**Introduction**

Peritoneal carcinomatosis (PC) carries a very poor prognosis. In fact, the median survival of patients with PC of gastrointestinal origin ranges between 6 and 8 months (1-2). Up till now, the standard treatment of PC was systemic chemotherapy associated in some cases with palliative surgery.

PC is very often associated with distant metastasis. However, in 20-25% of cases, particularly for gastrointestinal tumours, disease is confined to peritoneal cavity (3-4). Since a few years, a new treatment of PC has been developed and described by SUGARBAKER et al. (5). Although results of this technique were promising and seem to allow treatment of some patients with curative intent (6-7), there was no general acceptance because of a lack of randomized trial in this field. Overall 5-year survival of patients with peritoneal carcinomatosis treated by HIPEC is similar to that of patients with hepatic metastases treated with curative intent. Those patients should no longer be considered as patients with a terminal disease but as patients with a potentially treatable localized disease.

**Methods**

1. **Rationale for a complete resection**

Complete cytoreductive surgery is primordial before performing intraperitoneal chemotherapy because tissue penetration of chemotherapy is limited to a few cell layers and chemotherapy will be efficient only on millimetric and/or inframillimetric residual disease (0-2 mm) (10-11).

Complete surgical resection is a primordial factor in the treatment of PC since we cannot hope for a curative treatment in cases of macroscopic residual disease as several studies have reported no 5-year survival in patients treated by HIPEC with incomplete cytoreductive surgery (12-13).

2. **Rationale for intraoperative hyperthermic chemotherapy**

**Intraperitoneal administration**: hyperthermic intraperitoneal chemotherapy makes possible to reach local concentrations of chemotherapy which are 20 to 1000 times higher than that permitted by systemic way according to the product used (14-15).

Hyperthermia: elevated temperatures of 40-44 degrees C increase the actions of various anticancer drugs (cytotoxic antibiotics and platinum analoga). The association of hyperthermia with intraperitoneal chemotherapy has two aims. Firstly, it allows a direct cytotoxic effect related to the effects of hyperthermia itself and secondarily allows a synergistic effect because of a better penetration of chemotherapeutic drugs in tissues and cells (3-15).

**Timing**: intraperitoneal chemotherapy is performed in the operative room after complete cytoreductive surgery. Two different techniques of administration have been described. The intraperitoneal chemotherapy can be administrated intraoperatively, immediately after the
cytoreductive surgery (HIPEC). It is essential that HIPEC is performed immediately after surgery in order to prevent residual tumoral cells from being trapped in postoperative adherences. Indeed, these physiological adherences are formed in less than 20 minutes after surgery (16). Otherwise, it is possible to administrate the intraperitoneal chemotherapy by a drain after performing the cytoreductive surgery, the intestinal anastomosis and the closure of the abdominal wall (immediate intraperitoneal postoperative chemotherapy (IIPC)). Actually, although cheaper than HIPEC, the disadvantages of the IIPC are numerous. It does not make possible to apply the cytotoxic and synergistic effect of hyperthermia. The risk of anastomotic fistula is higher because anastomoses bathe in chemotherapy during 5 days. Finally its effectiveness is less compared to HIPEC ‘in term of survival’ as reported by randomized studies carried out on animal and on human (17-20).

Techniques

1. Surgical techniques

The first part of surgery is the exploration of the peritoneal cavity. It must be complete and can last several hours. First one explores area where to perform complete resection (technically and/or functionally) can be problematic. Generally, the resection starts in the area of the abdomen which seems to be the most problematic, and so on, in a decreasing way. The two most frequently limiting area are the liver (hepatic pedicle, vena cava, supra-hepatic vessels), the small intestine and his mesentery. It is also necessary to make sure there is no latero-aortic lymph nodes metastases. Indeed, the presence of involved latero-aortic lymph nodes will signified a more advanced disease (disease not only localized in the peritoneal cavity) and will preclude the performance of HIPEC (21). The decision to make the combined treatment is finally made only if we estimate we are be able to carry out the complete resection of macroscopic lesions. In cases of diffuse carcinomatosis involving large amount of small intestine serosa and requiring extended resection, the intervention is stopped. In fact, a minimum of 2 meters must be preserved to prevent the patient from developing a “short bowel syndrome” with nutritional deficit. A paramount concept must be respected : despite of a surgery requiring extended resection, the patient must preserve a normal or subnormal life (i.e. with maximum 3-5 defecations per day). It is important to quantify PC with a score to permit a prognostic evaluation and also compare results reported in the literature by different teams. The main score used is the “Peritoneal Cancer Index” of Jacquet & Sugarbaker (22) (Fig. 1). Although the threshold score for its potential benefits is not yet fully established, Sugarbaker has reported a poor prognosis for patients with a PCI > 20 in patients with colorectal cancer and suggested to treat those patients only with palliative intent (23).

