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REVIEW

Peritoneal carcinomatosis

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Abstract

Several gastrointestinal and gynecological malignancies have the potential to disseminate and grow in the peritoneal cavity. The occurrence of peritoneal carcinomatosis (PC) has been shown to significantly decrease overall survival in patients with liver and/or extraperitoneal metastases from gastrointestinal cancer. During the last three decades, the understanding of the biology and pathways of dissemination of tumors with intraperitoneal spread, and the understanding of the protective function of the peritoneal barrier against tumoral seeding, has prompted the concept that PC is a loco-regional disease: in absence of other systemic metastases, multimodal approaches combining aggressive cytoreductive surgery, intraperitoneal hyperthermic chemotherapy and systemic chemotherapy have been proposed and are actually considered promising methods to improve loco-regional control of the disease, and ultimately to increase survival. The aim of this review article is to present the evidence on treatment of PC in different tumors, in order to provide patients with a proper surgical and multidisciplinary treatment focused on optimal control of their locoregional disease.

Key words: Carcinosis; Peritoneal; Ovarian; Gastric; Colorectal; Hipec; Intraperitoneal chemotherapy; Cytoreductive surgery; Cancer; Advanced

Core tip: This review aims to present the evidence on treatment of peritoneal carcinosis in different tumors, in order to provide patients with a proper surgical and multidisciplinary treatment focused on optimal control of their locoregional disease.

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INTRODUCTION

Several gastrointestinal and gynecological malignancies have the potential to disseminate and grow in the peritoneal cavity. This condition is often associated with disease progression and poor prognosis. The occurrence of peritoneal carcinomatosis (PC) has been shown to significantly decrease overall survival in patients with liver and/or extraperitoneal metastases from gastrointestinal cancer. Moreover, overall survival in patients with

PC is generally only slightly influenced by systemic chemotherapy, so that the occurrence of PC is traditionally regarded by the surgeon as a terminal condition.

In 10%-35% of patients with recurrent colorectal cancer (CRC) and in up to 50% of patients with recurrent gastric cancer (GC), tumor recurrence is confined to the peritoneal cavity: those patients have been shown to ultimately die from complications of locoregional tumoral widespread, in most cases without occurrence of metastases in other sites. This natural unfavorable evolution of recurrence is commonly observed in epithelial ovarian cancer (EOC) too, a condition always associated with PC and in which locoregional widespread of the tumor is the most common cause of death. However, while in EOC there is general agreement that complete removal of peritoneal seedings is associated with longer survival, in CRC and GC complete removal of peritoneal carcinomatosis is usually followed by short-term recurrence, so that patients are usually treated with limited palliative resection or gastrointestinal bypass without the intent for complete cytoreduction.

On the other hand, almost 15% of patients with colorectal cancer and almost 40% of patients with stage Ⅱ-Ⅲ gastric cancer present with PC at abdominal exploration: in these cases there are no standardized indications for surgery, and operations vary from simple exploration and biopsy to palliative resection of the primary tumor, the latter procedure being associated with wide interruption of the peritoneal integrity and further seeding of neoplastic cells.

Preoperative diagnosis of PC could be very difficult. Imaging techniques (mainly based upon computed tomography-scan and magnetic resonance imaging), could assist in planning cytoreduction but also in preventing unwarranted laparotomy in patients with unresectable disease. However, they are limited in their ability to visualize localized PC, having low sensitivity for small-volume disease. The gold standard in diagnosing PC continues to be the direct peritoneal visualization, either by laparotomy or laparoscopy.

During the last three decades, the understanding of the biology and pathways of dissemination of tumors with intraperitoneal spread, and the understanding of the protective function of the peritoneal barrier against tumoral seeding, has prompted the concept that PC is a loco-regional disease: in absence of other systemic metastases, multimodal approaches combining aggressive cytoreductive surgery (CRS), intraperitoneal hyperthermic chemotherapy (HIPEC) and systemic chemotherapy have been proposed and are actually considered as promising methods to improve loco-regional control of the disease and ultimately to increase survival. Even if evidence of efficacy of these multimodal approaches comes from several phase-Ⅱ studies, a few phase-Ⅲ studies have been published for CRC and GC, and other are ongoing for EOC. HIPEC privileges consist in increasing loco-regional drugs concentration limiting their systemic diffusion and consequentially their toxicitys and adverse events. The role of peritoneal plasma barrier in promoting a loco-regional high-dose effect is very important. Indeed, peritoneum has the capability to limit the systemic drugs diffusion in the peritoneal space. Moreover, the hyperthermia enhances the efficacy and the penetration of many of the drugs employed.

The renewed interest on treatment of PC is going to change the attitude of the surgeon towards tumors with peritoneal seeding, thus new paradigms are focusing on the proper behavior that the surgeon should adopt when PC is encountered during operation. Consideration should be given to the different proposed approaches facing different degrees of peritoneal cancer dissemination, but, above all, the question should be: what shouldbe done if PC is encountered? In presence of PC, therapeutic algorithms should be addressed, taking into account the different pathologies and the risk-benefit balance.

The aim of this review article is to present the evidence on treatment of PC in different tumors and to give indications to surgeons who deal with patients with PC, in order to provide patients with a proper surgical and multidisciplinary treatment focused on optimal control of their locoregional disease.

