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REVIEW ARTICLE

The role of cytoreductive surgery and HIPEC in epithelial ovarian cancer

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Summary

Epithelial ovarian cancer (EOC) is the most common cause of death from gynecological cancer in the Western world. The current standard treatment of these patients consists of cytoreduction and systemic chemotherapy. One of the most distinct features of EOC is the tendency to disseminate into the peritoneal cavity and remain confined to the peritoneum and intra-abdominal viscera. This makes it an ideal target for loco-regional therapy. Improved long-term results can be achieved in highly selected patients using cytoreductive surgery (CRS), in combination with intra-operative hyperthermic intra-peritoneal chemotherapy (HIPEC). Optimal cytoreduction of advanced ovarian cancer is currently the most relevant prognostic factor. However, even when a complete resection is possible, the appearance of recurrences during follow-up is very common, due to the presence of microscopic residual disease, not visible to the surgeon. HIPEC has become a useful therapeutic strategy to obtain a higher degree of debulking by trying to eliminate the residual microscopic component responsible for recurrences. A summary of the current clinical evidence suggests that the most interesting settings first to explore in randomized trials are secondary CRS after upfront incomplete CRS for stage III ovarian cancer and salvage CRS for recurrent ovarian cancer, two time-points representing failure to initial standard therapy. There is much less indirect evidence for a potential benefit of HIPEC for less advanced stages (I – II) and for earlier time-points in the treatment of ovarian cancer (upfront, interval and consolidation). CRS and HIPEC offer a significant survival benefit in patients with recurrent EOC. This observation applies to both platinum-sensitive and platinum-resistant disease.

Key words: *HIPEC, ovarian cancer, peritoneal carcinomatosis*

Introduction

EOC is the most common cause of death from gynecological cancer in the Western world and approximately two thirds of the patients present with advanced disease at diagnosis (International Federation of Gynecology and Obstetrics [FIGO] stage III or IV) [1,2].

The current standard treatment of these patients consists of cytoreduction (residual disease <0.2cm) and systemic chemotherapy with paclitaxel combined with platins, either carboplatin or cisplatin, with or without anti-angiogenic agents. This strategy provides complete remission in 60-80% of the cases with a median survival of 35-38 months [3]. However, 20-30% of the patients have tumors resistant to systemic cisplatin from the onset and nearly 60-70% of those who respond to platinum will relapse within 3 years [4]. This interval to the development of drug resistance is defined by the time to recurrence after the first-line treatment, a definition that might be questionable. Patients who relapse before the sixth month are considered chemoresistant, and those who relapse after six months are considered chemosensitive. The prognosis for these two groups

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is ambiguous and effective therapy with curative intent is very doubtful [5,6].

One of the most distinct features of EOC is the tendency to disseminate into the peritoneal cavity and remain confined to the peritoneum and intra-abdominal viscera. This makes it an ideal target for loco-regional therapy [6,7].

The extent of cytoreduction has a direct impact on survival, and maximal cytoreduction was found to be one of the most powerful determinants of survival among patients with stage III or IV EOC, in a meta-analysis of almost 7,000 patients [3]. In 2006, the National Cancer Institute issued a Clinical Announcement suggesting that intraperitoneal (IP) chemotherapy should become the standard of care for patients with newly diagnosed stage III optimally cytoreduced EOC following a publication of the landmark study, GOG protocol 172. Unfortunately, toxicity and catheter complications and dose schedule resulted in poor uptake of the IP route [8].

Improved long-term results can be achieved in highly selected patients with CRS, including parietal and visceral peritonectomy procedures, in combination with HIPEC [9-14].

Platinum-based chemotherapeutic regimens have been shown to produce high response rates and to penetrate tumor tissue much more deeply under hyperthermic conditions when administered IP. Because of the peritoneal-plasma barrier, platinum derivatives remain in the peritoneal cavity longer, permitting prolonged exposure to the drug. Despite extended surgery, most patients return to baseline or better levels of function within 3 months after treatment and long-term survival with good quality of life is possible [7,15].

Cytoreductive surgery

Favorable oncological outcomes have been reported regarding the introduction of a more aggressive surgical approach to resect ovarian cancer peritoneal carcinomatosis (PC). A historical meta-analysis supporting the importance of CRS in the treatment of EOC was published by Bristow et al. [3]. They retrospectively evaluated the relative effect of percent maximal CRS and other prognostic variables on survival among 81 cohorts of studies, including 6885 patients with stage III/IV EOC, treated with cisplatin-based chemotherapy. Maximal cytoreduction was concluded to be one of the most powerful determinants of survival.

CRS may be considered for EOC at the time of initial treatment (frontline), following neoadjuvant chemotherapy (interval debulking) and with recurrence [16,17].

There is a list of possible indications and time-points for surgical intervention in EOC [18]. In the past, CRS with residual cancerous lesions >1 cm or <2 cm in greatest dimension was considered "optimal" (Table 1). However, the precise definition of optimal or complete cytoreduction has been open to wide differences of opinion and has changed considerably overtime. Optimal cytoreduction definitely improves the survival and requires peritonectomy prodecures and visceral resections depending on the extent of peritoneal metastases (Table 2).

