Ascites and malnutrition are predictive factors for incomplete cytoreductive surgery for peritoneal carcinomatosis from gastric cancer

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Peritoneal carcinomatosis (PC) is detected in 10% to 20% of patients with gastric cancer during the initial diagnosis. Moreover, peritoneal recurrence may occur in up to 60% of patients even after curative resection. In the European multicenter Evolution of Peritoneal Carcinomatosis 1 study, prognosis in PC from gastric cancer was very poor, with a median survival time of 3.1 months. Thus, PC is mostly considered a terminal condition in patients with gastric cancer, and the current standard treatment is palliative systemic chemotherapy.

However, a new multimodal therapy linking cytoreductive surgery (CS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has been developed during the past 20 years. This procedure has demonstrated promising results in numerous types of PC, including gastric cancer. Yonemura et al reported a median survival time after complete cytoreduction of 15.5 months. A multicenter study, similar results were reported, with an overall median survival time of 15 months. In addition, a randomized trial comparing CS alone with CS plus HIPEC recently demonstrated the superiority of the combined treatment. Thus, this procedure could become a standard treatment for selected patients.
In all studies, the quality of the surgical cytoreduction, measured by the completeness of cytoreduction (CC) score, is the most decisive prognostic factor.\textsuperscript{4–9} This is not surprising, because the depth of penetration of HIPEC does not exceed 2 mm.\textsuperscript{10} Thus, if CS is not optimal, HIPEC has no rationale and should not be performed. The completeness of PC resectability is directly correlated with the extent of PC.\textsuperscript{11} Computed tomography (CT) is usually considered the best examination for staging PC. Nevertheless, the extent of peritoneal disease is often underestimated, and surgery is required to achieve a precise exploration.\textsuperscript{12} Therefore, the challenge is to identify before surgery those patients in whom CS may be incomplete, to avoid unnecessary laparotomy.

The main purpose of our study was to find predictive factors for incomplete CS in patients with PC arising from a gastric origin. Secondary aims were to evaluate the efficacy and safety of this procedure.

**Methods**

From January 1999 to December 2010, 45 patients with PC from gastric cancer that was apparently resectable were included in this study. All patients underwent laparotomy, with the intention of performing HIPEC. Fourteen patients (31\%) had optimal CS according to CC score (0 or 1). HIPEC was performed for this group of patients (the CS-HIPEC group). For the other 31 patients (69\%), PC was considered unresectable; that is, CS would have left deposits exceeding 2.5 mm (CC score of 2). For these patients, forming the no-HIPEC group, the laparotomy was closed or palliative surgery was performed if necessary. All patients were included in a prospective database and provided written informed consent. The study protocol was approved by our institutional ethics committee.

**Inclusion criteria**

All primary gastric cancers were confirmed by biopsy.

Staging systematically included thoracoabdominal CT with oral and intravenous contrast agents and endoscopic ultrasonography. From 2004, positron emission tomography (PET) was additionally performed.

Anesthetic evaluation, echocardiography, and spirometry were performed on all patients.

Patients were then selected preoperatively according to the criteria defined by the Peritoneal Surface Malignancy Group adapted for gastric cancer:\textsuperscript{13,14} (1) PC from gastric cancer; (2) aged <65 years and good general status (World Health Organization performance status <2); (3) no extra-abdominal disease; (4) no multiple, diffuse, and huge tumoral peritoneal deposits on CT; (5) no evidence of intestinal obstruction or involvement; (6) small-volume disease in the gastrohepatic ligament; (7) no evidence of biliary or ureteral obstruction; and (8) no massive and total abdominal involvement on clinical examination.

For borderline cases, laparoscopy was performed preoperatively.