ROLE OF CYTOREDUCTIVE SURGERY AND HIPEC IN THE TREATMENT OF ABDOMINAL CARCINOMATOSIS FROM DIFFERENT PRIMARY MALIGNANCIES

Biological research has identified three pattern of peritoneal cancer spread: (1) random proximal distribution (RPD), in which early peritoneal implantation is due to the presence of adherence molecules on cancer cell surface, even when ascites is present; this is typical of moderate-grade and high-grade cancers, such as adenocarcinoma and carcinoid of the appendix, non-mucinous colorectal cancer, gastric cancer and serous ovarian cancer; (2) complete redistribution (CRD), in which there is no adhesion to the peritoneal surface close to the primary tumor, due to the low biologic aggressiveness of tumor cells; this distribution is typical of pseudomyxoma peritonei and diffuse malignant mesothelioma; and (3) widespread cancer distribution (WCD), in which there is presence of adherence molecules on the surface of cancer cells that produce a great amount of mucus, interfering with cell adherence: this biological behavior is found in aggressive and undifferentiated tumors such as G2-G3 cistoadenocarcinoma of the appendix, mucinous colorectal cancer and mucinous ovarian cancer.

Information about patterns of spread are very important to plan the best surgical treatment. In fact, while RPD should be treated by a selective parietal peritonectomy of the macroscopically involved regions, for CRD and WCD a complete peritonectomy and an extended cytoreduction are needed[1].

PERITONEAL MESOTHELIOMA

Malignant mesothelioma is an uncommon tumor arising from the serosal layer of pleura, peritoneum, pericardium and tunica vaginalis testis.

The incidence of this disease has been rising worldwide since 1970, due to widespread exposure to asbestos during previous decades, and it is not expected to decrease before the next 20 years. In the United States, approximately 2500 new cases of mesothelioma are registered each year. Diffuse malignant peritoneal mesothelioma accounts for 10% to 30% of all mesotheliomas.

Despite the absence of randomized studies, which are obviously difficult in a rare disease, clinical results obtained with the combination of CRS and HIPEC support the adoption of this procedure as a treatment of choice for peritoneal mesothelioma.

In historical series, standard therapy with palliative surgery and systemic chemotherapy is associated with a median survival of about one year, ranging from 9 to 15 mo. Whit such a classical approach, the disease tends to remain within the abdominal cavity throughout its clinical course; an autopsy study demonstrated that 78% of patients had died because of complications directly related to local-regional progression .

On the contrary, Yan *et al*[2] in a recent multi-institutional study examined 407 patients affected by peritoneal mesothelioma treated with CRS and HIPEC in 7 different surgical centers. The mean age of the patients was 50 years, 89% of the cases were epithelial mesothelioma while 11% were sarcomatoid or bifasic. CC0-CC1 rates was achieved in 46% of cases, lymph nodes metastases were find in 6% and distant metastases in 3% of the patients. After a mean follow up of 30 mo, the median survival was 53 mo. A multivariate analysis showed as independent prognostic factor the histological type of the mesothelioma, the level of cytoreduction achieved, lymph node metastases, and the possibility to perform HIPEC.

PRIMARY PERITONEAL CARCINOMA

Primary peritoneal carcinoma (PPC), was described for the first time by Swerdlow[3]. Its pathogenesis has been controversial. Some Authors believe that PPC develops from a malignant transformation of embryonic germ cell nests cells[4], other from the celomic epithelium lining the abdominal cavity (peritoneum) and the ovaries (germinal epithelium), manifesting a common response to an oncogenic stimulus[5]. A multifocal origin have been suggested by Muto *et al*[6] with clonality studies, while other authors suggest an unifocal origin[7].

Even if from an histological and a clinically point of view PPC is similar to advanced epithelial ovarian cancer, it diffusely involves the peritoneum by papillary carcinoma in the absence of an obvious primary site and grossly normal ovaries[8]. It accounts for 10% of all pelvic serous carcinomas. Most reported cases of PPC have been described in women, usually elderly; however, rare cases have been reported in children and males. Histologically most reported PPC cases are primary peritoneal serous papillary carcinoma, while rarely are they are described as peritoneal mixed epithelial carcinoma and malignant mixed Mullerian tumor.

The prognosis of PPC is poor, the median survival time ranging between 7 and 27.8 mo; 5-year survival rates range from 0% to 26.5%[9].

PPC diagnosis cannot be easily made preoperatively, being typically made by exclusion after both operative assessment and pathological study. In fact if ovaries seem normal with widespread disease elsewhere in the abdomen, PPC may be considered as a diagnostic possibility. However, because surface involvement of the ovaries is present in approximately 96% of the cases, the distinction between extra ovarian primary peritoneal cancer and epithelial ovarian carcinoma may only be made after histological examination to evaluate the extent of ovarian invasion by tumor[10].

Therefore, surgery remains critically important for both diagnosis and therapy of PPC. Once the diagnosis has been established and the extent of disease documented, maximal cytoreduction becomes the primary goal of the procedure. Excision of all visible implants is the hallmark of cytoreductive efforts. To the best of our knowledge, no study has been conducted assessing the efficacy of CRS with HIPEC for this kind of carcinomatosis, even if it is reasonable that this approach should be taken in consideration in the contest of clinical studies.

PSEUDOMYXOMA PERITONEI

Pseudomyxoma peritonei (PMP), a syndrome firstly described by Rokitansky in 1842, is an enigmatic, often fatal intra-abdominal disease characterized by gelatinous ascites and multifocal peritoneal epithelial implants secreting copious globules of extracellular mucin. This condition is almost always due to a perforated epithelial appendix cancer. Three pathologic variant of PMP are known: disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA), and peritoneal mucinous carcinomatosis with intermediate or discordant features.