Table 1. Indications for surgery in ovarian cancer

(i) Diagnostic laparotomy or laparoscopy	Exploration performed at any time in the course of ovarian cancer to obtain a histological diagnosis.
	A *second-look surgery* is performed in patients who are clinically, biochemically, and radiologically free of disease after completion of chemotherapy with the purpose to confirm the response status.
(ii) Staging laparotomy	Surgery performed in patients with clinically early ovarian cancer aiming at the detection of tumor spread.
(iii) Primary cytoreductive surgery	Surgery with the aim of complete resection of all macroscopic tumors in patients with first diagnosis of advanced ovarian cancer before any other treatment (e.g., chemotherapy).
(iv) Secondary surgery/Interval debulking	Surgery performed in patients usually after 3 cycles of chemotherapy, with an attempt to remove any remaining tumor that has not been eradicated by chemotherapy.
(v) Surgery for progressive ovarian cancer	Surgery with the purpose of removing obviously resistant tumors, which have not responded to chemotherapy and progressed during primary chemotherapy.
(vi) Surgery for recurrent ovarian cancer	Surgery aiming at complete resection of all macroscopic tumor in patients with recurrent ovarian cancer after completion of primary therapy including a subsequent period without any signs of disease.
(vii) Palliative surgery	Surgery performed in patients with symptoms caused by progressive disease or sequelae aiming to relieve symptoms and not towards survival prolongation.

Table 2. Peritonectomy procedures and resections that are combined to complete cytoreduction procedure

Peritonectomy	*Resections*
Anterior parietal peritonectomy	Old abdominal incisions, umbilicus, and epigastric fat pad
Left upper quadrant peritonectomy	Greater omentectomy and spleen
Right upper quadrant peritonectomy	Tumor on Glisson's capsule of the liver
Pelvic peritonectomy	Uterus, ovaries, and rectosigmoid colon
Omental bursectomy	Gallbladder and lesser omentum

After finishing the CRS, it is important to determine the completeness of cytoreduction score (CCs):

CC-0 indicates no visible residual tumor

CC-1 indicates residual nodules<2.5 mm

CC-2 indicates residual nodules>2.5 mm and <2.5 cm

CC-3 indicates residual nodules > 2.5 cm

This score proposed by Sugarbaker and Chang has been accepted worldwide by the teams of peritoneal surface malignancy treatment groups [19].

The term "optimal debulking" has been introduced for primary CRS. Retrospective studies reported a threshold of ≤1 cm of residual tumor as cut-off for inclusion criteria for complete cytoreduction. Nowadays, the definition of complete CRS has changed to indicate complete resection of all visible tumors and the Gynecologic Cancer Interstudy Group (GCIG) has changed the official nomenclature to indicate this. However, the concept of "optimal debulking" has not been established in CRS for recurrent disease [20,21].

Several factors concur for the accomplishment of an optimal cytoreduction: accurate preoperative identification of resectable cases, experience of the surgical team, favorable clinical condition of the patient, biological aggressiveness of the disease, the surgeon and patient's willingness to challenge the inherent increased morbidity of an extended operation. However, the essence of the problem is not operational. Although universally accepted as standard of care, the term CRS has been the subject of myriad of interpretations resulting in different concepts of optimal residual disease and advisable limits of radicality [22].

Peritonectomy procedures are necessary to successfully treat peritoneal surface malignancies with curative intent. Peritonectomy procedures are used in areas of visible cancer progression so that only microscopic residual disease remains. Isolated tumor nodules are removed using electro-evaporation, and involvement of the visceral peritoneum frequently requires resection of a portion of the stomach, small intestine or colorectum. Layering of cancer on a peritoneal surface or a portion of the bowel requires peritonectomy or bowel resection for complete removal.

In order to adequately perform peritonectomy, the surgeon must use electro-surgery. Peritonectomies and visceral resection using traditional scissor and knife dissection will unnecessarily disseminate a large number of tumor cells within the abdomen. High-voltage electro-surgery leaves a margin of heat necrosis that is devoid of viable malignant cells. Not only does electro-evaporation of tumor and normal tissue at the margins of resection minimize the likelihood of persistent disease but it also minimizes blood loss. When using techniques other than electro-surgery profuse bleeding from stripped peritoneal surfaces may occur [23].

Lysis of adhesions: Before proceeding with peritonectomies or visceral resections, all adhesions are separated. Scar tissue holding bowel loops together is resected using ball tipped electro-surgery and generous cooling using room-temperature saline irrigation. To facilitate the dissection, adhesions are thinned out using strong compression of tissue between thumb and index finger. If possible, these adhesions are resected and submitted as a pathological specimen. The mechanism whereby cancer cells are fixed at sites of prior surgical dissection is referred to as the "tumor cell entrapment hypothesis" [24].

Xiphoidectomy: If preoperative radiologic studies suggest the need of right and left subdiaphragmatic peritonectomy, a xiphoidectomy should be performed to gain maximal exposure beneath the right and left hemidiaphragms. The xiphoid is released from the sternum. The broad attachments of the diaphragm muscle to the xiphoid are divided as it is peeled away from the underlying tissues.

Total anterior parietal peritonectomy: As the peritoneum is dissected away from the posterior rectus sheath, if cancer nodules are palpated on the parietal peritoneum a complete dissection may be indicated to achieve a complete cytoreduc-

tion. If the parietal peritoneum is not involved by peritoneal metastasis except for the small defect, the remainder of the peritoneum is maintained intact. The superior limit of dissection is achieved with the stripping of the peritoneum from the undersurface of the hemidiaphagm. In some instances, dissection from inferior to superior aspects of the abdominal wall facilitates clearing in this area. The dissection blends in with the right and left subphrenic peritonectomy superiorly and with the complete pelvic peritonectomy inferiorly [24,25].

Left subphrenic peritonectomy: The epigastric fat and peritoneum at the edge of the abdominal incision are stripped off the posterior rectus sheath. Strong traction is exerted on the tumor specimen throughout the left upper quadrant to separate tumor from the diaphragmatic muscle, the left adrenal gland and the superior half of the pre-renal fat.