**Surgical procedures**

Surgery was performed through a large midline incision from xiphoid to pubis. After an extensive and complete exploration of the abdominal cavity, the extent of the PC was calculated for each patient using the peritoneal cancer index (PCI), as described by Sugarbaker et al.\textsuperscript{15}

If the PC was resectable (CS-HIPEC group), CS was performed by resection or destruction by electrovaporation of all peritoneal lesions. This consists of a series of peritonectomy procedures, visceral resections, or destruction by electrovaporation of all peritoneal implants. Their use depends on the volume, distribution, and depth of invasion of the nodules within the peritoneal surfaces. In case of synchronous PC, a gastrectomy was performed with a modified radical lymphadenectomy (D1.5). Splenectomy with or without distal pancreatectomy was associated in case of locoregional involvement or PC in this area. At the end of this surgical procedure, patients were classified according to CC score as follows: CC score 0 = no residual macroscopic nodules; CC score 1 = residual tumor <2.5 mm.\textsuperscript{15} This subjective measure was based on a macroscopic visual assessment of any residual lesions. Only these patients were considered to have optimal CS and were eligible for the HIPEC procedure. Mitomycin C was administered into the peritoneal cavity, using the coliseum technique with a Thompson self-retaining retractor.\textsuperscript{16} The dose was 12.5 mg/m\textsuperscript{2} for men and 10 mg/m\textsuperscript{2} for women, in 2 L/m\textsuperscript{2} of 1.5\% dextrose peritoneal dialysis solution. The heated perfusion solution was infused at a rate of 1 L/min. A heat exchanger kept the intraperitoneal temperature at 42°C to 43°C for 60 to 90 minutes. Anastomoses were usually performed after HIPEC, and 2 suction drains were placed in the peritoneal cavity.

Despite a strict selection of patients, multiple causes of incomplete resectability were discovered during surgical exploration. For these patients (the no-HIPEC group), there was no interest in completing the full combined procedure. Finally, the laparotomy was closed, possibly after a palliative procedure.

**End points and evaluation criteria**

The primary aim of this study was to find preoperative factors allowing us to identify patients for whom CS may be incomplete. The parameters studied to achieve this objective were (1) history: completion of preoperative systemic chemotherapy and synchronous or metachronous PC; (2) clinical: sex, body mass index <18 kg/m\textsuperscript{2}, and presence of ascites before surgery (regardless of quantity); (3) biologic: an increase in the carcinoembryonic antigen level (>5 ng/ml), malnutrition as determined by an assessment of the nutritional status by the prognostic nutrition
index (PNI), calculated as $10 \times \text{serum albumin (g/dL)} + .005 \times \text{total lymphocyte count (per mm}^3\})^{17}$ (a PNI value $<45$ was regarded as indicating moderate to severe malnutrition); (4) imaging: presence of direct or indirect signs related to PC on PET and CT ($^{18}$F-fluorodeoxyglucose uptake, ascites, peritoneal nodules or bulky mass lesions, peritoneal thickening, mesenteric effacement, and luminal narrowing); (5) histologic: presence of signet ring cells; (6) progression of PC under systemic chemotherapy on the basis of clinical examination, carcinoembryonic antigen level, and imaging; and (7) laparoscopic exploration.

Another objective was to analyze the morbidity and mortality observed for all patients. Mortality and morbidity were defined, respectively, as death or medical and surgical postoperative complications occurring $<30$ days after surgery or until hospital discharge. Finally, we studied the oncologic results by measuring the overall survival in the 2 groups. All patients were followed every 6 months with clinical examinations, thoracoabdominal CT, and carcinoembryonic antigen measurement. Survival was defined from the time of the surgical procedure to death or to the last follow-up date.

Statistical analysis

Patients were prospectively registered, but the analysis of the assessment criteria was done retrospectively. Mann-Whitney tests were performed to determine intergroup differences between mean values. Bivariate analysis was performed to find correlations between quantitative variables. We used Fisher’s exact test to examine the associations between each categorical variable. Variables with $P$ values $<.20$ on univariate analysis were included in multivariate analysis to identify independent predictive factors for optimal CS. These variables were entered into a logistic regression model.

