Peritoneal carcinomatosis from unusual cancer origins: Is there a role for hyperthermic intraperitoneal chemotherapy?


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Summary

Introduction: Complete cytoreductive surgery (CCRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) is the gold standard for curative treatment of peritoneal carcinomatosis (PC) arising from colorectal cancer, peritoneal mesothelioma and peritoneal pseudomyxoma peritonei (PMP). The results of HIPEC remain controversial in PC that originates from ovarian cancer, stomach cancer, neuroendocrine tumors, or sarcoma. HIPEC has also been used, although very rarely, for other malignant carcinomatoses. Its use has been exceptional due either to the rarity of the tumor or because such disease is usually widespread and rarely confined to the peritoneum. The aim of this study was to evaluate the results of CCRS plus HIPEC in patients with PC of unusual origin.

Methods: We performed a retrospective analysis of all patients who underwent CCRS plus HIPEC for PC whose origin was neither gastric, ovarian or colorectal carcinoma, nor neuroendocrine tumor, mesothelioma, PMP or sarcoma.

Results: Between 1995 and 2013, 31 patients with 15 PC arising from unusual primary tumors underwent CCRS plus HIPEC. After a median follow-up of 90 months, 10 patients were alive and without recurrence. The overall survival rate at 5 years was 33% with a median survival of 37 months. In univariate analysis, factors of poor prognosis and predictors of recurrence were the performance of immediate postoperative intraperitoneal chemotherapy instead of HIPEC and a peritoneal index > 12. No prognostic impact due to tumor origin could be demonstrated.

Conclusion: The decision to perform CCRS plus HIPEC for PC arising from unusual cancer origins remains difficult. These patients should be prospectively entered into registries of rare tumors that involve the peritoneum in order to better define indications.

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Introduction

Complete cytoreductive surgery (CCRS) associated with hyperthermic intraperitoneal chemotherapy (HIPEC) is the gold standard for curative treatment of isolated peritoneal carcinomatosis (PC) from colorectal origin and rare primary peritoneal cancers, peritoneal pseudomyxoma peritonei (PMP) and peritoneal mesotheliomas [1–6]. For PC arising from ovarian or gastric carcinoma, or neuroendocrine carcinoma, the results of CCRS plus HIPEC remain controversial [7]. Several studies are currently underway, but most expert centers do not recommend HIPEC for these indications outside of a clinical trial [7]. Much more exceptionally, this treatment has been used for PC arising from other origins. These are exceptional cases of PC of non-gastrointestinal origin; however, these cases usually present with diffuse extraperitoneal dissemination and it is rare that dissemination is exclusively limited to the peritoneum. There are also abdominal malignancies with known major peritoneal tropism but whose rarity is such that their description in the literature does not exceed occasional clinical case reports. The objective of this study was to analyze the long-term results of CCRS plus HIPEC in patients with PC of unusual origin.

Methods

All patients treated by CCRS plus HIPEC consecutively at our center for PC arising from origins other than colorectal, gastric, or ovarian carcinoma, neuroendocrine tumor, PMP, mesothelioma, or sarcoma (soft tissue sarcomas [STS] or gastrointestinal stromal tumor [GIST]) were included in this study. Patient data were analyzed retrospectively from a dedicated prospective data collection system. The extent of peritoneal carcinomatosis was routinely measured using the peritoneal index (formerly called the Sugarbaker score) with a range from 1 to 39 [8]. The quality of cytoreductive surgery has been defined according to the "Sugarbaker completeness of cytoreduction score" (CC):

- CC-0: no macroscopic residual tumor;
- CC-1: tumor residua less than 2.5 mm;
- CC-2: tumor residua between 2.5 mm and 25 mm;
- CC-3: tumor residua > 25 mm [8].

Cytoreductive surgery was considered to be complete when a score of CC-0 or CC-1 was attained. Intraperitoneal treatment consisted of either immediate postoperative intraperitoneal chemotherapy (IPIPC) or HIPEC with the abdomen open, the so-called Coliseum technique. The practical details of these procedures have been previously described [9]. Surgical complications were retrospectively graded by the Dindo/Clavien classification [10]. Grade ≥ 2 complications were considered severe. Long-term follow-up was carried out according to the underlying pathology of the PC. Recurrences were diagnosed based on clinical, radiological or histological findings and were consistently confirmed in multidisciplinary conferences.