Right subphrenic peritonectomy: The peritoneum is stripped from beneath the right posterior rectus sheath to begin peritonectomy in the right upper quadrant of the abdomen. The stripping of the tumor from the right hemidiaphragm continues until the base area of the liver is encountered. At that point, tumor on the superior surface of the liver is electro-evaporated until the liver surface is cleared.

Tumor from beneath the right hemidiaphragm from the right subhepatic space and from the surface of the liver forms an envelope as it is removed *en bloc* [24-26].

Greater omentectomy and splenectomy: To free the mid-abdomen of a large volume of tumor, greater omentectomy-splenectomy is performed. The greater omentum is evaluated and separated from the transverse colon using electro-surgery. The dissection continues beneath the peritoneum that covers the transverse mesocolon in order to expose the lower border of the pancreas. With traction on the spleen, the peritoneum superior to the pancreas may be stripped from the gland bluntly or by using electro-surgery. If the peritoneum covering the pancreas is free of cancer implants, it remains intact.

Lesser omentectomy, cholecystectomy and stripping of the hepatoduodenal ligament: The gallbladder is removed in a routine fashion from its fundus towards the cystic artery and cystic duct. The hepatoduodenal ligament is characteristically heavily layered with tumor. After dividing the peritoneal reflection into the liver, the cancerous tissue that coats the porta hepatic is bluntly stripped from the base of the gallbladder bed toward the duodenum.

Stripping of the floor of the omental bursa: Performing stripping of the omental bursa after dividing the peritoneal reflection between left caudate lobe and superior vena cava.

Pelvic peritonectomy: After dissecting generously the peritoneum on the right and left sides of the bladder, the urachus is localized. The peritoneum and underlying fatty tissues are stripped away from the surface of the bladder. Broad traction on the entire anterior parietal peritoneal surface and frequent saline irrigation clears the point of tissue transaction, which is precisely located between the bladder musculature and its adherent fatty tissue with peritoneum. The inferior limit of dissection is the cervix in females or the seminal vesicles in males. The peritoneal incision around the pelvis is connected to the peritoneal incisions of the right and left paracolic sulci. In the female patients the round ligaments are divided as they enter in the internal inguinal ring. In women, the right and left ovarian veins are ligated at the level of the lower pole of the kidney and divided. The sigmoid colon is divided just above the limits of the pelvic tumor. The inferior mesenteric artery is suture-ligated and divided, which allows one to pack all of the visera including the proximal sigmoid colon into the upper abdomen [24-26].

Cytoreductive surgery is the cornerstone of therapy for EOC. There are several potential benefits of aggressive primary surgical management in women with EOC, particularly those with advanced disease:

a) Optimal response to postoperative chemotherapy is achieved in the setting of minimal disease burden.

Chemotherapeutic drugs exert their maximum effects on small tumors that are well perfused and therefore mitotically active. Larger tumor size is associated with poorer perfusion and a greater chance of subepithelial cellular damage as well as the emergence of multidrug resistant clones. These pharmacologic principles are supported clinically by the observation that both the relapse-free interval and median survival are inversely related to the size of the largest residual tumor mass at the completion of initial debulking prior to the start of induction chemotherapy.

b) Disease-related symptoms (e.g. abdominal pain, increased abdominal girth, dyspnea, early satiety) are related to tumor burden. Removal of bulky rapidly improves symptoms and quality of life.

c) Ovarian neoplasms produce multiple cytokines at least some of which are immunosuppressive (e.g. interleukin-10, VEGF). Removal of tumor bulk may improve or restore host immune competence [28-31].

Despite the survival benefit of cytoreduction these procedures may be associated with significant morbidity and a potential delay in the initiation of chemotherapy. There are three exceptions to an initial surgical approach to management:

Firstly, patients with a complex ovarian cyst in whom an extra ovarian primary tumor has not been excluded. Secondly, patients with suspected ovarian cancer that are poor candidates for surgery because of significant comorbidities (e.g. pre-existing medical conditions, severe malnutrition, massive ascites). In such patients, an extensive surgical procedure confers a high risk of perioperative morbidity and mortality. Thirdly, patients in whom initial cytoreduction is not feasible because of disease bulk [32,33].

In patients with bulky disease or poor performance status, an alternative approach is to establish the diagnosis of presumed ovarian cancer by a confirmatory biopsy or cytologic specimen (e.g. from a peritoneal implant or ascitic fluid) followed by the administration of neoadjuvant chemotherapy [32].

Since the clinical experience and aggressiveness of the surgeon are key determinants of optimal surgical resection, the intraoperative quantification of residual disease diameter is estimated by the surgeon and has a subjective component. However, the accuracy of CT for assessing residual disease has not been validated either. Poor correlation between the surgeon's estimate of residual disease and the postoperative CT could be due to the surgeon's underestimation of residual disease, rapid regrowth of the tumor following surgery or postoperative changes and inflammation following surgery that look like residual disease on CT scan [34]. In several studies, factors limiting the ability to achieve optimal cytoreduction are presence of extra-abdominal or retroperitoneal disease or large tumor bulk, bowel involvement (small bowel mesentery), parenchymal liver involvement, presence of ascites, and poor nutritional state [35].

Rectosigmoid colon resection should be attempted in women with bulky abdominal disease if the procedure provides an opportunity for maximal cytoreduction. However, gastrointestinal surgery can add significant morbidity to surgical treatment. A thorough assessment of the intraabdominal findings should be performed prior to attempted resection. Bowel surgery is of little value if there are other areas of grossly unresectable disease, except to relieve gastrointestinal obstruction. Parenchymal hepatic metastases are not necessarily a contraindication to initial cytoreductive surgery. The risk/benefit ratio for optimal hepatic cytoreduction may be unfavorable if hepatic disease is bulky or involves major vessels [36,37].