The natural history of this disease has been drastically changed by the introduction of CRS combined with HIPEC. Ronnett *et al*[11] found a significant difference in the prognosis of patients affected by this three different form of PMP. The most important prognostic variable affecting 10 years survival rates are the possibility to achieve CC0-CC1 (the more the complete cytoreduction, the longer the survival) and the pathological feature of PMP. Deraco *et al*[12] reported an overall 10 years survival rate of 78.9% in patients affected by PMP and treated with CC0-CC1 CRS, while no patient with CC2-CC3 CRS survived 10 years. Patients affected by DPAM had a 10 years survival of 67% while those affected by PMCA had no more than 40.7% 10 years survival rate. Baratti *et al*[13] recently published a study on prognostic

value of serum tumor markers in patients with PMP undergoing CRS and HIPEC. It is clear that pre-operative normal values of C385 were statistically related to the ability to perform an adequate cytoreduction and that elevated pre-operative values of C17.9 were associated with reduced progression-free survival. CEA has also been shown to have good sensitivity in case of progression. Chua *et al*[14] published the results of a retrospective multi-institutional study. The purpose of this study was to evaluate outcome and long-term survival after CRS and HIPEC in PMP patients. The registry included 2296 patients from 16 centers with a mean PCI of 20, CCR0/1 was achieved in 83%, mortality was 2% and major morbidity was 24%. Median survival was 196 mo, disease free median survival was 98 mo, and 10 and 15 years survival was respectively 63% and 59%. Multivariate analysis have identified as negative prognostic factor for overall survival: previous chemotherapy courses, PMCA histological type, major postoperative complication, CCR 2/3, older age, while negative prognostic factor for progression free survival were all the above plus high peritoneal cancer index and not using HIPEC.

PERITONEAL CARCINOMATOSIS FROM GASTRIC CANCER

Penetration of the gastric serosa and lymphatic spread are the two most important factors affecting prognosis in gastric cancer (GC)[15-17]. When the gastric serosa is infiltrated by tumor, PC becomes pravery frequent[18]. Subsequently, up to half of the patients with advanced gastric cancer (AGC) will develop a peritoneal carcinomatosis in spite a radical surgery[19-22], and PC is quite common in gastric cancer, being already present in 5%-20% of patients explored for potentially curative resection[18,23]. There are several methods for detecting the presence of free peritoneal tumor cells (FPTC) with different sensitivity[24-26]. FPTC in the washing could be identified in up to 24% of stage IB and up to 40% of stage Ⅱ or Ⅲ GC patients[27]. Moreover, after radical resection, the peritoneum is the only site of recurrence in 10%-34% of cases, and one of the recurrences sites in 29%-44% of cases[28-32].

The five-year survival rate in patients with peritoneal carcinosis from GC (PCGC) is lower than 3%[33], with an overall mean and median survival of 6.5 and 3.1 mo, respectively[34]. Among the non-gynecologic malignancies, PCGC has a better prognosis than PC from pancreatic cancer but worse than PC from CRC[34]. Saito *et al*[35] reported a 5-year survival rate of advanced GC with FPTC of 15.3%, similar to that of patients having macroscopical peritoneal metastasis (14.8%). As a counterpart, there are no 5-year survivors among patients with distant peritoneal metastases.

Systemic chemotherapy may improve median survival up to 12 mo in advanced/metastatic GC[36-39], but a similart survival benefit has not been reported in macroscopic PC[40-43]. One possible explanation seems to be that systemic chemotherapy inadequately reaches the abdominal cavity[44]. Yonemura *et al*[45] demonstrated a survival benefit by treating patients with PFTC with radical resection followed by adjuvant systemic chemotheraphy. Patients treated with adjuvant chemotherapy survived significantly longer than patients in control group: the 1 and 2-year survival rates were 88% and 44%, and 53% and 9%, in adjuvant group and control group, respectively. The mean overall survival was 21.1 and 9.1 mo for adjuvant and control group ($P < 0.05$). The ineffectiveness of systemic chemotherapy in PC may be related to a number of factors, such as the peritoneal-plasma barrier, the intraperitoneal poor blood supply and oxygenation of cancer cells, and the low apoptotic potential of such hypoxic tumor cells[37,46-48]. Neoadjuvant chemotherapy (NACT) has been described to decrease the load of macroscopic PCGC[37,49]. Yano *et al*[50] reported a small series of 4 out of 26 (15.4%) patients affected by PCGC with complete remission of peritoneal metastasis with after NACT. All these patients subsequently underwent curative resection. Inokuchi *et al*[51] reported a partial response in 9 out of 13 patients (69%). However,one further study suggests that after NACT the detection of FPTC can change from positive to negative and vice versa. This change is not linked to the response to the systemic chemotherapy. Ten out of 42 (24%) patients with negative peritoneal cytology shifted into positive for FPTC during NACT, while 7 out of 19 (37%) with FPTC positive cytology at staging laparoscopy turned negative[52].

GC peritoneal spread remains a major problem, and some Authors finally suggest that there is no role for surgery in PCGC[53]. Since the 80s, Japanese surgeons combined CRS, regional hyperthermia and intraperitoneal chemotherapy in a multimodal approach[54]. As for other types of PC, in GC HIPEC after CRS is accomplished to eliminate FPTC and to prevent or delay PC[53,55]. A number of studies have been conducted, with the aim to demonstrate a significant reduction in the rate of subsequent PC and an increase in survival of patients with AGC when radical surgery was combined with HIPEC[20,56-61]. Yonemura *et al*[62] demonstrated that HIPEC could improve significantly the median survival from 15 to 48 mo and the 5-years survival rate from 12% to 42% in patients with PFTC. On the other hand, the combined CRS and HIPEC treatment of PCGC seems to be the one with less encouraging results in terms of survival and of morbidity and mortality when compared to other types of PC[63,64]. A French retrospective, multicenter study published in 2010 evaluated toxicity and significant prognostic factors after CRS and HIPEC (and/or early postoperative intraperitoneal chemotherapy, EPIC) for PC from nongynecologic neoplasms[65]. The study involved 1290 patients from 25 French institutions who underwent 1344 CRS procedures between 1989 and 2007. HIPEC was made in 1154 cases (86.4%). The principal origin of PC was CRC (n = 523, 40.5%), and no more than 159 GC cases were present in this series