Statistical analysis was performed using the IBM SPSS statistics software, version 20.0. Categorical variables were compared using the Fisher exact test. A *P*-value < 0.05 was considered the limit for statistical significance.

Results

Between 1995 and 2013, 31 patients underwent CCRS plus HIPEC for PC of unusual origin, representing 3.5% of all patients treated with HIPEC during the same period. There were 18 women (58%) and 13 men (42%), with a median age of 37 years (range: 10–61). Fifteen unusual histologic origins of PC were included and are detailed in Table 1. PC developed metachronously in 19 (61%) patients, appearing after a median of 24 months (range: 6–462) and was the only metastatic site in 22 patients (71%). The median intraoperative peritoneal index was 11/39 with a range of 4 to 28. Cytoreductive surgery was complete in all patients (CC-0: 97%, CC-1: 3%). The median operating time was 330 (range: 150–720) minutes and median blood loss was 300 (range: 0–2100) mL. Regarding the modality of intraperitoneal therapy, 20 patients (65%) had an open abdominal HIPEC and 11 patients (35%) had IPIPC. Postoperative morbidity was 48%. No patient died postoperatively. The median hospital stay was 21 (range: 6–78) days. After a median follow-up of 90 months, 10 patients (32%) were alive without recurrence. Among the 21 patients with recurrence, peritoneal recurrences were most common (81%) and were the only metastatic site in 23% of cases. The overall 5-year survival rate was 33% and median survival was 37 months. In univariate analysis, positive prognostic factors were performance of open-abdomen HIPEC vs. IPIPC (*P*=0.002), and a peritoneal index less than 12 (*P*=0.011) while factors predictive of recurrence were performance of IPIPC vs. HIPEC (*P*=0.049) and a peritoneal index > 12 (*P*=0.048). No predictor of peritoneal recurrence was identified.

Discussion

Since its first description by Spratt et al. in 1980, the treatment of PC by CCRS plus HIPEC has demonstrated a survival benefit for many indications while proving to be ineffective for others [7,11]. However, for PC arising from unusual origins, the evaluation of the benefit of CCRS plus HIPEC is more complex. This work retraces 18 years of experience in the treatment of PC in an expert center, during which time only 31 patients underwent treatment for PC from 15 unusual origins.

Preoperative patient selection

In the absence of available factual evidence, the selection criteria of candidates for CCRS plus HIPEC for PC of unusual origin was initially extrapolated from standard criteria used for the selection of patients with classical indications such as colorectal cancer, mesothelioma, or PMP:

- a patient with a physiological age < 70 years, in good condition and with no major comorbidities;
- a high probability that complete peritoneal cytoreductive surgery could be performed;
- absence of extraperitoneal disease;
- disease responsive to chemotherapy or only slowly progressive.

To these criteria, we must now add a fifth – the primary origin of carcinomatosis.

In retrospectively interpreting the selection of patients in our series, the median age of 37 years easily fulfills the first criterion but it could also reflect a different tumor
HIPEC in peritoneal carcinomatosis from unusual cancer origins

<table>
<thead>
<tr>
<th>Tumor of origin giving rise to PC</th>
<th>Total</th>
<th>Isolated PC</th>
<th>Metachronous PC</th>
<th>Median tumor-free interval (months)</th>
<th>Median peritoneal index</th>
<th>Median follow-up after HIPEC (months)</th>
<th>Death during follow-up period</th>
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<tr>
<td>Desmoplastic small round cell tumor</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>N/A</td>
<td>21</td>
<td>29</td>
<td>3</td>
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<td>Adrenocortical carcinoma</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>12</td>
<td>11</td>
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<td>3</td>
<td>0</td>
<td>N/A</td>
<td>11</td>
<td>20</td>
<td>1</td>
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<tr>
<td>Fibrolamellar hepatocellular carcinoma</td>
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<td>1</td>
<td>1</td>
<td>11</td>
<td>7</td>
<td>37</td>
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<tr>
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<td>2</td>
<td>168</td>
<td>10</td>
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<td>75</td>
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<td>2</td>
<td>2</td>
<td>47</td>
<td>13</td>
<td>44</td>
<td>0</td>
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<tr>
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<td>2</td>
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<td>11</td>
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<tr>
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<td>1</td>
<td>159</td>
<td>4</td>
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<td>103</td>
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<td>100</td>
<td>6</td>
<td>15</td>
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<td>6</td>
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<tr>
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<td>1</td>
<td>24</td>
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<td>41</td>
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</table>

