limited PTC, and favourable histology (Peritoneal Surface Disease Severity Score I) had a median overall survival (OS) of 86 months; those with some combination of severe symptoms, extensive PTC, and worse histology, such as signet-ring cells (Peritoneal Surface Disease Severity Score III or IV) had a median OS of only 28 months. Patients in the intermediate category (Peritoneal Surface Disease Severity Score II) had a median OS of 48 months.

Each patient who is a potential candidate for CRS and HIPEC should be discussed in a multidisciplinary team[11]. When considered a good candidate, the patient must be included in detailed discussions about the various parts of the treatment—in particular, discussions about the probabilities of various organ resections, ostomies, postoperative morbidity, quality of life, and risks of recurrence. Moreover, the individual patient's motivation is important because it will influence the entire postoperative course[11].

RECENT CLINICAL DATA CONCERNING CYTOREDUCTIVE SURGERY AND HIPEC

The therapeutic approach of CRS and HIPEC has been used for a number of primary and secondary peritoneal malignancies. Here, some of the most recent clinical data about this treatment for the most common disease indications are discussed.

PMP

Pseudomyxoma peritonei is a rare condition characterized by the presence of widespread mucinous deposits within the peritoneal cavity. It represents one of the most classical indications for CRS and HIPEC. The natural history of PMP is, in most cases, a result of a ruptured appendiceal mucinous tumour.

The clinicopathologic features of PMP greatly influence the disease course. The most benign form is classified as disseminated peritoneal adenomucinosis, and the most malignant type, as peritoneal mucinous carcinomatosis (PMCA). There is also an intermediate hybrid form called $PMCA_I$[22].

Conventional treatment with serial debulking surgery and systemic chemotherapy is associated with a high recurrence rate, greater difficulty in obtaining optimal debulking with each ensuing operation, and finally, a short small bowel that is not compatible with physiologic life. The 5- and 10-year OS rates with this traditional approach were approximately 50% and 20%–30% respectively[23]. When Memorial Sloan Kettering Cancer Center compared aggressive CRS with HIPEC with function-sparing debulking surgery and systemic chemotherapy as applied in the past[24], a remarkable difference in long-term OS for patients with low-grade mucinous appendiceal neoplasms was observed (20-year OS: 70% vs. 0%)[25]. In a retrospective multi-institutional registry of 2298 patients in 16 centres having all subtypes of PMP and being treated with CRS followed in 89% of the cases by HIPEC with mitomycin C or oxaliplatin, a median progression-free survival of 98 months, a median OS of 196 months, and 10- and 15-year survival rates of 63% and 59% respectively were found[26]. Recently, highly favourable results of this approach were also reported in a retrospective multicentre French study[27] of 301 PMP patients (5-year OS: 73%) and in a multicentre prospective nationwide Dutch database study[28] of 300 PMP patients (median progression-free survival: 53 months; median OS: 130 months; 5-year OS: 65%). In the case of disease recurrence after CRS and HIPEC, selected patients can undergo salvage surgery with satisfactory outcomes[29]. Completeness of CRS, favourable histologic subtype, absence of prior chemotherapy treatment, limited disease extension, and absence of major postoperative complications are independent predictors for improved disease-free survival and OS[26]. The role of tumour biology is significant, with prognosis improving across the categories of PMCA, $PMCA_I$, and disseminated peritoneal adenomucinosis[26,30]. Recently, preoperative elevated tumour markers (carcinoembryonic antigen, carbohydrate antigen 19-9, and cancer antigen 125) were demonstrated, in 519 patients, to predict an increased risk of recurrence and reduced survival after complete CRS and HIPEC[31]. In contrast, in a smaller study, elevated carbohydrate antigen 19-9, together with preoperative inflammation-based scores, was the only tumour marker with an independent prognostic value[32]. The discrepancy most likely reflects cell biology in these mucinous tumours.

An important question that arises in patients with PMP is the influence of perioperative systemic chemotherapy in their management. Histologic subtype and tumour marker status can be helpful in selecting patients for postoperative systemic chemotherapy. Whether preoperative systemic chemotherapy could be beneficial in PMCA was recently investigated in two relatively small studies. In the first[33], preoperative systemic chemotherapy was associated with a significant rate of histologic response that reduced the tumour burden and facilitated less aggressive and more complete CRS. Although a significant histologic response was associated with better short-term survival, preoperative systemic chemotherapy did not improve survival in the entire group of patients. In the second study, preoperative systemic chemotherapy was associated with improved survival only in the subgroup of patients with high-grade PMCA and signet-ring cell histology[34].

Malignant Peritoneal Mesothelioma

Diffuse malignant peritoneal mesothelioma (DMPM) is a locally aggressive primary malignancy of the serosal peritoneal surface with, generally, a poor prognosis. Historically, patients treated with palliative surgery with or without chemotherapy experienced a median OS of approximately 1 year[35,36]. With novel systemic chemotherapy regimens consisting of a combination of pemetrexed and platinum compounds or gemcitabine, the median OS has reached 8.7–26.7months[37,38]. The implementation of CRS and HIPEC has further improved survival.

In a systematic review of seven prospective observational studies including 240 DMPM patients, median OS ranged from 34 months to 92 months[39], and analysis of a multi-institutional data registry revealed a median OS of 53 months and 3- and 5-year OS rates of 60% and 47% respectively[40]. The most recent meta-analysis (twenty publications reporting on 1047 patients), complete CRS was achieved in 67% of cases (range: 46%–93%), and pooled estimates of survival yielded 3- and 5-year OS rates of 59% and 42% respectively[41]. The drugs used for HIPEC are doxorubicin, cisplatin, mitomycin C, and docetaxel.

Long-term survivors have been noted among DMPM patients treated with complete CRS and HIPEC. The survival curve appears to plateau 7 years after treatment, which might suggest that the approximately 40% of patients still living at that time point could have a hope for cure[42]. Repeat HIPEC for DMPM recurrence is feasible and associated with favourable survival[43].