(12.3%). The whole group overall 3- and 5-year survival rates were 49% and 37% respectively. The PCGC group showed the worse outcome with a 3- and 5-year survival rates of 18% and 13%, respectively. The overall median survival of the whole group and of the PCGC group were 34 and 9 mo respectively. Li *et al*[66] from China reported in 2010 a series of 128 patients with PCGC. Fifty-four (42.2%) underwent gastrectomy, and 10 underwent resection with HIPEC. The other 74 (57.8%) received non-resection surgery. The median survival in the unresected group was 6 mo compared to 11.8 mo of the resected patients. Moreover, they observed a significantly improved survival in the patients treated with surgery and HIPEC compared to those treated with surgery alone[67]. Post-operative complications were more frequent in the HIPEC than in the resection alone group (20.0% *vs* 13.2%, $P = 0.34$). Yang *et al*[68] published the final results of a phase Ⅲ randomized trial, performed in China in order to evaluate the efficacy and safety of CRS plus HIPEC for the treatment of PCGC. The median overall survival was 6.5 mo in CRS alone group and 11 mo in the CRS + HIPEC group ($P = 0.046$). This outcome was even more significant in patients with synchronous PCGC ($n = 51$), being the median overall survival 12 mo in CRS + HIPEC group ($n = 24$) and 6.5 mo in the CRS group ($n = 27$, $P = 0.029$). The 1-, 2-, and 3-year survival rates were 29.4%, 5.9% and 0% for CRS group, and 41.2%, 14.7% and 5.9% for CRS + HIPEC group, respectively. The CC-score has been demonstrated to influence survival, but HIPEC obtained a significant advantage both in CC 0-1 and CC 2-3 patients. In the CRS + HIPEC patients, the median overall survival in CC 0-1 ($n = 20$) and in CC 2-3 subgroups ($n = 14$) was 12 and 8.2 mo respectively. In CRS patients, the median overall survival in CC 0-1 ($n = 20$) and in CC 2-3 subgroup ($n = 14$) was 11 and 4 mo respectively. Serious adverse events arose in 9 patients, 4 in the CRS group (11.7%) and 5 in the CRS + HIPEC group (14.7%) ($P = 0.839$). Multivariate analysis recognized CRS + HIPEC, synchronous PC, CC 0-1, systemic chemotherapy and no serious adverse events as major independent predictors for better survival. HIPEC was about 2.6 times likely to increase survival.

Gill *et al*[67] published a systematic review analyzing survival, mortality and morbidity in the treatment of PCGC with CRS and HIPEC. Ten studies were included. Overall median survival was 7.9 mo. In the subgroup of patients with residual nodules after CRS, less than 0.25 cm in size, the median survival raised up to 15 mo. The 1- and 5-year survival were 43% and 13%. The treatment-related mortality rate was 4.8% and the morbidity was 21.5%.

Recently, Yonemura *et al*[61], proposed a multimodal strategy which associates neoadjuvant intraperitoneal and systemic chemotherapy (NIPS), CRS + HIPEC and early postoperative intraperitoneal chemotherapy (EPIC). The rationale of this method is to reduce tumor burden before surgery with NIPS, a bidirectional chemotherapy that attacks PC from both sides of peritoneum (from the peritoneal cavity and from sub-peritoneal blood vessels), and reducing macroscopic and microscopic PC with CRS + HIPEC. At the end, the use of EPIC is proposed to eradicate residual intraperitoneal cancer cells before fibrin and adhesion development. Authors recommend two cycles of NIPS to achieve a negative cytology status. Severe complication post-NIPS have been reported in 4 out of 79 patients. This strategy allowed to obtain a change in washing cytology from positive to negative in 41 out of 79 patients (63%).

Three recent meta-analysis of randomized trials analyzing patients with advanced GC (with or without PC) demonstrated the survival benefit offered by HIPEC[69-71].

In the last ten years, a new drug for intraperitoneal treatment of GC has been developed in Germany. Catumaxomab (trade name Removab®) is a rat-mouse hybrid monoclonal antibody that is made up of one "half" (one heavy chain and one light chain) of an anti-Epithelial cell adhesion molecule (EpCAM) antibody and one half of an anti-CD3 antibody, thus finally binding both EpCAM and CD3. EpCAM is an epithelial differentiation antigen that is expressed on normal epithelial cells and on almost all carcinomas (especially gastrointestinal and ovarian carcinomas) and functions as cell adhesion molecule[72]. In addition, the Fc-region can bind to an Fc receptor on accessory cells like other antibodies, which has led to calling the drug a trifunctional antibody. Actually Catumaxomab is used to treat malignant ascites, because of the intraperitoneal application of this anti-EpCAM antibody has shown significant benefits in puncture-free survival (survival without repeated paracentesis) for patients with malignant ascites in a phase Ⅲ randomized trial[73]. This study demonstrated no statistically significant increases in median overall survival for other cancers, while in patients with GC a small survival increase was associated with the use of Catumaxomab[73]. Progression-free survival has been analyzed in a phase Ⅱ studie with the use of intraperitoneal catumaxomab in gastrointestinal $EpCAM^+$ tumors[74]. Furthermore two phase 2 studies are ongoing (follow-up phase), evaluating resectable advanced GC patients treated with adjuvant intraperitoneal Catumaxomab.