PC: peritoneal carcinomatosis; N/A: non applicable.
biology from classic indications that typically involve older patients. This young age could also explain our marked willingness to push the boundaries of care. Our attitude was not to propose HIPEC unless the second, third, fourth criteria were also met; our results therefore only apply to these selected patients. It should nevertheless be noted that the tumor progression slope depends very specifically on the underlying histological type; we will further develop this concept. Beyond the strictly technical aspects of resectability, the presence of extraperitoneal metastatic disease calls into question any possible benefit of CCRS plus HIPEC. However, the prognostic impact of extraperitoneal disease varies based on the primary tumor type. Some patients with less aggressive ‘tumor biology’ might benefit from CCRS with HIPEC combined with resection of extraperitoneal metastases, as has been the case for patients with colorectal cancer and for 29% of the patients in this series. Due to the extreme rarity of PC of unusual origin, we have not been able to demonstrate the prognostic significance of extraperitoneal disease.

Retrospective analysis of our results does not allow us to define the impact of the cellular origin of the PC on long-term results. To answer this question, we have therefore matched the diagnoses of our cases with a review of the literature, pathology by pathology. In our study, we deliberately excluded tumors that had already been the subject of other studies in order to focus on unusual cellular origins of PC.

The influence of the cellular origin of peritoneal carcinomatosis

Desmoplastic small round cell tumor

There have been about 450 reported cases of desmoplastic small round cell tumors reported since its first description by Gerald et al. in 1991; these are very aggressive malignancies typically arising intra-abdominally in adolescent or young adult Caucasians [12]. A specific translocation of the EWSR1-WT gene (t 11;32) (p13; q12) establishes a formal diagnosis [13]. The cellular origin of this tumor is unknown but PC almost always occurs, while extraperitoneal metastases involving liver, lung or lymph node are present in half of the cases at the time of diagnosis [14]. When extraperitoneal metastasis is present, surgery has not been shown to be of benefit [14]. Treatment of isolated peritoneal disease relies on perioperative chemotherapy combined with CCRS and postoperative pan-abdominal radiotherapy; this treatment results in a median overall survival of 38 months and a median relapse-free survival of 16 months [14]. The completeness of CCRS is crucial since median survival is only 13–15 months when CCRS is incomplete [14,15]. The role of HIPEC for this indication remains controversial. The only published study with over three cases reported a median survival of 31 months after CCRS plus HIPEC [15]. Excluding patients whose follow-up was less than 3 months, all patients treated for desmoplastic small round cell tumors by CCRS plus HIPEC in our series recurred in the peritoneum within 11–16 months, which is comparable to results of surgery without HIPEC.

Fibrolamellar hepatocellular carcinoma

Fibrolamellar hepatocellular carcinoma is an unusual hepatocellular carcinoma arising in healthy liver and representing less than 1% of all primary malignant liver tumors. It is rare, typically occurs in young patients, and has a better prognosis than conventional hepatocellular carcinoma with a median survival of 73 months after surgery [16,17]. No data are available on the incidence and treatment of PC arising from fibrolamellar hepatocellular carcinoma. In our series, all patients treated by CCRS plus HIPEC for PC arising from fibrolamellar hepatocellular carcinoma recurred intraperitoneally within 2 years but also developed distant metastasis; the disease-free survival of 13 months suggests little or no benefit for this morbid and costly treatment.

Mucinous carcinoma of the urachus

The urachus is a remnant of fetal development that can give rise to benign or malignant mucinous tumors. Extension of these tumors into the peritoneal cavity results in a clinical picture similar to PMP. The standard approach in this situation is to treat it like PMP by CCRS plus HIPEC, regardless of its cellular origin, although mucinous urachal carcinoma is deemed to have a worse prognosis [2,18,19]. Of the three patients in our series, two are alive and disease-free at 20 and 37 months. The third patient developed early peritoneal recurrence and liver metastasis, demonstrating unusual tumor aggressiveness, and died after 14 months.