Pre- and postoperative (modern) systemic chemotherapy does not seem to improve survival in DMPM patients treated with CRS and HIPEC[44]. Another theoretically attractive treatment option—adjuvant bidirectional chemotherapy with IP pemetrexed and IV cisplatin after CRS and HIPEC for DMPM—can be used with low morbidity[45]. Whether such adjuvant treatment results in increased survival remains to be demonstrated.

Prognostic factors for survival after CRS and HIPEC include histologic subtype, proliferative index, lymph node status, disease burden, preoperative serum cancer antigen 125, completeness of CRS, and major postoperative morbidity[40–44,46–48]. In a single preliminary study[49], expression of Glut1 was the only factor independently associated with OS in multivariate analysis.

Recently, a nomogram to predict survival in patients undergoing CRS and HIPEC for DMPM was developed[47]. The resulting estimation of survival might prevent the use of CRS and HIPEC in patients unlikely to achieve favourable outcomes. Moreover, the use of cisplatin or carboplatin during HIPEC seems to result in better survival than when mitomycin C is administered[47,48,50].

Gastric Cancer

Peritoneal metastasis is present in 5%–30% of patients undergoing potentially curative surgery for gastric cancer[51]. Systemic chemotherapy does not improve on survival in PTC from gastric origin, and median survival duration in these patients has been reported to be 1–3 months[52].

Meta-analyses of HIPEC (compared with surgery alone) as adjuvant treatment for resectable high-risk gastric cancer demonstrated improved survival and decreased peritoneal recurrence risk[53,54]. Because most of those studies were conducted in Asia, the GASTRICHIP study has been designed and is ongoing to address the benefit of adjuvant HIPEC in Western patients with locally advanced gastric cancer[55].

The benefit of CRS and HIPEC in manifest peritoneal dissemination of gastric cancer remains controversial. The joint experience of 15 Western centres with CRS and HIPEC for PTC of gastric origin, comprising150 patients, revealed an overall median survival duration of 9.2 months and a 5-year survival rate of 13%[56]. Lately, in the first randomized trial of HIPEC for PTC of gastric origin, 68 Chinese patients were allocated to CRS with or without HIPEC[57]. Morbidity did not vary, but HIPEC with mitomycin C and cisplatin improved the OS duration (11.2 months vs. 5.6 months, $p = 0.046$). Synchronous (compared with metachronous) PTC, complete CRS, 6 or more cycles of systemic chemotherapy, and an absence of serious adverse effects were independent predictors for better survival. More recently, in a very small randomized trial of 16 patients with established PTC of gastric origin, a survival benefit was observed for gastrectomy, CRS, HIPEC, and systemic chemotherapy compared with systemic chemotherapy only (median OS: 11.3 months vs. 4.3 months, *p* value not provided)[58]. To summarize, the survival of patients with PTC of gastric origin after CRS and HIPEC, although improved, remains considerably poor.

A new strategy in the treatment of PTC of gastric origin involves the application of neoadjuvant bidirectional (intraperitoneal and systemic) chemotherapy before CRS and HIPEC. Recently, a specialized Japanese centre reported on its experience in 194 patients[59]. Only the 152 patients with negative peritoneal cytology after the bidirectional chemotherapy proceeded to CRS and HIPEC. In one third of those patients, a major pathologic response was observed. The strategy had acceptable morbidity and mortality at the specialized centre. The median survival of patients who proceeded to CRS and HIPEC was 15.8 months, and their 2- and 5-year survival rates were 32% and 11% respectively. The patients with positive cytology after neoadjuvant treatment experienced a median survival duration of 7.5 months. Pathologic response, low tumour burden, and completeness of CRS were independent predictors of better prognosis.

Colorectal Cancer

Approximately 5% of patients with colorectal cancer present with PTC, and 8% of colorectal patients develop synchronous or metachronous PTC[60,61]. In about 5% of patients, PTC is the sole site of metastasis at the time of diagnosis of metastatic disease. Synchronous and metachronous PTC is more common in patients with colonic cancer than in those with rectal cancer (10% vs. 4%)[60]. Approximately 20% of patients with recurrent colorectal cancer have peritoneal metastases, and in 40% of those cases, the peritoneal surface is the only site of recurrent disease[62]. Hence, patients with PTC of colorectal origin are suitable candidates for CRS and HIPEC.

Survival after diagnosis of colorectal PTC is reported to be approximately 6 months when untreated[60]. Even when treated with modern systemic chemotherapy, survival is poor—worse than that in patients with distant metastasis (12.7 months vs. 17.6 months, $p < 0.001$)[63]. In an earlier

multi-institutional study comprising 506 patients from 28 centres[64], CRS and HIPEC or immediate postoperative IP chemotherapy (or both) resulted in an overall median OS of 19.2 months. Complete CRS was associated with an overall median survival of 32.4 months; survival after incomplete CRS was poor (8.4 months, $p < 0.001$). The latter observation emphasizes once more the need for adequate patient selection.

The only randomized trial that has been published so far concerning the efficacy of CRS and HIPEC for colorectal PTC reported a median survival of 12.6 months in the systemic chemotherapy arm compared with 22.3 months in the CRS and HIPEC arm ($p = 0.032$) after a median follow-up of 21.6 months[65]. Long-term survivors have been observed after lengthy follow-up[66]. The 5-year survival was 45% for patients who had undergone complete CRS and HIPEC. Criticism concerning this trial refers to the specific systemic chemotherapy used, which is considered to be less effective than current regimens, and to poor patient selection. Moreover, a question of whether the survival benefit was attributable to CRS only or to the combination of CRS and HIPEC arose. This interesting topic is now being investigated in ongoing randomized trials in the United States (NCT00769405) and in France (Prodige 7, NCT00769405).