Technical aspects of the resection of macroscopic lesions will not be detailed herein. They have been described by Sugarbaker (24) and Elias et al. (25) and include peritonectomy.

In cases of peritoneal pseudomyxoma, it is recommended to perform systematically the excision of the appendix. No intestinal anastomosis is performed before the realization of HIPEC in order to avoid the entrapment of tumoral cells in the suture line.

2. Hyperthermic Intraperitoneal chemotherapy

During HIPEC, the whole of the parietal and visceral peritoneal area must be bathed so that it can be reached by chemotherapy. In addition, it is essential to obtain a homogeneous hyperthermia to 40-43 °C in the abdominal cavity. Therefore, a technique with open abdomen, skin in traction upward, called “coliseum technique” is used allowing an expansion of the abdominal wall. The procedure with open abdomen allows the surgeon to permanently mobilize the intestine, and so to treat the entire peritoneal surface. Furthermore, it allows to obtain a higher thermal homogeneity than it is possible with closed abdomen techniques (17).

Technically (flows, number of drains, volume of peritoneal solution and solution concentration) various
Hyperthermic Intraperitoneal Chemotherapy

modalities are used and reported in the literature (26-28). Some groups use a constant volume of peritoneal solution to perform the HIPEC. The same volume and concentration of chemotherapeutic agent are administered to the patients (27-28). Our group uses a volume of peritoneal solution adapted to the body surface of the patients (L/m²). So, the volume used is adapted to each patient as is the concentration of chemotherapeutic agent (mg/m²). The length of HIPEC varies from 30 to 90 minutes according to teams. It is obvious that for each drug used in HIPEC, a preliminary pharmacological study must be carried out since its pharmacokinetic is related to its concentration and its duration use (3, 29). Mitomycine C and cisplatin are the classic drugs used for HIPEC (30). However, more recent drugs including the oxaliplatin and the irinotecan were studied and seem very promising (31).

The duration of the intervention varies from 6-14 hours and depends on the extent of peritoneal carcinomatosis. The blood losses range between 0.5 and 2 litres. The postoperative courses of this multimodal treatment (surgery, chemotherapy and hyperthermia) are complex and require experience (7-8, 18). In the event of extended peritonectomies, the patient must be managed as a severely burnt person. Postoperative mortality is between 3 and 8% and morbidity between 23 and 60% for experienced teams (13-32). The main cause of mortality is septic shock. The major intraabdominal complications are anastomotic leak and/or bowel perforation and intraabdominal infections. Major medical complications are pulmonary infections, acute renal failure and neutropenia (grade 3 and 4) (33). It has been reported that the number of resections, anastomoses and duration of surgery is related to a significantly higher rate of complications (34).

Results

The first step is to evaluate and to select patients who will benefit from this new treatment. This type of combined treatment is heavy to support for the patient and it can be carried out only on subjects in good general condition. In general, age limit to benefit from HIPEC is 65 years (varies from 60 to 70).

The preoperative evaluation includes a clinical examination in which the rectal examination is primordial to detect and evaluate the extent of peritoneal carcinosis. Otherwise, a biological assessment including tumoral markers, a radiological assessment with abdominopelvic and thoracic CT and a preoperative cardiac ultrasonography are performed. This medical check-up allows to select patient for intervention.