When a recurrence is detected during the follow-up period, a second surgery, termed secondary cytoreduction, may be performed in a medically fit and selective patient population under certain circumstances. The best evidence suggests that aggressive surgical debulking is critical to outcome. A second attempt at cytoreduction after chemotherapy for suboptimally debulked disease does not provide an outcome that is equivalent to that achieved by aggressive initial surgical debulking followed by paclitaxel and platinum-based combination chemotherapy. However, if the initial surgical attempt of cytoreduction was not a maximal surgical effort, then chemotherapy followed by secondary surgical cytoreduction might be beneficial [38,39]. In several studies on secondary cytoreduction, several clinical variables were found to be independently associated with survival on multivariate analysis. These included age, initial stage (III C vs V), ascites ≤1 lt, histology (all other vs mucinous/clear all), disease-free interval >12 months, limited (1-2) sites of recurrence, tumor size <6 cm, diagnosis to recurrence time >18 months and treatment-free interval <24 months. A proposed guideline for selection of patients who may benefit from secondary surgical cytoreduction includes disease-free interval and number of sites of recurrence. In general, patients who are considered candidates for secondary cytoreduction have platinum-sensitive disease (recurrence beyond 6 months after completion of adjuvant platinum-based chemotherapy) [40].

The literature on surgical cytoreduction for EOC beyond the secondary setting is limited. For recurrence after secondary cytoreduction, studies on survival benefit of tertiary cytoreduction also focus on residual disease as the most important prognostic factor [55]. Ideally, tertiary cytoreduction should control the disease, diminish the complaints associated with the tumor load, increase survival and improve the quality of life without increasing morbidity. Issues with regard to tertiary cytoreduction include selecting the appropriate candidates for the extensive surgery, determining the prognostic value and identifying the limits of

how aggressive the surgery must be in order to achieve the best outcome [40-42]. It appears that maximal surgical effort aiming at optimal tumor reduction remains of high value throughout the entire natural course of EOC from the primary to secondary, tertiary and even quaternary setting. Future larger multicenter, prospectively assessed evaluations are warranted to validate the present findings (Table 3) [43].

Rationale for HIPEC in ovarian cancer

The route of chemotherapy administration for EOC has traditionally been intravenous (IV). In the 1960s IP chemotherapy was introduced with the aim of controlling malignant ascites. It was found that certain drugs, such as cisplatin, were cleared from the peritoneal cavity slowly, which meant that a high concentration of the drug could be delivered IP without resulting in a systemic overdose of the drug. Drugs that ar particularly suited for IP delivery have high molecular weight and are water-soluble, resulting in a delayed peritoneal, but high systemic clearance, giving rise to pharmacological advantage for treating peritoneal disease [6]. Ovarian cancer is an ideal cancer for treatment via an IP route. The propensity for peritoneal recurrences as the only site of disease makes this cancer the ideal candidate for such loco-regional treatment. The rationale behind HIPEC is the ability to deliver high concentrations of the appropriate drug to the site that is most likely to develop recurrences after performing complete cytoreduction, with eradication of all visible disease. It is critical that no gross residuals are present, as penetration of IP chemotherapy is up to a depth of 2-2.5 mm, hence there is a inherent risk that larger volumes of tumor deposits will not be adequately treated by the intraperitoneal chemotherapy. HIPEC has several advantages over simple intraperitoneal chemotherapy: the administration is performed immediately following surgical cytoreduction in an abdomen free of adhesions at the moment when the tumor burden is at its lowest [6,43].

Table 3. Retrospective studies with regard to cytoreduction

First author [Ref]	*Year*	*No. of patients*	*Platinum sensitive patients*	*OS* (months)*	*DFS* (months)*	*Major complication rate (%)*	*Operative mortality (%)*	*Complete tumor resection rate (%)*	*Independent factors associated with survival*	*Median tumor size (cm)*	*Multiple site recurrence rate (%)*
Leitao et al. [94]	2004	26	42	36	10	8	0	53	Optimal TC and TFI	5	57
Karam et al. [95]	2007	47	0	24	16	14	0	64	Presence of diffuse peritoneal disease	5	NA
Gulfekin et al [96]	2008	20	0	32	6	0	0	35		4	50
Shih et al [97]	2010	77	28	60	13	13	0	72	Extent of debulking	5	62
Fotopoulou et al. [98]	2011	135	19	37	7	20	5.8	39	Complete tumor resection, interval to primary diagnosis >3 years and serious papillary histology	NA	85
Hizli et al. [99]	2012	23	0	NA	NA	4	0	65	Complete tumor resection	4	83
Fotopoulou et al. [42]	2013	406	38	49	12	26	3.2	54	High grade histology, tumor residuals at 2nd and 3rd surgery, interval to second relapse, ascites, upper abdominal involvement, distant metastases and non-platinum third-line chemotherapy	NA	NA

*In optimally-debulked (no visible tumor) patients (in suboptimally-debulked patients overall survival, instead of DFS is stated). TFI: treatment free interval, NA: not available

During HIPEC, moderate intra-abdominal hyperthermia is obtained by heating the carrier solution. The target intra-abdominal temperature differs slightly between centers, but is usually between 40° and 43°C. Similar to the drugs that are intra-peritoneally delivered, heat has a limited penetration depth during HIPEC, implying once again the need for optimal CRS. Hyperthermia enhances chemotherapy efficacy in a number of ways: it increases drug uptake into malignant cells, alters cellular metabolism and cellular drug pharmacokinetics, increases drug penetration depth in tissue, and provides temperature-dependent increases in drug action and inhibition of repair mechanisms. A potential drawback of HIPEC is the short tumor exposure time. However, experimental studies have demonstrated that even short time exposure of tumor cells to high drug concentrations, as is the case during HIPEC, is extremely sufficient to induce extended cell growth arrest and tumor cell death [44].