In a recent systematic review[67], survival was better with CRS and HIPEC (1884 patients) than with palliative surgery and systemic chemotherapy (1408 patients): median OS was 33.0 months compared with 12.5 months, and 5-year survival was 40% compared with 13%. The most recent meta-analysis of three case–control studies and a single randomized trial suggested that survival was significantly improved after CRS, HIPEC, and systemic chemotherapy compared with systemic chemotherapy alone[68]. A pooled analysis demonstrated superior 2-year (odds ratio: 2.78; $p = 0.001$) and 5-year survival (odds ratio: 4.07; $p = 0.001$) with CRS and HIPEC ($n = 187$) than with systemic chemotherapy alone ($n = 155$).

As already discussed, patients with limited PTC and fewer than 3 resectable liver metastases can also be good candidates for HIPEC, with a reasonable possibility of achieving prolonged survival[12–14].In a recent case–control study[13], 37patients with PTC and liver metastases were matched with 61 patients having PTC alone. All underwent CRS, resection of liver metastases (when present), and HIPEC. Patients with limited PTC and 1 or 2 liver metastases had a median survival duration of 40 months; those with a high PTC tumour load or with 3 or more liver metastases had a median survival duration of 27 months. Patients with limited PTC without liver metastases had a median OS of 76 months. In another retrospective study[14], no noteworthy difference in survival was observed between 16 HIPEC patients who had PTC alone and 39 who had also had liver metastases resected or ablated (2-year OS: 68% vs. 65%; $p = 0.77$)

Whereas metastasectomy for colorectal liver metastases is generally accepted as the standard of care in selected patients, CRS and HIPEC are still not widely accepted as definitive treatment for PTC of colorectal origin. The consideration of PTC as a regional and not, *per se,* a systemic disease is also supported by a comparison of outcomes data for CRS and HIPEC in PTC where data for liver surgery for hepatic metastases was available in colorectal cancer patients. In two recent comparative studies[69,70], the survival of patients who underwent margin-negative hepatectomy for colorectal metastases was entirely similar to that of patients with PTC of colorectal origin treated with optimal CRS and HIPEC. Additionally, the morbidity and mortality of both procedures did not differ significantly. Hence, just as a consideration of selected patients with liver metastases for hepatectomy is the accepted strategy, selected colorectal cancer patients with PTC should be considered for CRS and HIPEC.

Mitomycin C has been the traditional drug for HIPEC in colorectal PTC, but the use of high-dose oxaliplatin for a shorter duration has been advocated, especially by Elias and colleagues[71]. In two recent comparative studies[72,73], no clear benefit in outcome for HIPEC with oxaliplatin or with mitomycin C could be demonstrated overall. In one study[72], a logistic regression analysis comparing oxaliplatin with mitomycin C (corrected for the extent of PTC) revealed nonsignificant hazard ratios for relapse-free survival and OS: 1.24 ($p = 0.39$) and 1.37 ($p = 0.32$) respectively. In the other study[73], although median OS after complete CRS and HIPEC with mitomycin C ($n = 392$) or oxaliplatin ($n = 155$) was not different (32.7 months vs. 31.4 months, $p = 0.925$), mitomycin C was a statistically more effective agent than oxaliplatin for HIPEC in colorectal cancer patients with favourable histology and a low burden of disease (median OS: 54.3 months vs. 28.2 months, $p = 0.012$).

Recent retrospective studies suggest that the administration of neoadjuvant systemic chemotherapy with bevacizumab before CRS and HIPEC for colorectal PTC could considerably improve survival[74], but at the cost of increased postoperative morbidity[75].

Another interesting novel topic is the role of systematic "second-look" laparotomy in patients at high risk for colorectal PTC. A systematic review[76] revealed 3 situations that could result in a substantially higher risk of recurrent PTC after curative surgery for colorectal cancer: resected minimal synchronous macroscopic PTC, synchronous isolated ovarian metastases, and a perforated primary tumour at initial surgery. In a preliminary study[77], 41 such patients with no evidence of PTC during follow-up underwent second-look surgery with CRS when peritoneal recurrence was detected, followed by HIPEC 6 months after completion of postoperative systemic chemotherapy. In 56% of the patients, macroscopic PTC was found. The 5-year OS rate was 90%, and the 5-year disease-free survival rate was 44%. Even in the absence of macroscopic disease, omentectomy, oophorectomy, and HIPEC have been recommended in these cases[78]. Those promising results have led to the initiation of the randomized PROPHYLOCHIP trial (NCT01226394), in which 130 patients will be enrolled. Most recently, a randomized trial has been initiated in which the role of adjuvant HIPEC in high-risk colorectal cancer is being investigated (NCT02231086). The results of those interesting trials are eagerly awaited.

Ovarian Cancer

In most affected patients, epithelial ovarian cancer is diagnosed when peritoneal dissemination is present. After surgery and systemic chemotherapy, disease commonly

recurs, mostly to the serosal peritoneal surfaces. Because epithelial ovarian cancer can remain confined to the peritoneal cavity for a prolonged period during the disease course, there is definitely a rationale and opportunity for directed regional treatment.

Various large randomized trials[79–81] and a meta-analysis of completed trials[82] have demonstrated a survival benefit with the addition of postoperative IP chemotherapy after CRS for primary ovarian cancer with peritoneal dissemination. Given that evidence, the U.S. National Cancer Institute issued a clinical announcement recommending that women with optimal CRS in stage III ovarian cancer and their physicians consider a combination of postoperative IV and IP chemotherapy[83]. Although ample evidence is available, IP chemotherapy has not, for various reasons, been widely applied in clinical practice[84].