In conclusion, in PCGC CRS and HIPEC proved with good evidence to improve survival with acceptable morbi-mortality. It is very important to obtain the diagnosis and the diffusion grade of PCGC before the CRS and HIPEC with the use of staging laparoscopy. The role of surgery is fundamental, complete cytoreduction demonstrated to be strictly related to an improvement in survival. In patients with PCGC, multimodal treatment should be mandatory, leaving a pivotal role to HIPEC after CRS.

PERITONEAL CARCINOMATOSIS FROM OVARIAN CANCER

Nowadays, the treatment diagram for advanced EOC

has been universally accepted as a combination of maximal CRS and adjuvant chemotherapy, including cases with grossly peritoneal diffuse disease. Grade ⅢC and Ⅳ are no longer considered as "lost". Different studies demonstrated that a progressively more aggressive surgical effort is associated with improvements in disease-free and overall survival rates. It is suggested that aggressive surgery should be performed in dedicated centers with high volume of cases, offering in-hospital mortality significantly lower than low volume ones[75]. The more the surgeon became radical and increases his/her surgical volume, the more he/she prolongs the disease-free and overall survival and reduces the in-hospital mortality. As a counterpart, the tumor biology and the initial disease diffusion have been suggested as the most important factors in survival benefit of surgery[76-79]. It's still undefined how the intrinsic features of the tumor make intra-abdominal implants easier to remove[80]. In general, upper abdominal tumor implants are suggestive of an aggressive tumor biology[81]. Covens and Berman criticized the role of CRS in advanced EOC. They proposed that both survival and surgical resectability are mostly determined by tumor biology instead of the operative effort by the surgeon[82,83]. The retrospective review of data from the Scottish Randomized Trial in Ovarian Cancer revealed in a population of 889 patients with disease stage ranging from IC to Ⅳ that the benefit of optimal debulking surgery seems to depend from the extent of disease before surgery[79]. Hager *et al*[84] analyzing 456 women with advanced stage Ⅲ/Ⅳ ovarian cancer, demonstrated no correlation between nodal status and survival. Moreover in advanced EOC nodal status was not a prognostic factor for patients undergone to optimal cytoreduction.

Complete cytoreduction is reached when no visible tumor remains after the surgical procedure. Starting from this classification a number of prospective and retrospective studies have been conducted to investigate the feasibility and the impact on survival of CRS in advanced EOC.

Up to now, the majority of available series report cases treated with the standard systemic platinum-taxanes chemotherapy and CRS. Only one study analyzed cases treated also with intraperitoneal chemotherapy[85].

Between 2003 and 2010, 15 studies have been published analyzing patients treated with CRS and systemic chemotherapy for advanced EOC. The overall survival (OS) ranges between 46.5 and 106 mo for patients with complete CRS (no residual disease) and between 12 and 39 mo for incomplete CRS (residual disease of more than 1 cm)[85-92]. All these papers demonstrated that CRS plays a central role in advanced EOC treatment. The necessity of adjuvant chemotherapy has already been demonstrated. Surgical effort must be absolute.

Between 2000 and 2010, 20 observational studies have been published about CRS + HIPEC in treating PC from advanced and recurrent EOC. The first was published by Cavaliere *et al*[93] reporting about 20 patients with recurrent EOC. They reported a median OS of 25 mo with a 3-year survival of 50%.

De Bree *et al*[94] and Chatzigeorgiou *et al*[95] reported about 19 and 20 patients respectively with recurrent ovarian cancer. They found median DFS of 26 and 21 mo, respectively. De Bree reported a median OS of 54 mo and Chatzigeorgiou a median OS for optimally cytoreducted patients (considered as residual disease of < 1.5 cm) of 29 mo. De Bree found a 3 and 5 year survuival of 63% and 42%. Both studies reported a perioperative mortality rate of about 10%.

Four studies have been published in 2004[96-98]. Zanon *et al*[96] described a cohort of 19 patients with recurrent EOC. They reported a median DFS of 17 mo with a median OS and OS in optimally cytoreducted patients (residual disease < 0.25 cm) of 28 and 38 mo respectively. Three and 5-year survival were 35% and 12% respectively. Perioperative mortality rate was 3 % with grade 1 or 2 morbidity rate of 27% and 3% respectively and with grade 3 and 4 morbidity of 7%.

Piso *et al*[97] reported a series of 19 patients with peritoneal carcinomatosis due to primary or recurrent EOC. The median DFS was 18 mo, with mean OS and OS in optimally cytoreducted patients (residual disease < 0.25 cm) of 33 and 44 mo respectively and a 5-year survival rate of 15%. Perioperative mortality rate was 3%, grade 1-2 morbidity rate was 10% and grade 3-4 morbidity of 10% and 15% respectively[97].

Ryu *et al*[98] reported a series of 57 patients with advanced EOC. The median DFS was 26 mo. Median OS in optimally cytoreduced patients (residual disease < 1 cm) was 41 mo. The OS at 5-year was 54%. The survival advantage has been found to be more pronounced in stage 3 disease. Multivariate analysis showed HIPEC as an independent prognostic factor. Perioperative mortality was 4 % with grade 1, 2 and 4 morbidity rate of 14%, 5% and 4%, respectively.

Gori *et al*[99] and Reichman *et al*[100] reported about 29 and 13 patients respectively with advanced EOC. Median DFS were 15 and 11 mo respectively, with a median OS in Gori's paper of 64 mo and a 3-year survival rate in Reichman's study of 55%. None of these two studies reported morbidity nor mortality.