Exclusions criteria are :

- patients with extraabdominal metastases;
- patients with liver metastases (relative contraindication);
- patients with renal, cardiac and/or pulmonary comorbidities.

The major published results concerning the results of HIPEC with the level of evidence is reported in Table 1 and are as follow :

- **Pseudomyxoma peritonei**

There are no prospective randomized trials in view of the rarity of the pathology, but several studies have been published showing a beneficial effect of HIPEC on survival (35-36). **Elias et al.** reported a 5-year survival of 66%. The main prognostic factors were the completeness of resection and the histological tumoral grade (36).

The largest series (550 patients) is that of **Sugarbaker et al.** (35) who reported a 5-year survival of 58% (72% in complete resection) in patients treated by cytoreductive surgery with IIPC or HIPEC compared with a 5-year survival of 53% of patients treated only by standard cytoreductive surgery in the series of the Mayo Clinic (37). It is important to note that in the later series, intraperitoneal chemotherapy was used in 13% of patients and there was a trend toward improved survival rates in those patients.

**Sugarbaker et al.** reported in a series of 174 patients treated by incomplete cytoreductive surgery bad outcome results with a 3-year and 5-year survival rates of 34% and 15%, respectively. About 20% of these patients did not receive intraperitoneal chemotherapy. Patients treated by HIPEC seem to have better outcome than those treated without HIPEC (median survival of 39.4 months and 18.1 months respectively) (38). There is an expert agreement (lowest level of evidence) to consider HIPEC as first treatment (36, 39-40). There is a highest agreement for grade 2 and 3 tumours (peritoneal mucinous carcinomatosis with intermediate or discordant features (grade 2) and peritoneal mucinous carcinomatosis (grade 3)) than for grade 1 tumours (disseminated peritoneal adenomucinosis). Indeed, grade 2 and 3 tumours are aggressive tumours and their prognosis are poorer than grade 1 tumours.

- **Gastric cancer**

Most patients with PC die within 6 months of diagnosis and the 5-year survival rate is 0% (41). The majority of published studies are from Japanese teams (42-44). The only prospective controlled non randomized study is that of **Fujimoto et al.** reporting a 5-year survival of 31% in the HIPEC group versus 0% in the control group (42). **Yoneura et al.** have reported beneficial survival results in a series of 83 patients with PC treated by HIPEC (43). The overall 5-year survival was 11% (17% in complete
resection vs 2% in patients with residual disease). Long-term outcome in patients with residual disease was observed in chemo-sensitive patients. GLEHEN et al have reported beneficial survival results in a small prospective series including 49 patients with peritoneal carcinomatosis, treated by cytoreductive surgery in addition of intraperitoneal chemohyperthermia, with a survival of 41% at 3 years (45). The overall 5-year survival was 16%. In those studies, the most important prognostic factor seems to be the completeness of cytoreductive surgery. In patients with residual nodules of less than 5mm, median survival was 21.3 months in contrast with 6.1 months in patients with residual nodules of more than 5mm. These results have not yet been confirmed by randomized clinical trial.

- Colorectal cancer

Recently, two studies (including the results of a prospective randomized study and a multicentric study) underlined the interest of intraperitoneal chemotherapy in the treatment with curative intent of peritoneal carcinomatosis of colorectal origin (8-13).

- The study of VERWAAL has the merit to be the first published prospective randomized study (8). The standard treatment (chemotherapy associated both with or without palliative surgery) is compared with chemotherapy associated with HIPEC in PC of colorectal origin. This study showed the superiority of HIPEC arm on standard treatment. The median survival was respectively 12.6 months and 22.3 months (standard versus HIPEC) and this in spite of the fact that a part of patients in HIPEC underwent only an incomplete resection of PC.