Currently, less hard evidence supports HIPEC for ovarian cancer than supports postoperative IP chemotherapy. The data consist mainly of relatively small case series, comparative nonrandomized studies, and systematic reviews. Cautious extrapolation of the data from randomized trials of postoperative IP chemotherapy[79–82] and data from phase II and nonrandomized comparative HIPEC studies suggests that HIPEC delivered at the time of surgery for ovarian cancer has definite potential[84]. Cytoreductive surgery and HIPEC have been performed at several time points in the disease course: as frontline treatment, after neoadjuvant chemotherapy and interval CRS, for persistent and for recurrent disease, and as consolidation treatment[84]. The greatest benefit of HIPEC is anticipated at the beginning of the treatment course (that is, as frontline treatment), before tumour cells become chemoresistant, or as consolidation treatment when the disease has been demonstrated to be chemosensitive[84–86]. In a recent French multicentre retrospective cohort study involving 566 patients with advanced ovarian cancer treated with CRS and HIPEC[87], mortality was very low and morbidity was acceptable, with the median OS being 35 months and 46 months for primary and recurrent disease respectively. Remarkably, and in contrast to other studies[88], survival was not different in patients with chemosensitive (recurrence >6 months after standard first-line chemotherapy) and chemoresistant (recurrence <6 months after standard first-line chemotherapy) recurrent disease[87]. The peritoneal tumour burden, the completeness of CRS, the presence of lymph node metastases, age, and performance status were noted as prognostic factors for OS and disease-free survival[84,86–89]. Cisplatin, doxorubicin, oxaliplatin, and mitomycin C were most frequently used for HIPEC. Paclitaxel and docetaxel seem to be attractive alternatives because of their highly favourable pharmacokinetic profiles[90,91].

Relatively small nonrandomized comparative studies have suggested improved outcomes after HIPEC as consolidation treatment and for persistent and recurrent disease[84]. However, the heterogeneity of ovarian cancer patients requires that randomized trials be conducted to obtain definite evidence of benefit. The first randomized study of HIPEC for ovarian cancer was just recently published[88]. It randomized 120 patients with recurrent disease after initial CRS and systemic chemotherapy. The addition of HIPEC to CRS and systemic chemotherapy resulted in a significantly improved median OS (26.7 months vs. 13.4 months, $p < 0.006$) and 3-year survival (75% vs. 18%, $p < 0.01$). The survival benefit was observed in both platinum-resistant and platinum-sensitive recurrent disease.

Currently, at least seven randomized studies are investigating the benefit of HIPEC. A large randomized study (280 patients to be enrolled) conducted by the Netherlands Cancer Institute (NCT00426257) and another smaller study (NCT01628380) are investigating the benefit of HIPEC after interval CRS for primary ovarian cancer. The largest ongoing randomized study (444 patients to be enrolled) is the French CHIPOR study (NCT01376752), which is evaluating the efficacy of HIPEC in patients with platinum-sensitive recurrent disease. Two other randomized HIPEC trials (NCT01539785, NCT01767675) are also enrolling patients with recurrent disease, and another is investigating the role of HIPEC after frontline CRS (NCT01091636). Most interestingly, one randomized trial is comparing the efficacy of CRS, HIPEC, and IV chemotherapy with that of CRS and postoperative IP and IV chemotherapy in primary ovarian cancer (NCT02124421). The interim and final reports of the foregoing studies are eagerly awaited.

MORBIDITY RELATED TO CRS AND HIPEC, AND QUALITY OF LIFE

The survival benefit achieved with CRS and HIPEC can come at the expense of morbidity. Mean duration of the full procedure varies from 5 to 10 hours[10]. Being a major operation that can involve resection of multiple abdominal organs, CRS with HIPEC carries considerable potential for postoperative morbidity and mortality. The risk is, however, comparable to that for any major abdominal surgery—for example, a Whipple procedure[10]. In a recent Dutch nationwide study (966 patients), the major complication rate (grades 3 and 4) was 31%, and the mortality rate was 3%[28]. In the French registry study[25] of 1290 patients treated at 25 centres, severe complications occurred during the learning-curve phase in 34% of patients, and the postoperative mortality rate was 4%. A systematic review revealed a mean major morbidity rate of 28.8%, a mean reoperation rate of 11.2%, and a mean mortality rate of 2.9% in 2787 patients, with lower rates noted for established institutions[10].

In other recent studies, the substantial learning curve that precedes a decline in the risk of severe complications and mortality and an improvement the completeness of CRS has been confirmed, thus emphasizing the need for the procedures to be performed in experienced centres[10,92–96]. Surgical tutoring was able to significantly shorten the steep learning curve associated with CRS and HIPEC[95]. Risk factors for severe morbidity and mortality include disease-related parameters such as histologic type, extent of PTC, and extent of surgery needed (number of organs resected), as well as patient-related parameters such as performance status, comorbidities, smoking, and age[10,92,93,96–98]. In a recent study, diabetes was found to be a highly significant independent predictor of increased morbidity and mortality[99].

The most common complications include bleeding, wound infection, sepsis, abscess, anastomotic leakage, perforation, fistula formation, ileus, renal insufficiency,

thromboembolic episodes, pleural effusion, and chemotherapy-related hematologic toxicity[10,92]. Intraoperatively unrecognized small-bowel damage is a major cause of postoperative morbidity. To preserve the tissue plane and avoid subsequent bowel-related complications because of division of dense adhesions, minimal tissue dissection should be performed at the primary treatment centre. That approach could greatly reduce the risks of bowel injury at the time of CRS and HIPEC.

Recent systematic reviews[99,100] and a meta-analysis[100] of fifteen studies (1583 patients), demonstrated that health-related quality of life declines immediately after CRS and HIPEC. However, at 6–12 months after the procedure, health-related quality of life improves from its preoperative level. At 1 year after CRS and HIPEC (compared with the preoperative assessment), postoperative scores on the Functional Assessment of Cancer Therapy and the European Organisation for Research and Treatment of Cancer quality-of-life questionnaire were significantly improved for overall health status ($p = 0.001$) and emotional health ($p = 0.001$); physical health ($p = 0.83$), social health ($p = 0.48$), and functional health ($p = 0.24$) remained similar[100]. The indicated benefits can persist for up to 5 years. Evidence about health-related quality of life compared with reference populations is inconclusive.