One should not assume that the intraperitoneal administration of chemotherapy eliminates systemic toxicities. Although the drugs are sequestered within the peritoneal space, they eventually are cleared into the systemic circulation. For this reason, the safe doses of most drugs instilled into the peritoneal cavity are identical to the intravenous doses.

Tumor cell entrapment may explain the rapid progression of peritoneal surface malignancy in patients who undergo surgical treatment alone. This theory relates the high incidence and rapid progression of peritoneal surface implantation to fibrin entrapment of intra-abdominal tumor emboli on traumatized peritoneal surfaces and progression of these entrapped tumor cells through growth factors involved in the wound healing process. Tumor cell entrapment may cause a high incidence of local-regional treatment failure in patients treated for EOC peritoneal carcinomatosis. The reimplantation of malignant cells into peritonectomized surfaces in a reoperative setting must be expected unless intraperitoneal chemotherapy is used. A high dose of heated chemotherapy can then be delivered in the operating room to eradicate tiny tumor nodules and microscopic cancer cells so that all abdominal and pelvic components of the cancer are exposed to chemotherapy and may respond (Table 4) [24,45].

CRS + HIPEC as front-line therapy

Standard upfront treatment was analyzed in the study by Vergote et al. [46], who compared CRS+systemic chemotherapy vs neoadjuvant chemotherapy+CRS+systemic chemotherapy. Median overall survival (OS) was 30 and 29 months respectively, and median disease free survival (DFS) was 12 months. In this phase III study, the requirement for CRS was residual disease <1 cm, therefore the results cannot be compared with those of studies based on maximal surgical effort surgery. A more suitable comparison would be with the results of maximum CRS studies involving access to the upper abdomen, such as those described by Eisenkop et al. [47], and Chi et al. [48]. In these studies, the median OS was 58.2 and 54 months, with a 5-year OS of 49%, respectively.

Standard first-line treatment demands complete CRS along with adjuvant or perioperative chemotherapy using carboplatin and taxol, delivered either systemically or intraperitoneally.

Antiangiogemic agents may also be used. Radicality of cytoreduction is the main independent prognostic factor. Other prognostic factors such as the extensiveness of peritoneal carcinomatosis as evaluated by the Sugarbaker's Peritoneal Cancer

Index (PCI) or the chemoresistance to platinum compounds are also fundamental prognostic factors. However, there is great variation in the

Table 4. Rationale for the use of a heated intraoperative intraperitoneal chemotherapy solution

- Heat increases drug penetration into tissue.
- Heat increases the cytotoxicity of selected chemotherapy agents.
- Heat has antitumor effect by itself.
- Intraoperative chemotherapy allows manual distribution of drug and heat uniformly to all surfaces of the abdomen and pelvis.
- Renal toxicities of chemotherapy given in the operating room can be avoided by careful monitoring of urine output during chemotherapy lavage.
- Time that elapses during the heated perfusion allows for normalization of main physiologic parameters (temperature, blood clotting, hemodynamics, etc.)
- Access to the peritoneal cavity over 90 min allows time for meticulous removal of tumor nodules from small bowel surfaces and a mechanical disruption of cancer cells from within blood clots and fibrin accumulations.

criteria for inclusion of patients in various trials of standard first-line HIPEC treatment.

This makes comparisons very difficult. Comparative results are summarized in Table 5. The number of patients in series that evaluated first-line HIPEC are usually quite limited but the reported median survival in selected patients is superior to those obtained with standard systemic chemotherapy. The survival results of the French Registry are lower, but this series included patients who were refractory or resistant to first-line treatment and thus have poorer prognosis [6,49,50]. The data suggests that with HIPEC, the 2-year OS and progression-free survival were not significantly different with those of CRS and systemic chemotherapy. These results are compara-

Table 5. Results from the use of HIPEC in the treatment of ovarian cancer

A/Survival results for first line HIPEC treatment for advanced ovarian cancers

First author [Ref]	*Year*	*Number of patients*	*Chemotherapy*	*Cytoreduction*	*Median survival (months)*	*Survival*
Vergote et al. [46]	2010	334	Neoadjuvant IV	<1 cm	30	
			Adjuvant IV		29	
Eisenkop et al. [47]	2003	408	IV	<1 mm	58	49% at 5 years
Chi et al. [48]	2009	408	IV	<1 mm	54	47% at 5 years
Armstrong et al. [100]	2006	214	IP	<1 cm	66	
		215	IV		50	
Helm et al. [53]	2010	20	HIPEC	<1 cm	58	
Pomel et al. [81]	2010	31	HIPEC	<1 mm		67% at 2 years
Deraco et al. [101]	2011	26	HIPEC	<1 mm	NR	61% at 5 years
Bakrin et al. [44]	2013	92	HIPEC	<1 mm	42	17% at 5 years
Gonzalez Bayon et al.[102]	2013	15	HIPEC	<1 mm	78	72% at 5 years

IV: intravenous, IP: intraperitoneal, HIPEC: hyperthermic intraperitoneal chemotherapy, NR: not reported