Survival analysis was performed using the Kaplan-Meier method and compared using the log-rank test. No patient was excluded from survival analysis, and no data were missing.

$P$ values $<.05$ were considered significant. Statistical analysis was performed using R version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Predictive factors for suboptimal cytoreductive surgery

A comparison of the preoperative CS-HIPEC and no-HIPEC groups is given in Table 1. On univariate analysis, the presence of ascites before surgery ($P = .0031$) and nutritional status measured using the PNI ($P = .0029$) were the only 2 predictive factors for suboptimal CS (Fig. 1). The presence of either of these 2 factors allowed us to predict suboptimal CS in 90% of the patients (28 of 31) in the no-HIPEC group.

On multivariate analysis, these 2 factors were also independent risk factors for incomplete CS (for ascites: hazard ratio, .09; 95% confidence interval, .010–.48; $P = .0103$; for PNI: hazard ratio, .11; 95% confidence interval, .0019–.54; $P = .027$).

Analysis of the cytoreductive surgery-hyperthermic intraperitoneal chemotherapy group

In the CS-HIPEC group, the mean PCI was 11 ± 5.7 (range, 3–22). Eight procedures (57%) were considered CC score 0 cytoreduction, and 6 procedures (43%) were CC score 1 cytoreduction. Procedure-related mortality was null. Five patients (36%) had $\geq 1$ complication (Table 2). The mean length of hospital stay was 23.6 ± 19.8 days (range, 12–90). The median overall survival duration was 18 months. The survival curve for the CS-HIPEC group is shown in Fig. 2.

Analysis of the no-hyperthermic intraperitoneal chemotherapy group

In the no-HIPEC group, the mean PCI was 16.3 ± 9.6 (range, 8–26). Causes of nonresectability in the no-HIPEC group are reported in Fig. 3. The main cause was the diffuse extent of the PC throughout the abdominal cavity. Palliative surgery was performed in 8 patients (26%). These procedures included digestive bypass ($n = 3$), distal gastrectomy ($n = 2$), jejunostomy tube ($n = 2$), and small bowel resection. Postoperative mortality was 6%. Eight patients (26%) had $\geq 1$ complication (Table 2). The mean length of hospital stay was 11.5 ± 6.5 days (range, 4–34). The median overall survival duration was significantly lower than that of the CS-HIPEC group: 6 vs 18 months ($P = .0007$). The survival curve for the no-HIPEC group is shown in Fig. 4.

Comments

There is no standard treatment for PC from gastric cancer. Several studies have shown that CS plus HIPEC may significantly improve prognosis in selected patients for whom optimal CS (CC scores of 0 or 1) can be obtained. In our peritoneal cancer center, we follow this indication, and we do not perform HIPEC for CC score 2 surgery. Despite compliance with the recommendations of the Peritoneal Surface Malignancy Group adapted for gastric cancer, accurate preoperative staging remains difficult, and the indication to perform HIPEC is frequently based on intraoperative exploration. Thus, only 31% of patients had optimal CS and were treated with HIPEC in our study. These results are slightly lower than those reported by Glehen et al or Yonemura et al with, respectively, 51% and 43% of CC score 0 and CC score 1 CS. But in
their series, all patients underwent HIPEC, and some patients who had undergone only exploratory laparotomy were probably not included.

To avoid unnecessary laparotomy, we looked for other factors that might be useful to select the right candidates for the combined treatment. Thus, we showed that 2 preoperative factors were independent risk factors of nonresectability: the persistence of ascites and nutritional status assessed using the PNI. The detection of ascites just before surgery is a predictive factor of suboptimal CS that has already been reported for colorectal PC but never for gastric cancer.\(^{18}\) In an expert consensus document, Bozzetti et al\(^ {14}\) reported that only 33% of participants recommended the full procedure in case of ascites. Surprisingly, no study has ever shown that the presence of ascites was correlated with the extent of PC. Cancer-associated malnutrition is multifactorial: reduced nutritional intake, alterations in nutrient metabolism, and production of agents by the tumor (such as hormones or proinflammatory cytokines) are implicated in the pathophysiology of malnutrition. Nutritional status has already been correlated with surgical resectability rates, as in esophageal cancer.\(^ {19}\) Severe malnutrition is often an indicator of tumor extension. In our series, the mean PNI was 40 in the no-HIPEC group. This very low rate demonstrates severe malnutrition and reflects indirectly on the tumor extension.