SUMMARY

As discussed, CRS and HIPEC have been shown to improve survival in selected patients with peritoneal surface malignancies and can be considered the standard of care for the treatment of PMP, peritoneal mesothelioma, and (limited) PTC of colorectal origin. The benefit of CRS with HIPEC remains significant in the era of modern chemotherapy and targeted therapy. Although the first positive randomized trial for PTC of both gastric and ovarian cancer has been published, and although it is highly probable that CRS and HIPEC will be useful in particular settings, the exact role of this treatment is still under investigation. In patients with a high risk of developing PTC, HIPEC can also be used in the prophylactic setting, and the first results of the second-look approach are promising. Results of the many ongoing randomized trials in various tumour types are eagerly awaited. Future randomized trials are mandatory to focus on treatment protocols that combine CRS plus HIPEC with systemic chemotherapy regimens including new drugs or monoclonal antibodies.

Patient selection is of utmost importance, as already emphasized. In the absence of a more efficacious and proven method of treating PTC, the risks of perioperative morbidity and mortality, which are analogous to those accompanying any other major gastrointestinal surgery, have to be weighed against the anticipated survival benefit, which, among other factors, depends on tumour biology, the extent of disease, and the probability of achieving complete CRS. To achieve optimal results for each patient, discussion in a multidisciplinary team and identification of the benefit–cost ratio is important. Cytoreductive surgery and HIPEC should remain a treatment option for selected patients who are suitable candidates to undergo this treatment and for whom a curative and life-prolonging treatment can avoid and delay the inevitable culmination of this rapidly progressive terminal condition. In brief, the combination of CRS and HIPEC appears to be an indispensable tool in the oncologist's armamentarium.

ACKNOWLEDGMENTS

We thank Eugenia Bolbasis for linguistic review of the manuscript.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

*1st Department of Surgery, Metaxa Cancer Institute, Piraeus, Greece; †Peritoneal Surface Malignancy Unit, IASO General Hospital, Athens, Greece; ‡Department of Surgical Oncology, Medical School of Crete University Hospital, Heraklion, Greece.

REFERENCES

1. Sugarbaker PH. Peritoneal carcinomatosis: natural history and rational therapeutic interventions using intraperitoneal chemotherapy. *Cancer Treat Res* 1996;81:149–68.
2. Witkamp AJ, de Bree E, Van Goethem R, Zoetmulder FAN. Rationale and techniques of intra-operative hyperthermic intraperitoneal chemotherapy. *Cancer Treat Rev* 2001;27:365–74.
3. de Bree E, Tsiftsis DD. Principles of perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis. *Recent Results Cancer Res* 2007;169:39–51.
4. Spiliotis J, Halkia E, Efstathiou E. Peritoneal carcinomatosis 2011; it's about time for chemosurgery. *J BUON* 2011;16:400–8.
5. de Bree E, Tsiftsis DD. Experimental and pharmacokinetic studies in intraperitoneal chemotherapy: from laboratory bench to bedside. *Recent Results Cancer Res* 2007;169:53–73.
6. de Bree E. Optimal drugs for HIPEC in different tumors. *J BUON* 2015;20(suppl 1):S40–6.
7. Hildebrandt B, Wust P, Ahlers O, *et al.* The cellular and molecular basis of hyperthermia. *Crit Rev Oncol Hematol* 2002;43:33–56.
8. Spiliotis J, Efstathiou E, Halkia E, Vaxevanidou A, Datsis A, Sugarbaker P. The influence of tumor cell entrapment phenomenon on the natural history of pseudomyxoma peritonei syndrome. *Hepatogastroenterology* 2012;59:705–8.
9. Sugarbaker PH. Peritonectomy procedures. *Ann Surg* 1995;221:29–42.
10. Chua TC, Yan TD, Saxena A, Morris DL. 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* 2009;249:900–7.
11. Piso P, Glockzin G, von Breitenbuch P, *et al.* Patient selection for a curative approach to carcinomatosis. *Cancer J* 2009;15:236–42.
12. Elias D, Benizri E, Pocard M, Ducreux M, Boige V, Lasser P. Treatment of synchronous peritoneal carcinomatosis and liver metastases from colorectal cancer. *Eur J Surg Oncol* 2006;32:632–6.
13. Maggiori L, Goéré D, Viana B, *et al.* Should patients with peritoneal carcinomatosis of colorectal origin with synchronous liver metastases be treated with a curative intent? A case–control study. *Ann Surg* 2013;258:116–21.
14. Chua TC, Yan TD, Zhao J, Morris DL. Peritoneal carcinomatosis and liver metastases from colorectal cancer treated with cytoreductive surgery perioperative intraperitoneal chemotherapy and liver resection. *Eur J Surg Oncol* 2009;35:1299–305.
15. González-Moreno S, González-Bayón L, Ortega-Pérez G, González-Hernando C. Imaging of peritoneal carcinomatosis. *Cancer J* 2009;15:184–9.