B/Survival results for HIPEC for recurrent ovarian cancer

First author [Ref]	*Year*	*Number of patients*	*Treatment*	*Quality of cytoreduction*	*Median survival (months)*
Zanon et al. [103]	2004	23	CRS and HIPEC	Complete	38
		7		Incomplete	11
Harter et al. [104]	2006	170	CRS	Complete	45
		47		Incomplete	20
Benedetti Panici et al. [105]	2007	37	CRS	Complete	61
Oksefjell et al. [56]		10		Incomplete	19
	2009	68	CRS	Complete	54
		33		Residual tumor <2 cm	28
		95		Residual tumor >2 cm	8
Helm et al. [53]	2010	83	CRS and HIPEC	-	30
Bakrin et al. [49]	2013	356	CRS and HIPEC	Complete	52
		117		Incomplete	33

CRS: cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy

C/Case-control studies that compared CRS combined with HIPEC vs CRS alone for recurrent ovarian cancer

First author [Ref]	*Number of patients*	*Survival for CRS + HIPEC*	*Survival for CRS alone*	*p value*
Munoz-Casares et al. [106]	26	58% at 5 years	17% at 5 years	0.046
Spiliotis et al. [107]	48	50% at 3 years	18% at 3 years	0.01
Fagotti et al. [57]	67	68% at 5 years	42% at 5 years	0.017

CRS: cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy

ble but do not exceed studies with maximal CRS followed by systemic chemotherapy in front-line treatment in EOC [21,51].

HIPEC during interval cytoreduction

A major controversy concerns the optimal time-point in the natural history of EOC for the performance of CRS+HIPEC. Data suggest that maximal surgical effort combined with systemic and intraperitoneal chemotherapy in the primary setting represents indirect evidence that CRS+HIPEC could be tested as upfront treatment in the context of phase III trials.

The use of CRS following the maximal response from neoadjuvant systemic chemotherapy is theoretically the most optimal time-point for HIPEC [21,22,52]. The numbers of patients from different trials and especially from the HYPER-O study are small and the data difficult to interpret [53]. When one compares the survivals between patients when HIPEC was used as front line or used at the time of interval debulking following neoadjuvant chemotherapy, there is no significant difference. However, a large randomized study showed no difference in OS in women with stage III C and IV disease randomized to initial CRS then IV chemotherapy or neoadjuvant chemotherapy followed by interval debulking surgery, then further systemic chemotherapy [46] (Table 6).

Table 6. Interval CRS and HIPEC

First author [Ref]	*Treatment*	*N*	*FIGO III-IV (%)*	*FIGO III (%)*	*FIGO IV (%)*	*CC0 (%)*	*Mortality (%)*	*Follow-up*	*5-y DFS (%)*	*DFS*	*5-y OS (all) (%)*	*5-y OS (CC0) (%)*	*OS (all)*	*OS (CC0)*
Reichman TW et al. [82]	*CRS and HIPEC*	4	100				0			8.4				
Yoshida V et al. [83]	*CRS and HIPEC*	4	100	100	0		0			17.8			38.0	
Helm CW et al. [53]	*CRS and HIPEC*	19	100						9.6	16.8	50.2		68.6	
Roviello F et al. [14]	*CRS and HIPEC*	31	100	100	0	65	0				58			NR
Munoz-Casares FC et al. [84]	*CRS and HIPEC*	9	100	100	0	78	1/9				62		NR	
Carrabin N. et al. [85]	*CRS and HIPEC*	10	100	100	0	80	0			16.9				
Marice P et al. [86]	*CRS only*	34	100	88	12		0	>24					26	
Vergote I et al. [46]	*CRS only*	334	100	76	24	47	0.7	56		12	21.1	27.5	30	38.2
Sehouli J et al. [87]	*CRS only*	40	100	78	22	88	0	23*		14.6			36.5	37.9
Kumar L et al. [88]	*CRS only*	71	100					42		15			41	
Onda T et al. [89]	*CRS only*	53	100	66	34	55	0	39		14			45	
Lee SJ et al. [90]	*CRS only*	18	100	89	11		0	20		15			53	

Follow-up and survival figures are expressed as median values in months unless otherwise specified, N: number of patients, CCO: macroscopically complete cytoreduction, y: year, DFS: disease free survival, OS: overall survival, NR: not reached, CRS: cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy

CRS + HIPEC in recurrent EOC

Survival for patients with recurrent EOC treated with chemotherapy alone tends to be inferior to that reported for secondary CRS. The influence of secondary CRS without HIPEC on survival outcomes has been addressed in a substantial number of studies and has been recently systematically reviewed [54]. However, these were non-controlled studies and not strictly comparable, since chemotherapy trials will include patients not suitable for traditional cytoreduction, including patients with a high PCI. The prognostic factors that predict the survival outcome also define the criteria for "optimal" CRS+HIPEC in recurrent EOC [55]. These are age, performance status, interval from initial treatment to recurrence, PCI, completeness of cytoreduction, presence of lymph nodes and initial platinum response [21].

A recent study from our team [7] was a prospective randomized phase III study. A hundred and twenty women who experienced disease recurrence after initial treatment with conservative or debulking surgery and systemic chemotherapy (FIGO stage III C and IV) were randomized into two groups. Group A (60 women) was treated with CRS+HIPEC+systemic chemotherapy and Group B (60 women) was treated with CRS+systemic chemotherapy. The mean survival for group A was 26.7 vs 13.4 months in group B (p=0.006) and the 3-year survival was 75% in group A vs 18% in group B (p=0.03). In the HIPEC group the mean survival was not different between patients with platinum-resistant disease vs platinum-sensitive disease (26.6 vs 26.8 months). On the other hand, in the non-HIPEC group, there was a statistically significant difference between platinum sensitive vs platinum-resistant disease (15.2 vs 10.2 months) (p=0.002). Complete cytoreduction was associated with a significantly longer survival. Patients with a PCI <15 appeared also to have a significantly longer survival. One of the most significant findings in this study was that in the HIPEC group similar patient survival was observed, both in the platinum-sensitive and platinum-resistant disease, which was not the case in the non-HIPEC group. This observation can be attributed to several reasons: the role of hyperthermia, epigenetic alterations and the role of anthracyclines, such as doxorubicin [7].