Raspagliesi *et al*[101] and Rufián *et al*[102] published two reports with 40 and 33 patients respectively, with advanced and recurrent EOC. Median DFS and OS in the first paper were 11 and 32 mo, and median OS and OS in optimally cytoreduced patients (residual disease < 1 cm) were 48 and 66 mo respectively. Five-year survival in Raspagliesi' series was 15%; 3 and 5-year survival rate in Rufian study were 46% and 37%, respectively. Reported mortality for both papers was 0%. Raspagliesi reported 20% of grade 1 morbidity. Rufian reported grade 1 and 2 morbidity rate of 12% and 10% and grade 3 and 4 morbidity of 10% and 6% respectively.

Helm *et al*[103], Cotte *et al*[104] and Bae *et al*[105] published series of 18, 81 and 67 patients with recurrent (Helm and Cotte) and advanced EOC (Bae). Helm *et al*[103] reported a median DFS of 10 mo and median OS and OS

in optimally cytoreduced patients (residual disease < 0.5 cm) was 31 and 31 mo respectively Perioperative mortality was 6% and grade 1, 2, 3 and 4 complications have been reported in 11%, 50%, 40% and 13% of patients respectively.

Cotte *et al*[104] described a median DFS of 19 mo and an OS and OS in optimally cytoreduced patients (residual disease < 0.25 cm) of 28 and 55 mo respectively. Perioperative mortality was 3% and grade 1, 2, 3 and 4 complications have been reported in 6%, 1%, 5% and 2% of patients respectively.

Bae *et al*[105] reported a 5-year survival rate of 66%, with a 0% perioperative mortality and grade 1, 2, 3 and 4 morbidity rate of 14%, 13%, 0% and 0%, respectively.

Di Giorgio *et al*[106] published data about 47 patients with advanced and recurrent EOC. They reported a median DFS of 20 mo with an OS and OS in optimally cytoreduced patients (residual disease < 0.25 cm) of 24 and 26 mo respectively. Five-year survival rate was 17% and perioperative mortality 4%. Grade 2, 3 and 4 complication rate were 21%, 9% and 13% respectively.

Bereder *et al*[87], Guardiola *et al*[107], Fagotti *et al*[108], Pavlov *et al*[109] described results of CRS + HIPEC in advanced and recurrent EOC and in recurrent EOC.

Guardiola *et al*[107] published a series of 47 patients with a median DFS of 14 mo and a 5-year survival of 63%. Perioperative mortality rate was 0% and grade 4 complication rate was 13%. Fagotti *et al*[108] reported a median DFS of 10 mo, with 0% perioperative mortality and grade 2, 3 and 4 complication rate 36%, 8% and 8% respectively. Pavlov *et al*[109] described 56 patients with a median DFS and OS of 26 and 38 mo respectively. Perioperative mortality was 2% and grade 1, 2 and 4 complication rate were 5%, 11% and 2% respectively. Bereder *et al*[87] published the widest series reporting about 246 patients with advanced and recurrent EOC. Median DFS was 13 mo, median OS and OS in optimally cytoreduced patients (residual disease < 0 cm) were 49 and 56 mo respectively. Three and 5-year survival were 60% and 35%. Reported intraoperative mortality was 0.4% and grade 3 morbidity 12%.

Lastly, Deraco *et al*[110] published a multi-institutional phase 2 study evaluating the impact of CRS + HIPEC as upfront treatment on PFS and OS in 26 women with stage 3-4 advanced EOC. All enrolled patients underwent CRS, followed by HIPEC. Patients were then treated with adjuvant systemic chemotherapy. Macroscopically complete cytoreduction was achieved in 57% of patients, with minimal residual disease (≤ 2.5 mm) remaining in the other 43%. Five-year OS was 60.7% and 5-year DFS 15.2%. Excluding operative death, all the patients underwent a median of 6 cycles of systemic chemotherapy at a median of 46 d from combined treatment. Four patients experienced ≥ grade 3 morbidity, with one post-operative death due to sepsis.

Globally, 7 randomized controlled trials evaluating the effectiveness of HIPEC in advanced and recurrent OEC have been proposed: five are already ongoing[111-115] and two have been only proposed[116].

Ansaloni *et al*[117] reported about 39 patients with advanced and recurrent EOC. The mean DFS was 14 mo. Grade 1-3 post-operative complications occurred in 18% of patients. Perioperative mortality was 0.3%.

In conclusion, despite the lack of high evidence data that will be brought from the ongoing randomized trials, HIPEC associated to complete CRS seems to give survival results comparable to the standard treatment. Data are still heterogeneous due to the different meaning given to the completeness of cytoreduction, as showed in all the aforementioned studies. Some centers consider cytoreduction complete when there is no macroscopic residual disease, others follow more permissive limits. Moreover, confusion exists about "optimal" and "complete" cytoreduction. However, data clearly show as in patients with no macroscopic residual disease CRS + HIPEC increases the survival rates. These results could be overcome in terms of surgical effort and morbidity rate reduction by the use of NACT.

PERITONEAL CARCINOMATOSIS FROM COLO-RECTAL CANCER

The multi-disciplinary treatment of CRC is actually standardized up to stage ⅢC[118-120], while it is unclear and not supported by strong evidences for stages Ⅳa and Ⅳb. American guidelines from NCI recently consider liver resection as available treatment for Ⅳa stage, but they don't mention nowadays HIPEC as treatment option for Ⅳb CRC, including the peritoneal carcinomatosis (PCCRC).