16. de Bree E, Koops W, Kröger R, van Ruth S, Witkamp AJ, Zoetmulder FAN. Peritoneal carcinomatosis from colorectal or appendiceal origin: correlation of preoperative CT with intraoperative findings and evaluation of interobserver agreement. *J Surg Oncol* 2004;86:64–73.
17. Yan TD, Morris DL, Shigeki K, Dario B, Marcello D. Preoperative investigations in the management of peritoneal surface malignancy with cytoreductive surgery and perioperative intraperitoneal chemotherapy: expert consensus statement. *J Surg Oncol* 2008;98:224–7.
18. Courcoutsakis N, Tentes AA, Astrinakis E, Zezos P, Prassopoulos P. CT–enteroclysis in the preoperative assessment of the small-bowel involvement in patients with peritoneal carcinomatosis, candidates for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Abdom Imaging* 2013;38:56–63.
19. Cashin PH, Graf W, Nygren P, Mahteme H. Comparison of prognostic scores for patients with colorectal cancer peritoneal metastases treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol* 2013;20:4183–9.
20. Esquivel J, Lowy AM, Markman M, *et al.* The American Society of Peritoneal Surface Malignancies (ASPSM) multiinstitution evaluation of the Peritoneal Surface Disease Severity Score (PSDSS) in 1,013 patients with colorectal cancer with peritoneal carcinomatosis. *Ann Surg Oncol* 2014;21:4195–201.
21. Esquivel J, Garcia SS, Hicken W, Seibel J, Shekitka K, Trout R. Evaluation of a new staging classification and a Peritoneal Surface Disease Severity Score (PSDSS) in 229 patients with mucinous appendiceal neoplasms with or without peritoneal dissemination. *J Surg Oncol* 2014;110:656–60.
22. Bradley RF, Stewart JH 4th, Russell GB, Levine EA, Geisinger KR. Pseudomyxoma peritonei of appendiceal origin: a clinicopathologic analysis of 101 patients uniformly treated at a single institution, with literature review. *Am J Surg Pathol* 2006;30:551–9.
23. Gough DB, Donohue JH, Schutt AJ, *et al.* Pseudomyxoma peritonei. Long-term patient survival with an aggressive regional approach. *Ann Surg* 1994;219:112–19.
24. Miner TJ, Shia J, Jaques DP, Klimstra DS, Brennen M, Goit DC. Long term survival following treatment of pseudomyxoma peritonei: an analysis of surgical therapy. *Ann Surg* 2005;241:300–8.
25. Sugarbaker PH. New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome? *Lancet Oncol* 2006;7:69–76.
26. Chua TC, Moran BJ, Sugarbaker PH, *et al.* 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* 2012;30:2449–56.
27. Glehen O, Gilly FN, Boutitie F, *et al.* on behalf of the French Surgical Association. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. *Cancer* 2010;116:5608–18.
28. Kuijpers AM, Mirck B, Aalbers AG, *et al.* Cytoreduction and HIPEC in the Netherlands: nationwide long-term outcome following the Dutch protocol. *Ann Surg Oncol* 2013;20:4224–30.
29. Lord AC, Shihab O, Chandrakumaran K, Mohamed F, Cecil TD, Moran BJ. Recurrence and outcome after complete tumour removal and hyperthermic intraperitoneal chemotherapy in 512 patients with pseudomyxoma peritonei from perforated appendiceal mucinous tumours. *Eur J Surg Oncol* 2015;41:396–9.
30. Stewart JH 4th, Shen P, Russell GB, *et al.* Appendiceal neoplasms with peritoneal dissemination: outcomes after cytoreductive surgery and intraperitoneal hyperthermic chemotherapy. *Ann Surg Oncol* 2006;13:624–34.
31. Taflampas P, Dayal S, Chandrakumaran K, Mohamed F, Cecil TD, Moran BJ. Pre-operative tumour marker status predicts recurrence and survival after complete cytoreduction and hyperthermic intraperitoneal chemotherapy for appendiceal pseudomyxoma peritonei: analysis of 519 patients. *Eur J Surg Oncol* 2014;40:515–20.
32. Kusamura S, Baratti D, Hutanu I, *et al.* The role of baseline inflammatory-based scores and serum tumor markers to risk stratify pseudomyxoma peritonei patients treated with cytoreduction (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). *Eur J Surg Oncol* 2015;41:1097–105.
33. Bijelic L, Kumer AS, Stuart OA, Sugarbaker PH. Systemic chemotherapy prior to cytoreductive surgery and HIPEC for carcinomatosis from appendix cancer: impact on perioperative outcomes and short-term survival. *Gastroent Res Pract* 2012;2012:635314.
34. Milovanov V, Sardi A, Ledakis P, *et al.* Systemic chemotherapy (SC) before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) in patients with peritoneal mucinous carcinomatosis of appendiceal origin (PMCA). *Eur J Surg Oncol* 2015;41:707–12.
35. Baratti D, Kusamura S, Deraco M. Diffuse malignant peritoneal mesothelioma: systematic review of clinical management and biological research. *J Surg Oncol* 2011;103:822–31.
36. Manzini Vde P, Recchia L, Cafferata M, *et al.* Malignant peritoneal mesothelioma: a multicenter study on 81 cases. *Ann Oncol* 2010;21:348–53.
37. Carteni G, Manegold C, Garcia GM, *et al.* Malignant peritoneal mesothelioma—results from the International Expanded Access Program using pemetrexed alone or in combination with a platinum agent. *Lung Cancer* 2009;64:211–18.
38. Simon GR, Verschraegen CF, Jänne PA, *et al.* Pemetrexed plus gemcitabine as first-line chemotherapy for patients with peritoneal mesothelioma: final report of a phase II trial. *J Clin Oncol* 2008;26:3567–72.
39. Yan TD, Welch L, Black D, Sugarbaker PH. A systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for diffuse malignancy peritoneal mesothelioma. *Ann Oncol* 2007;18:827–34.
40. Yan TD, Deraco M, Baratti D, *et al.* Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. *J Clin Oncol* 2009;27:6237–42.
41. Helm JH, Miura JT, Glenn JA, *et al.* Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: a systematic review and meta-analysis. *Ann Surg Oncol* 2015;22:1686–93.
42. Baratti D, Kusamura S, Cabras AD, Bertulli R, Hutanu I, Deraco M. Diffuse malignant peritoneal mesothelioma: long-term survival with complete cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC). *Eur J Cancer* 2013;49:3140–8.
43. Wong J, Koch AL, Deneve JL, Fulp W, Tanvetyanon T, Dessurealt S. Repeat cytoreductive surgery and HIPEC may offer survival benefit for intraperitoneal mesothelioma: a single institution experience. *Ann Surg Oncol* 2014;21:1480–6.
44. Deraco M, Baratti D, Hutanu I, Bertuli R, Kusamura S. The role of perioperative systemic chemotherapy in diffuse malignant peritoneal mesothelioma patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol* 2013;20:1093–100.
45. Bijelic L, Stuart OA, Sugarbaker PH. Adjuvant bidirectional chemotherapy with intraperitoneal pemetrexed combined