Bakrin et al. have reported similar results [56]. In a multicenter retrospective French study including 474 patients with recurrent EOC, patients with platinum-resistant and platinum-sensitive disease treated with optimal cytoreduction had a similar survival of 51.6 and 47.2 months respectively (non-significant) [49]. Similarly, in the Spiliotis et al. study, survival was 26.6 months in platinum-sensitive and 26.8 months in platinum-resistant disease (non-significant).

Several other recent studies have been attempted to identify the role of CRS+HIPEC in recurrent EOC. A case-control study by Fagotti et al. [57] compared survival data in 30 platinum-sensitive EOC patients undergoing secondary CRS and HIPEC, vs 37 patients who did not undergo HIPEC. Statistically significant results were reported in favor of the HIPEC group regarding the rates of secondary recurrence, the duration of secondary response and mortality, with a DFS of 26 months in the HIPEC group vs 15 months in the non-HIPEC group [7].

So far, the management of recurrent EOC is based on systemic chemotherapy. However, the need for an alternative treatment modality has been pointed out by Stathopoulos et al., who stated that multiple chemotherapy lines (3-7 lines) do not offer a survival benefit vs 1 or 2 lines [58]. Finally, the need for appropriate surgical management in recurrent EOC has been shown in a study by Fotopoulou et al., describing tertiary CRS in the course of treatment of patients with multiple relapses [42] (Table 7).

Consolidation CRS + HIPEC

Consolidation treatment is defined as additional treatment following a complete response to front-line therapy. Patients with initial stage III EOC were treated with HIPEC at second laparotomy and compared with patients who had a complete response but did not receive HIPEC. The 5-year OS rate was 66.1% with HIPEC vs 31.3% in the control group [59].

In a prospective non-randomised study, consolidation CRS and HIPEC (29 patients) was compared with no treatment (in 19 patients in the same period who refused CRS and HIPEC) in patients with FIGO stage III EOC after upfront (near) complete CRS followed by adjuvant systemic chemotherapy [60]. Median OS was 64.4 months in the CRS+HIPEC group vs 46.4 months for the control group, but the difference failed to reach statistical significance [51] (Table 8).

CRS + HIPEC in malignant ascites-ROM EOC

Treatment of malignant ascites in advanced EOC patients remains controversial. The forma-

Table 7. Secondary CRS and HIPEC

First author [Ref]	*Treatment*	*N*	*FIGO III-IV (%)*	*FIGO III (%)*	*FIGO IV (%)*	*Mortality (%)*	*Follow-up*	*5-y DFS (%)*	*DFS*	*5-y OS (all) (%)*	*OS (all)*	*p value*
Bae JH et al. [59]	*CRS and HIPEC stage I-II*	23	0	0	0	0	62		NR	82.4	NR	(1)
Bae JH et al. [59]	*CRS only stage I-II*	5	0	0	0	0	52		NR	60.0	NR	(1)
Bae JH et al. [59]	*CRS and HIPEC stage III*	44	100	100	0	0	62		56	66.1	>60	(2)
Bae JH et al. [59]	*CRS only stage III*	24	100	100	0	0	52		15	32.8	31	(2)
Ryu KS et al. [91]	*CRS and HIPEC (all)*	57	61.4	61.4	0	3.5	47		48.7	63.4	76.1	(3)
Ryu KS et al. [91]	*CRS only (all)*	60	65	65	0	0	46		19.8	52.8	62.9	(3)
Ryu KS et al. [91]	*CRS and HIPEC stage I-II*	22	0	0	0		47	69.6		78.4		(4)
Ryu KS et al. [91]	*CRS only stage I-II*	21	0	0	0		46	77.8		89.6		(4)
Ryu KS et al. [91]	*CRS and HIPEC stage III*	35	100	100	0		47	26.9	26.4	53.8	60.9	(5)
Ryu KS et al. [91]	*CRS only stage III*	39	100	100	0		46	10.3	6.1	33.3	22.3	(5)
Cotte E et al. [12]	*CRS and HIPEC*	16							8		24.3	
Powel C et al. [81]	*CRS and HIPEC*	31	100	100	0	0			14.1		NR	
Rose BG et al. [92]	*CRS and IV chemotherapy only*	216	100	93	7		47		10.5		33.9	
Rose BG et al. [92]	*IV chemotherapy only*	208	100	96	4		48		10.7		33.7	

Follow-up and survival figures are expressed as median values in months unless otherwise specified. N: number of patients, CCO: macroscopically complete cytoreduction, y: year, DFS: disease free survival, OS: overall survival, NR: not reached, CRS: cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy
(1) p not significant for DFS and OS after CRS and HIPEC vs after CRS only
(2) p=0.003 for DFS and OS after CRS and HIPEC vs after CRS only
(3) p=0.002 for DFS; p=0.008 for OS after CRS and HIPEC vs after CRS only
(4) p not significant for DFS and OS after CRS and HIPEC vs after CRS only
(5) p=0.007 for DFS; p=0.002 for OS between CRS and HIPEC vs after CRS only

tion of malignant ascites and accumulation of abdominal fluid-filled pockets as a direct effect of cancer is a typical complication during late-stage EOC. The formation of malignant ascites occurs in virtually all EOC patients upon cancer progression. As the amount of ascites increases, patients generally report progressive symptoms of abdominal swelling, pain, nausea and dyspnea. Indeed, discomfort and decreased quality of life associated with symptomatic malignant ascites often exceeds that of the cancer itself, resulting in detrimental physiological and psychological states, leading to poor prognosis [61,62]. In the clinical setting, treatment of malignant ascites due to EOC is controversial. Some clinicians advocate first-line treatments with simple drainage while others select chemotherapy and debulking to treat the underlying cancer. However, neither type of treatment has been completely successful in reducing ascites and limiting additional ascites development. As a first-line treatment, simple drainage is often accomplished using diuretics, but their efficacy is relatively low and dosage increases are limited. Similarly, continuous paracentesis or manual removal of accumulated fluid from the abdominal cavity produces only temporary relief and must be repeated regularly to prevent symptoms of recurrence. Thus, there is a