- The multicentric study reports the carcinological results on 506 patients treated in 28 institutions by cytoreductive surgery associated with an intraperitoneal chemotherapy (HIPEC and/or IIPC) for PC of colorectal origin (13). The overall survival at 1, 3 and 5 years were respectively of 72%, 39% and 19%. The clinical and therapeutic prognostic factors that arise in multivariate analysis are the completeness of surgical resection with survivals at 1, 3 and 5 years respectively of 72%, 39% and 19%. The clinical and therapeutic prognostic factors that arise in multivariate analysis are the completeness of surgical resection with survivals at 1, 3 and 5 years respectively of 38-87%, 6-47% and 0-31% according to the type of excision carried out (Completeness of Cancer Resection (CCR) : CCR-0 = macroscopic complete resection ; CCR-1 = diameter of residual nodules < 5 mm ; or CR-2 = diameter of residual nodules > 5 mm). We observe a survival rate at 5 years equivalent to that of patients with surgically

<table>
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<tr>
<th>Authors</th>
<th>Origin of PC</th>
<th>5-y survival with IPC</th>
<th>5-y survival without IPC</th>
<th>Type of study</th>
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<tr>
<td>(28) SUGARBALKER et al.</td>
<td>PMP</td>
<td>58%</td>
<td>NS</td>
<td>Retrospective</td>
<td>IV</td>
</tr>
<tr>
<td>(36) ELIAS et al.</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>Retrospective</td>
<td>IV</td>
</tr>
<tr>
<td>(37) GOGGI et al.</td>
<td></td>
<td>NS</td>
<td>Retrospective</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>(45) GLEHEN et al.</td>
<td>Gastric cancer</td>
<td>16%</td>
<td>NS</td>
<td>Prospective†</td>
<td>III</td>
</tr>
<tr>
<td>(43) YONEMURA et al.</td>
<td></td>
<td>11%</td>
<td>NS</td>
<td>Prospective†</td>
<td>III</td>
</tr>
<tr>
<td>(42) FUHOTO et al.</td>
<td></td>
<td>2% (IR)</td>
<td>NS</td>
<td>Prospective non randomized</td>
<td>III</td>
</tr>
<tr>
<td>(8) VERWAAL et al.</td>
<td>Colorectal cancer</td>
<td>36% (3 y survival)</td>
<td>10%</td>
<td>Prospective randomized</td>
<td>II</td>
</tr>
<tr>
<td>(13) GLEHEN et al.</td>
<td></td>
<td>19%</td>
<td>NS</td>
<td>Retrospective (multicentric)</td>
<td>IV</td>
</tr>
<tr>
<td>(46) ELIAS et al.</td>
<td>Digestive endocrine carcinoma</td>
<td>40.9% (IR)</td>
<td>38% *</td>
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<td>IV</td>
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<tr>
<td>(47) VAN RUTH et al.</td>
<td>Mesothelial tumors of the peritoneum</td>
<td>66.2% (CR)</td>
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<td>(48) SEBBAG et al.</td>
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<td>(49) SETHNA et al.</td>
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<td>Case series</td>
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</table>

PC : peritoneal carcinosis ; PMP : pseudomyxoma peritonei ; CR : complete resection ; IR : incomplete resection ; *value obtained from the national US registry ; NS : not specificiate ; † non comparative.
Digestive well differentiated endocrine carcinoma

We recently reported a series of 37 patients with PC from a digestive well differentiated endocrine carcinoma. Patients were divided in two groups, one treated by incomplete resection of PC and one treated by complete cytoreductive surgery with HIPEC. The 5 year survival was 40,9% for incomplete resection and 66,2% for the other group. Furthermore, even if the 2 groups are not comparable, in the group treated by complete resection and HIPEC, the rate of death related to PC was significantly reduced from 40% to 5,8% 46).

Mesothelial tumours of the peritoneum

These are rare tumours. The majority of papers reported in the literature are isolated case series because of the rarity of these tumours (47-49). No prospective studies have been conducted for the same reason. Several reports have suggested that a complete cytoreductive surgery associated with intraperitoneal chemotherapy must be performed and could be beneficial for the patient (39, 48).

Conclusions

The multimodal treatment including cytoreductive surgery associated with hyperthermic intraperitoneal chemotherapy in the treatment of PC of colorectal origin appears to be a considerable evolution and makes possible to treat with curative intention patients formerly considered as incurable. Although experimented teams in HIPEC treatment have reported good results in PMP and HIPEC with oxaliplatin, wich is higher than the 39% reported in the multicentric study (31).