with intravenous cisplatin for diffuse malignant peritoneal mesothelioma. *Gastroenterol Res Pract* 2012;2012:890450.
46. Magge D, Zenati MS, Austin F, *et al.* Malignant peritoneal mesothelioma prognostic factors and oncologic outcome analysis. *Ann Surg Oncol* 2014;21:1159–65.
47. Schaub NP, Alimchandani M, Quezado M, *et al.* A novel nomogram for peritoneal mesothelioma predicts survival. *Ann Surg Oncol* 2013;20:555–61.
48. Alexander HR Jr, Bartlett DL, Pingpank JF, *et al.* Treatment factors associated with long-term survival after cytoreductive surgery and regional chemotherapy for patients with malignant peritoneal mesothelioma. *Surgery* 2013;153:779–86.
49. Hommell-Fontaine J, Isaac S, Passot G, *et al.* Malignant peritoneal mesothelioma treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: is Glut1 expression a major prognostic factor? A preliminary study. *Ann Surg Oncol* 2013;20:3892–8.
50. Shetty SJ, Bathla L, Govindarajan V, Thomas P, Loggie BW. Comparison of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with mitomycin or carboplatin for diffuse malignant peritoneal mesothelioma. *Am Surg* 2014;80:348–52.
51. Gill RS, Al-Adra PD, Nagendram J, *et al.* Treatment of gastric cancer with peritoneal carcinomatosis by cytoreductive surgery and HIPEC: a systematic review of survival, mortality, and morbidity. *J Surg Oncol* 2011;104:692–8.
52. Saito H, Kihava K, Kuroda H, Matsunega T, Totebe S, Ikeguchi M. Surgical outcomes for gastric cancer patients with intraperitoneal free cancer cell, but not macroscopic peritoneal metastasis. *J Surg Oncol* 2011;104:534–7.
53. Sun J, Song Y, Wang Z, *et al.* Benefits of hyperthermic intraperitoneal chemotherapy for patients with serosal invasion in gastric cancer: a meta-analysis of the randomized controlled trials. *BMC Cancer* 2012;12:526.
54. Mi DH, Li Z, Yang KH, *et al.* Surgery combined with intraoperative hyperthermic intraperitoneal chemotherapy (IHIC) for gastric cancer: a systematic review and meta-analysis of randomised controlled trials. *Int J Hyperthermia* 2013;29:156–67.
55. Glehen O, Passot G, Villeneuve L, *et al.* GASTRICHIP: D2 resection and hyperthermic intraperitoneal chemotherapy in locally advanced gastric carcinoma: a randomized and multicenter phase III study. *BMC Cancer* 2014;14:183.
56. Glehen O, Gilly FN, Arvieux C, *et al.* on behalf of the Association Française de Chirurgie. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. *Ann Surg Oncol* 2010;17:2370–7.
57. Yang XJ, Huang CQ, Suo T, *et al.* Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. *Ann Surg Oncol* 2011;18:1575–81.
58. Rudloff U, Langan RC, Mullinax JE, *et al.* Impact of maximal cytoreductive surgery plus regional heated intraperitoneal chemotherapy (HIPEC) on outcome of patients with peritoneal carcinomatosis of gastric origin: results of the GYMSSA trial. *J Surg Oncol* 2014;110:275–84.
59. Canbay E, Mizumoto A, Ichinose M, *et al.* Outcome data of patients with peritoneal carcinomatosis from gastric origin treated by a strategy of bidirectional chemotherapy prior to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in a single specialized center in Japan. *Ann Surg Oncol* 2014;21:1147–52.
60. Segelman J, Granath F, Holm T, Machado M, Mahteme H, Martling A. Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer. *Br J Surg* 2012;99:699–705.
61. Thomassen I, van Gestel YR, Aalbers AG, *et al.* Peritoneal carcinomatosis is less frequently diagnosed during laparoscopic surgery compared to open surgery in patients with colorectal cancer. *Eur J Surg Oncol* 2014;40:511–14.
62. van Gestel YR, Thomassen I, Lemmens VE, *et al.* Metachronous peritoneal carcinomatosis after curative treatment of colorectal cancer. *Eur J Surg Oncol* 2014;40:963–9.
63. Franko J, Shi Q, Goldman CD, *et al.* Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841. *J Clin Oncol* 2012;30:263–7.
64. Glehen O, Kwiatkowski F, Sugarbaker PH, *et al.* Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol* 2004;22:3284–92.
65. Verwaal VJ, van Ruth S, de Bree E, *et al.* Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003;21:3737–43.
66. Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 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* 2008;15:2426–32.
67. Chua TC, Esquivel J, Pelz JO, Morris DL. Summary of current therapeutic options for peritoneal metastases from colorectal cancer. *J Surg Oncol* 2013;107:566–73.
68. Mirnezami R, Mehta AM, Chandrakumaran K, *et al.* Cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy improves survival in patients with colorectal peritoneal metastases compared with systemic chemotherapy alone. *Br J Cancer* 2014;111:1500–8.
69. Cao CQ, Yan TD, Liauw W, Morris DL. Comparison of optimally resected hepatectomy and peritonectomy patients with colorectal cancer metastasis. *J Surg Oncol* 2009;100:529–33.
70. Elias D, Faron M, Iuga BS, *et al.* Prognostic similarities and differences in optimally resected liver metastases and peritoneal metastases from colorectal cancers. *Ann Surg* 2015;261:157–63.
71. Elias D, Leferre JH, Chevalier J, *et al.* Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol* 2009;27:681–5.
72. Hompes D, D'Hoore A, Wolthuis A, *et al.* The use of oxaliplatin or mitomycin C in HIPEC treatment for peritoneal carcinomatosis from colorectal cancer: a comparative study. *J Surg Oncol* 2014;109:527–32.
73. Prada-Villaverde A, Esquivel J, Lowy AM, *et al.* American Society of Peritoneal Surface Malignancies evaluation of HIPEC with mitomycin C versus oxaliplatin in 539 patients with colon cancer undergoing a complete cytoreductive surgery. *J Surg Oncol* 2014;110:779–85.
74. Ceelen W, Van Nieuwenhove Y, Putte DV, Pattyn P. Neoadjuvant chemotherapy with bevacizumab may improve outcome after cytoreduction and hyperthermic intraperitoneal chemoperfusion (HIPEC) for colorectal carcinomatosis. *Ann Surg Oncol* 2014;21:3023–8.
75. Eveno C, Passot G, Goéré D, *et al.* Bevacizumab doubles the early postoperative complication rate after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis of colorectal origin. *Ann Surg Oncol* 2014;21:1792–800.
76. Honoré C, Goéré D, Souadka A, Dumont F, Elias D. Definition of patients presenting a high risk of developing peritoneal carcinomatosis after curative surgery for colorectal cancer: a systematic review. *Ann Surg Oncol* 2013;20:183–92.