Another way to assess the actual relationship between HIPEC for PCCRC and Evidence Based Medicine is to measure the percentage of ongoing trials from the NCI database: worldwide, among 239 active registered trials on Ⅳb stage CRC, only eight include HIPEC as keyword (2 phase Ⅲ, 4 phase Ⅱ and 2 phase Ⅰ trials: from www.cancer.gov, consulted 26th of June 2013). The only concluded randomised clinical trial comparing systemic chemotherapy with cytoreduction plus HIPEC is the Dutch trial published in 2003[121]: 105 patients with PCCRC without evidence of hematogenous metastases enrolled between 1998 and 2001 were randomly allocated to receive 5-fluorouracil and leucovorin with or without palliative surgery or "aggressive" cytoreduction plus HIPEC followed by the same chemotherapy regimen. They demonstrated a median overall survival of 22.3 mo for the HIPEC arm against 12.6 mo for the standard therapy, with a significant difference (P = 0.032). Unfortunately, the value of this RCT is limited by several factors: it was based on a chemotherapy scheme that is not the actual gold standard (not including *i.e.*, Irinotecan and Oxaliplatin); appendiceal (n = 18) and rectal (n = 12) tumors were not balanced in the two groups; the HIPEC protocol was based only on mitomycin C in the perfusate; the role of surgery in the control arm was unclear and impossible to determine on available data. Another randomized trial was designed by Elias to com-

pare early postoperative intraperitoneal chemotherapy plus systemic chemotherapy with chemotherapy alone after complete cytoreductive surgery for the PCCRC treatment. In 2000, after 4 years and only 35 patients enrolled, the study was stopped and the partial results analysis did not demonstrate any advantage in term of survival[122].

Another attempt to design a RCT comparing standard systemic therapy with CRS + HIPEC + chemotherapy is the USMCI8214/ACOSOG Z6091 trial[123], a well designed study, trying to overcome the Dutch trial limitations, with a specific target population (peritoneal carcinomatosis only, colon cancer) and using advanced/state-of-the-art chemotherapy. This trial recently closed, failing to meet accrual and amplifying the concerning from Elias *et al*[122] about the feasibility of this kind of studies: basically, even if few trials are active nowadays (in particular the last could be the PRODIGE 7 French trial[124], with 150/280 patients enrolled at January 2012), the idea to get a level of evidence I a/ I b in support of HIPEC for PCCRC is near to be abandoned.

Anyway, the Dutch study was the base for several other trials more adequate and focusing on singular aspect, but without the same level of evidence: in particular three case control studies (evidence Ⅲa) have been published between 2009 and 2011. Elias *et al*[125] had the merit to include the oxaliplatin at 460 mg/m^2 dose in the perfusate, plus Irinotecan in 18/48 patients, comparing the HIPEC group with a standard therapy based on 5-fluorouracile (5-FU), folinic acid and systemic postoperative oxaliplatin (OX) or Irinotecan (IRI). They reached the impressive median survival of 63 mo, with a 5-year survival rate of 51% for the HIPEC group patients with a complete CRS. Franko *et al*[126] compared 67 patients treated with mitomycin C-based HIPEC with 38 controls and all the 105 patients received 5-FU, IRI, OX and bevacizumab/cetuximab. Unfortunately they included patients with liver metastases and the use of OX and target therapies was greater in the HIPEC group (78% *vs* 18% and 59% *vs* 18% respectively). Chua *et al*[127] included 294 patients, comparing supportive care and palliation with postoperative systemic chemotherapy based on 5-FU, IRI, OX, Capecitabine and monoclonal antibodies, with or without HIPEC (low-dose mitomycine C) and EPIC (high dose 5-FU). The difference between curative or palliative therapy was based on preoperative assessment of the Peritoneal Surface Disease Severity Score

Among not randomized, retrospective multi-institutional studies, the largest published series comes from the French registry, including 523 patients with PCCRC treated from 1990 to 2007 with CRS and HIPEC[128]. Even if a 16% of incomplete CRS, with macroscopic residual (CCR-1) makes it difficult to extrapolate data about survival and the great number of participants centres adds variability (relating in particular to learning curve and surgical standardization), the reported 30-d mortality was only 3%, absolutely lower than in the Dutch trial (8%).

The peritoneal cancer index (PCI) is a semi-quantitative powerful tool, easily reproducible and validated by several studies and expert consensus[129-132], which aims at defining and measuring the peritoneal involvement. However, using PCI to select PCCRC patients and to guide the therapeutic strategy need some comments: a threshold value to get a formal contraindication to CRS + HIPEC is not available today; a PCI greater than 20 is associated with a worse prognosis, even if in a small series (24 patients). Elias *et al*[133] described a significant advantage in survival even when PCI was over 24; for PCI < 10, there is agreement about the usefulness of CRS + HIPEC, and the median survival for these patients ranges from 31 to 48 mo[128,134-136]; similar data are provided by Gilly *et al*[137]; in currently active trials a high PCI value is generally not an exclusion criteria; different studies from the same center stressed the difference between the PCI declared at the beginning and at the end of surgery, suggesting to systematically add 2 point at the preoperative score[138]; Sugarbaker *et al*[139] suggest to correlate PCI with patients demographic when deciding to add or not HIPEC to their therapeutic scheme.

Pioneering studies about chemotherapeutic agent penetration in the tumor were available since early 90s[140,141] and have recently been confirmed[142], showing, for example, a diffusion depth of about 1-2 mm for Mitomycin C[143]. Nevertheless, even if the rationale is something more than the common principle of resect as more tumor as possible, the attitude to consider useful HIPEC only after an adequate CRS is a recent acquisition. Moreover, there is no accordance on the dimensional cut-off (1, 2.5 or 5 mm) and in different series the impact of CCR on survival varies enormously[129,131,136,144]. In particular, if the role of macroscopic residual (CCR-2) nodules seems clear and formally contraindicate HIPEC, it is unclear the difference between nothing (CCR-0) and very small nodules (up to 2.5 mm, CCR-1 in some series). Indeed, even in CCR-1 cases, CRS + HIPEC was reported to be related to a better prognosis[134,145-147].