Primary peritoneal serous carcinoma

Primary peritoneal serous carcinoma is a very rare form of peritoneal carcinomatosis occurring almost exclusively in females; it was first described by Swerdlow in 1959 and its exact incidence is unknown [20]. The largest published study described 36 patients from nine French and Italian centers (including the three patients described in this study). It reported overall 1-, 3-, and 5-year survival of 94%, 72%, and 57%, respectively, after CCRS plus HIPEC, with a median recurrence-free survival of 17 months [21]. Without a comparative study, no benefit can be ascribed to the addition of HIPEC to CCRS alone. However, since the clinical and prognostic characteristics of primary serous peritoneal carcinoma are comparable to those for PC from primary ovarian serous carcinoma (which is histologically indistinguishable), some authors suggest a common therapeutic strategy should be employed for both entities [21,22].

Pseudopapillary and solid pancreatic tumors

Pseudopapillary and solid tumors of the pancreas (or Frantz tumors) are rare indolent pancreatic tumors that preferentially affect young women [23]. Eleven cases of PC have been described in the literature, all occurring in the aftermath of a traumatic or iatrogenic tumor rupture. After treatment with CCRS without HIPEC, 58% recurred in the peritoneum after an interval of 12 to 228 months [23]. The only two cases of CCRS plus HIPEC performed for this indication are also reported in this series; they had a recurrence-free survival of 31 and 57 months respectively. It is a bit premature to conclude that HIPEC has benefit for this indication since the interval before recurrence may be as long as 20 years. However, an indirect argument in its favor may be suggested by the clinical history of one of our patients who had relapsed 8 months after CCRS alone and who is now alive without recurrence 57 months following repeat CCRS plus HIPEC.
Psammocarcinoma

The psammocarcinomas are extremely rare primary peritoneal carcinomas defined by the presence of PC with psammoma bodies within sheets of low-grade serous carcinoma without evidence of an associated ovarian primary lesion [24,25]. Their exact incidence is unknown, but 28 cases have been described in the literature since 1990 [24]. Although they are slow growing and have a very good prognosis, recurrence after CCRS alone is common and inexorably leads to death from intestinal obstruction after several years of peritoneal progression [25]. No data is yet available in the literature suggesting an additional benefit from the addition of HIPEC to CCRS [24]. In our series, one patient underwent CCRS plus HIPEC; she relapsed after 12 months but is still alive 4 years later.

Endometrial cancer

One HIPEC for a case of PC of endometrial origin was performed in our series. In the literature, 29 cases from five other retrospective studies have been reported [26–30]. Aggregated data from these series shows that 14 patients are alive without recurrence after a median follow-up of 30 months while nine died of early recurrence within the first postoperative year. There are no published data to confirm a potential benefit of the addition of HIPEC to CCRS, although we could not identify any way to discriminate the different profiles of aggressiveness.

Thymoma

No cases of HIPEC treatment for PC due to thymoma have been previously described in the literature. Our single case occurred 24 years after peritoneal dissemination linked to a trans-diaphragmatic breach during transthoracic resection of thymoma. Our rare form of peritoneal dissemination had already been described at the pleural level and treated by CCRS surgery plus hyperthermic intrapleural chemotherapy with benefits in relapse-free and overall survival [31–33]. These data on pleural recurrence could probably be extrapolated to peritoneal dissemination.

Other etiologies

There is no previously published data concerning the results of HIPEC for PC associated with malignant adrenocortical carcinomas, non-seminomatous germ cell tumors, nephroblastomas, Sertoli-Leydig cell tumors, cervical carcinoma, adeno cystic carcinoma, or embryonic rhabdomyosarcoma. Two cases of Wilms tumor and one case of Sertoli-Leydig cell tumor have been reported in the literature but their data have not been studied individually [34]. The results in our study do not allow us to draw conclusions regarding the benefit of HIPEC for these indications. However, except for a case of PC due to a Sertoli-Leydig tumor where a prolonged survival was observed, relapse within the year of HIPEC was observed in 60% of patients and only two of the patients were alive without recurrence in the long term. A recent American series, described, among others, the performance of CCRS plus HIPEC in seven patients with rhabdomyosarcoma of unspecified histological subtype; the authors showed that the chemotherapy was ineffective with a very poor prognosis, having an overall 1- and 2-year survival of 29% and 14% respectively [34].