77. Elias D, Honoré C, Dumont F, *et al.* Results of systematic second-look surgery plus HIPEC in asymptomatic patients presenting a high risk of developing colorectal peritoneal carcinomatosis. *Ann Surg* 2011;254:289–93.
78. Sugarbaker PH. Early intervention for treatment and prevention of colorectal carcinomatosis: a plan for individualized care. *Surg Oncol Clin N Am* 2012;21:689–703.
79. Alberts DS, Liu PY, Hannigan EV, *et al.* Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med* 1996;335:1950–5.
80. Markman M, Bundy BN, Alberts DS, *et al.* 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* 2001;19:1001–7.
81. Armstrong DK, Bundy B, Wenzel L, *et al.* Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 2006;354:34–43.
82 Jaaback K, Johnson N, Lawrie TA. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. *Cochrane Database Syst Rev* 2011;9:CD005340.
83. Trimble EL, Christian MC. Intraperitoneal chemotherapy for women with advanced epithelial ovarian carcinoma. *Gynecol Oncol* 2006;100:3–4.
84. de Bree E, Helm CW. Hyperthermic intraperitoneal chemotherapy in ovarian cancer: rationale and clinical data. *Expert Rev Anticancer Ther* 2012;12:895–911.
85. Helm CW, Richard SD, Pan J, *et al.* Hyperthermic intraperitoneal chemotherapy in ovarian cancer: first report of the HYPER-O registry. *Int J Gynecol Cancer* 2010;20:61–9.
86. Mulier S, Claes JP, Dierieck V, *et al.* Survival benefit of adding HIPEC of the different time-points of treatment of ovarian cancer: review of evidence. *Curr Pharm Des* 2012;18:3793–803.
87. Bakrin N, Bereder JM, Decullier E, *et al.* on behalf of the FROGHI (French Oncologic and Gynecologic HIPEC) group. Peritoneal carcinomatosis treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for advanced ovarian carcinoma: a French multicentre retrospective cohort study of 566 patients. *Eur J Surg Oncol* 2013;39:1435–43.
88. Halkia E, Spiliotis J, Sugarbaker PH. Diagnosis and management of peritoneal metastases from ovarian cancer. *Gastroenterol Res Pract* 2012;2012:541842.
89. Spiliotis J, Halkia E, Lianos E, *et al.* Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. *Ann Surg Oncol* 2015;22:1570–5.
90. de Bree E, Theodoropoulos PA, Rosing H, *et al.* Treatment of ovarian cancer using intraperitoneal chemotherapy with taxanes: from laboratory bench to bedside. *Cancer Treat Rev* 2006;32:471–82.
91. de Bree E, Rosing H, Filis D, *et al.* Cytoreductive surgery and intraoperative hyperthermic intraperitoneal chemotherapy with paclitaxel: a clinical and pharmacokinetic study. *Ann Surg Oncol* 2008;15:1183–92.
92. Mohamed F, Moran BJ. Morbidity and mortality with cytoreductive surgery and intraperitoneal chemotherapy: the importance of a learning curve. *Cancer J* 2009;15:196–9.
93. Kusamura S, Baratti D, Deraco M. Multidimensional analysis of the learning curve for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in peritoneal surface malignancies. *Ann Surg* 2012;255:348–56.
94. Polanco PM, Ding Y, Knox JM, *et al.* Institutional learning curve of cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion for peritoneal malignancies. *Ann Surg Oncol* 2015;22:1673–9.
95. Kusamura S, Baratti D, Virzì S, *et al.* Learning curve for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in peritoneal surface malignancies: analysis of two centres. *J Surg Oncol* 2013;107:312–19.
96. Halkia E, Kopanakis N, Nikolaou G, Spiliotis J. Cytoreductive surgery and HIPEC for peritoneal carcinomatosis. A review on morbidity and mortality. *J BUON* 2015;20 (suppl 1):S80–7.
97. Ihemelandu CU, McQuellon R, Shen P, Stewart JH, Votanopoulos K, Levine EA. Predicting postoperative morbidity following cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CS+HIPEC) with preoperative FACT-C (Functional Assessment of Cancer Therapy) and patient-rated performance status. *Ann Surg Oncol* 2013;20:3519–26.
98. Randle RW, Ahmed S, Levine EA, *et al.* Significance of diabetes on morbidity and mortality following cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. *J Surg Oncol* 2015;111:740–5.
99. Seretis C, Youssef H. Quality of life after cytoreductive surgery and intraoperative hyperthermic intraperitoneal chemotherapy for peritoneal surface malignancies: a systematic review. *Eur J Surg Oncol* 2014;40:1605–13.
100. Shan LL, Saxena A, Shan BL, Morris DL. Quality of life after cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy for peritoneal carcinomatosis: a systematic review and meta-analysis. *Surg Oncol* 2014;23:199–210.