Surprisingly, the tumor progression during neoadjuvant chemotherapy is not demonstrated to be an independent prognostic factor as for gastric cancer with PC and actually is not a formal contraindication to CRS + HIPEC[148,149].

As for other organs and pathologies, in the treatment of PCCRC the acronym HIPEC correlate to a wide spectrum of possible variation in temperature, molecules, concentration and contact time[129,131,134,145,146,150,151]. The associated systemic chemotherapy is highly variable too. This great number of parameters makes a standardization difficult: the statement from Elias *et al*[124] on the necessity to follow the most experienced centers protocols is acceptable and functional, though not methodologically correct. Finally, the lack of evidence suggests the enrollment of as many patients as possible into well designed randomized trials.

Among the most significant HIPEC protocols, those based on Oxaliplatin in the perfusate have to be report-

ed. From first demonstrations of the rationale[152] and the pharmacokinetic[153] during hyperthermic application, few phase Ⅱ trials included OXt in their protocols[145,154]. In particular, Elias *et al*[133] published a series of 24 patients treated with Oxaliplatin in the perfusate at 460 mg/m^2 in 2 L/m^2, during 30 min at 43 ℃ and later a revised protocol including 106 consecutive patients treated with lower dose of oxaliplatin (360 mg/m^2) combined with irinotecan (360 mg/m^2) in 2 L/m^2 of 5% dextrose, for the same time at 43 ℃. The usefulness of the Irinotecan association is controversial and may be the cause of an increased toxicity[155].

Starting from 1995, several attempts were done to clarify the relationship between the primary tumor pathology and the outcome of PCCRC: tumor site (appendix, colon and rectum), grading, nodal and liver metastases were analyzed[130,131,146,150,156-158]. Following the substantial failure of this search (no strong correlation at several multivariate analysis), researchers lost their attention on tumor demographic in more recent publication, maintaining some interest only for tumor size[159]. Moreover, earlier reports on HIPEC suffered from the very small number of included patients, making any stratification impossible. However, beside their role as independent prognostic factors, tumor characteristics are mandatory to get a better stratification, given that the only outcome parameter used is the overall survival, whereas only few studies considered quality of life and PC-free survival[160-162].

The combined treatment of synchronous liver metastases in patient with PCCRC is beyond the scope of this review, but this topic is strongly related to HIPEC: a variable percentage of patients included in retrospective studies underwent at the same time liver resection and CRS[128-130,145,163,164]; the report of a different impact of liver metastasis in patient accordingly to the CCR (with a significant prognostic negative value only for CCR-0 patients) underlines the possible different meaning of these two types of tumor spread ("local" *vs* "systemic"); even if a liver metastasis is not considered an absolute but only a relative contraindication to HIPEC, it seems logical that all the randomized recently designed study on HIPEC should exclude cases with liver involvement.

Currently, the main research effort is forwarded to RCTs evaluating mandatory second-look surgery with CRS + HIPEC in patients at high risk of developing PCCRC versus standard of care (control arms)[165]. Background for this new field of interest mainly are: increasing importance assigned to metachronous PC in the natural history of the tumor; definition of parameters to estimate the risk of secondary PC[166], including synchronous completely resected PC, ovarian metastases, perforated primary tumor and in some experiences pT$_4$ tumor, colon occlusion and positive peritoneal cytology[124,167]; a great percentage of asymptomatic and work up negative high risk patients were diagnosed to harbor macroscopic PC during second look laparotomy at one year[168]. As expression of the two main groups working on HIPEC for CRC (American and French), two different RCTs are enrolling patients to demonstrate the usefulness of an early second look treatment for high risk patients to detect and treat (with CRS + HIPEC) metachronous PC, with acceptable morbidity and mortality[165].

In summary, to date there is no level Ⅰ or Ⅱ evidence that HIPEC increases the survival of patients with PC-CRC when added to modern perioperative chemotherapy protocols. The role of a complete cytoreduction, even if well recognized as beneficial and mandatory to allow a rational use of HIPEC, is not supported by RCTs.

In this lack of evidence, there are two opposite attitudes: the NCI does not even mention HIPEC among the treatment options, while the French guidelines recommended it in the treatment of patients with PC from CRC.

Beside its role as prognostic factor, the PCI is a fundamental tool to guide toward a tailored therapy, shifting from the idea of a threshold value to a parameter integrating with every tumor biology data and the clinical status of the single patient.

The next goal will be the demonstration of the usefulness of the "second-look strategy" for high risk patients in terms of overall survival and PC-free survival.

CONCLUSION

Peritoneal carcinomatosis is a real challenge for oncologists and surgeons, which treatment is very difficult. Many surgeons and oncologists are still use to raise the white flag in discovering them. The loco-regionality of PC and the real characteristic and barrier ability of peritoneum with its proper lymphatic system have not still sufficiently investigated.

Substantial differences exist in treating the different form of PC from different diseases among different centers and countries. Consequently different evidences in results still remain and are undoubtedly discussed. For this reason the chemosurgery (association of chemotherapy and surgery as one entity) is not yet considered as a definitive valid option.

The different forms of PC from different diseases should not continue to be treated in unique centers. Advanced diseases should be centralized in all countries, and centers performing chemosurgery should not continue to treat all diseases, but disease-specialized centers should start to apply chemosurgery to the different forms of PC. The major risk is to lose the link between the PC and the primary tumor: waiting for a better understanding of the peritoneal diffusion pathophysiology and trying to redefine its prognostic role, it would be prudent to mention the pathological classification of the primitive tumor, that is frequently missed.

Lastly, to increase knowledge and overcome the actual limits, we all need a big effort toward a multidisciplinary approach, selection and discussion of the different cases with a reciprocal knowledge increase. More importance and credit should be given to translational medicine.

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