Although we have no cases in our series, we would cite a series of five patients with isolated PC arising from breast cancer who underwent CCRS plus HIPEC for an initial diagnosis of ovarian cancer; after a median follow-up of 56 months, four are alive and without recurrence. [35]. Finally, a single series of seven patients with PC from granulosa-cell tumors underwent CCRS plus HIPEC; two patients were alive without recurrence after a median follow-up of 32 months, leading the authors to conclude that HIPEC offered no benefit for this indication compared to surgery alone [36].

After this exhaustive analysis, we propose a categorization based on tumor origin as follows:

- probable benefit from CCRS plus HIPEC: PC arising from mucinous carcinoma of the urachus, pseudopapillary and solid tumors of the pancreas, or thymoma;
- probable benefit from CCRS but with uncertain controversial or unverifiable benefit of HIPEC: PC arising from desmoplastic small round cell tumor, psammocarcinoma, Sertoli-Leydig tumors, granulosa tumors, or primary serous peritoneal carcinoma;
- uncertain or unverifiable benefit of CCRS: PC originating from breast cancer, endometrial cancer, non-seminomatous germ cell tumor, malignant adrenocortical carcinoma, adenocystic carcinoma, nephroblastoma, fibrolamellar hepatocellular carcinomas, cervical carcinoma, embryonic rhabdomyosarcoma.

Intraoperative patient selection

In addition to the preoperative selection criteria, two prognostic and predictive factors of recurrence must enter into the intraoperative decision to perform CCRS plus HIPEC: tumor burden as evaluated by the peritoneal index and the mode of administration of intraperitoneal chemotherapy. While the decision to perform HIPEC rather than IPPCP is fairly straightforward, the interpretation of the peritoneal index is much more complicated and it is probably unethical to consider an index ≥ 12 to be an absolute contra-indication for HIPEC. If we consider an analogy with colorectal cancer, there is a linear correlation between the peritoneal index and overall survival after CCRS plus HIPEC; instead of having a fixed limit, there are three overlapping categories of patients; a strong indication for those who have a low index, an intermediate zone where other prognostic factors must be considered when deciding on the indication for surgery, and a high index where HIPEC is contra-indicated [37]. In the setting of PC of unusual origin, these limits are less well defined but a peritoneal index of 12 may be the tipping point for determining what decision should be made.

Modality of intraperitoneal chemotherapy

Review of published data shows at least six different modalities of HIPEC that have been used to treat 141 patients after CCRS for PC arising from 17 unusual origins [15,21,26–30,34]. It is tempting to determine a personalized treatment based on the particular tumor origin but heterogeneity makes any subgroup analysis impossible. Moreover, since no comparative or retrospective study has ever shown the benefit of one or another type of intraperitoneal chemotherapy in terms of survival for the conventional indications of CCRS plus HIPEC, there is no factual evidence to validate a choice of a particular treatment.
Strengths and weaknesses of the study

This study suffers from the classic biases of retrospective studies on rare tumors. It nevertheless has the merit of updating the current situation, while emphasizing the paucity of data. This should encourage us to set up a prospective registry within the rare peritoneal tumors network (RENAPE), which could permit better definition of indications for CCRS and HIPEC for these unusual indications.

Conclusion

The decision of whether to perform CCRS plus HIPEC for PC arising from unusual malignancies remains difficult. It must be based on the patient’s age, general condition, comorbidities, a high probability of achieving complete cytoreductive surgery, exclusion of extra-peritoneal metastasis, a chemosensitive tumor or one with a slow biologic progression, primary tumor origin, and tumor burden as measured by the peritoneal index. Prospective registration in the rare peritoneal tumor registries (the French Network for Rare Peritoneal Malignancies [RENAPE] in France, and/or the Peritoneal Surface Oncology Group International [PSOGI] internationally) could lead to better definition of indications.

Disclosure of interest

The authors declare that they have no competing interest.

References


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