Table 8. Consolidation CRS and HIPEC

First author [Ref]	*Treatment*	*N*	*FIGO III-IV (%)*	*FIGO III (%)*	*FIGO IV (%)*	*CC0 (%)*	*Mortality (%)*	*Follow-up*	*5-y DFS (%)*	*DFS*	*5-y OS (all) (%)*	*5-y OS (CC0)*	*OS (all)*	*p value*
Gori J et al. [60]	*CRS and HIPEC*	29	100	100	0	100	0	73				98	64.4	(1)
Gori J et al. [60]	*no treatment*	19	100	100	0			73				51	46.4	(1)
Hel CW et al. [53]	*CRS and HIPEC*	12							24.2	29.6	42.4	67	53.7	
Yoshida V et al. [83]	*CRS and HIPEC*	4	100	100	0		0			82.8		90.1	88.3	
Markman M et al. [93]	*paclitaxel IV x 3*	146	100							14		57	48	
Markman M et al. [93]	*Paclitaxel IV x 12*	150	100							22		61	53	

Follow-up and survival figures are expressed as median values in months unless otherwise specified. N: number of patients, CCO: macroscopically complete cytoreduction, y: year, DFS: disase free survival, OS: overall survival, NR: not reached, CRS: cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy
(1) p not significant for OS after CRS and HIPEC vs after no treatment

need for improved treatment options for treating the underlying cancer, thereby preventing symptomatic recurrence [61,63].

Laparoscopic approaches for HIPEC have recently been proposed for patients who are not eligible for CRS [64-67]. Based on increasing reports of successful outcomes following laparoscopy-assisted HIPEC techniques, B-mode ultrasound-guided HIPEC was developed. The use of this technique has been reported to produce satisfactory therapeutic results.

Consequently, different treatment strategies are recommended to improve the prognosis of EOC patients with malignant ascites [68,69]. Generally, good results of the palliative (laparoscopic) administration of HIPEC without CRS have been reported recently in patients with refractory ascites due to recurrent gastric cancer, colorectal cancer, ovarian cancer, breast cancer and peritoneal mesothelioma with limited morbidity, complete clinical and radiological disappearance of ascites in 94% of the cases, and improvement of the Karnofsky performance status [70-72].

Discussion

EOC is one of the most common malignancies in women and causes more deaths than any other female reproductive cancer. Over the past two decades, only moderate improvements in long-term survival of EOC patients have been reported, mainly due to increased application of modern chemotherapy regimens [73].

In 1978, Dedrick et al. proposed the intraperitoneal administration of chemotherapy, which allowed a significantly higher intraperitoneal drug concentration than by the intravenous route [74]. Optimal cytoreduction of disease in advanced EOC is currently the most relevant prognostic factor [75,76]. However, in patients with stage IV disease at diagnosis, unresectable disease at diagnosis or patients with general conditions that demand an initial complex surgery, such as patients with advanced age, neoadjuvant systemic chemotherapy and subsequent surgery has been proposed as a reasonable alternative [46]. In the appearance of recurrences, HIPEC has become a useful therapeutic strategy to obtain a higher degree of debulking by trying to eliminate this residual component, responsible for microscopic recurrences [77,78].

The technical particularities of HIPEC include installation circuit, the timing of parietal closure (before or after HIPEC), the duration of treatment target temperatures and the choice and dosage of antimitotic agents [6]. The rationale for the choice of a particular chemotherapy agent is based on its clinical efficacy and the pharmacokinetics in the peritoneal cavity. HIPEC's toxicity when combined with CRS is manifested largely as surgical complications (anastomotic leakage, intraperitoneal septic complications, bleeding). Complications specific to HIPEC are mainly hematologic, as well as the risk of kidney failure related to the

predominant use of cisplatin [6,80].

A summary of the current clinical evidence suggest that the most interesting settings first to explore in randomized trials are secondary CRS after upfront incomplete CRS for stage III EOC and salvage CRS for recurrent EOC, two time-points representing failure to initial standard therapy. There is much less indirect evidence for a potential benefit of HIPEC for less advanced stages (I-II) and for earlier time-points in the treatment of EOC (upfront, interval and consolidation) [51].

Mortality from HIPEC in a review of the largest international series was reported to be 3%. Independent risk factors for morbidity included the extensiveness of carcinomatosis, the radicality of CRS, the duration of the total procedure, the extent of peritoneal resection and the number of anastomoses. Grade 3-4 morbidity occurred in 8-31% of the cases, particularly in patients whose bone marrow has already been impaired by multiple cycles of systemic chemotherapy using agents similar to those used for HIPEC. This specific morbidity is also linked to the type of chemotherapeutic agent used [49,81].

CRS and HIPEC offer a significant survival benefit in patients with recurrent EOC. This observation applies to both platinum-sensitive and platinum-resistant disease. Maximum efficacy of HIPEC is noted when complete cytoreduction is achieved [7].

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