**Table 1** Identification by univariate analysis of preoperative predictive factors of suboptimal CS for gastric PC

<table>
<thead>
<tr>
<th>Variable</th>
<th>CS-HIPEC group (n = 14)</th>
<th>No-HIPEC group (n = 31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>9/14 (65%)</td>
<td>17/31 (55%)</td>
<td>.74*</td>
</tr>
<tr>
<td>Male</td>
<td>5/14 (35%)</td>
<td>14/31 (45%)</td>
<td>.59*</td>
</tr>
<tr>
<td>Female</td>
<td>9/14 (65%)</td>
<td>17/31 (55%)</td>
<td>.72*</td>
</tr>
<tr>
<td>Age (y)</td>
<td>50 ± 10</td>
<td>53 ± 9</td>
<td>.0029*</td>
</tr>
<tr>
<td>BMI &lt; 18 kg/m²</td>
<td>3/14 (21%)</td>
<td>10/31 (32%)</td>
<td>.72*</td>
</tr>
<tr>
<td>PNI</td>
<td>48 ± 9</td>
<td>40 ± 6</td>
<td>.0031*</td>
</tr>
<tr>
<td>Synchronous PC</td>
<td>12/14 (86%)</td>
<td>24/31 (78%)</td>
<td>.70*</td>
</tr>
<tr>
<td>Preoperative chemotherapy</td>
<td>13/14 (93%)</td>
<td>25/31 (80%)</td>
<td>.40*</td>
</tr>
<tr>
<td>Progression with chemotherapy</td>
<td>2/13 (15%)</td>
<td>6/25 (24%)</td>
<td>.69*</td>
</tr>
<tr>
<td>Abnormal results on CT</td>
<td>8/14 (57%)</td>
<td>18/31 (58%)</td>
<td>.96*</td>
</tr>
<tr>
<td>Abnormal results on PET</td>
<td>4/8 (50%)</td>
<td>13/21 (62%)</td>
<td>.69*</td>
</tr>
<tr>
<td>Carcinoembryonic antigen level &gt;5</td>
<td>6/14 (43%)</td>
<td>16/31 (52%)</td>
<td>.75*</td>
</tr>
<tr>
<td>Ascites</td>
<td>2/14 (14%)</td>
<td>20/31 (65%)</td>
<td>.32*</td>
</tr>
<tr>
<td>Signet ring cells</td>
<td>7/14 (50%)</td>
<td>21/31 (68%)</td>
<td>.19</td>
</tr>
<tr>
<td>Preoperative laparoscopy</td>
<td>4/14 (29%)</td>
<td>16/31 (52%)</td>
<td>.19</td>
</tr>
</tbody>
</table>

Data are expressed as number (percentage) or as mean ± SD. Significant P values are in boldface type.

BMI = body mass index; CS = cytoreductive surgery; CT = computed tomography; HIPEC = hyperthermic intraperitoneal chemotherapy; PC = peritoneal carcinomatosis; PET = positron emission tomography; PNI = prognostic nutrition index.

*Fisher’s exact test.
†Mann-Whitney test.

**Figure 1** Prediction of performance of HIPEC by regression analysis of the PNI. The threshold value of the PNI is measured at 45. Gray area represents the confidence interval.

**Figure 2** Overall survival curve of the CS-HIPEC group (14 patients with gastric PC treated with optimal CS plus HIPEC). The median overall survival was 18 months.
Yonemura et al.\textsuperscript{11} clearly established that CS was correlated with the extent of PC. For gastric cancer, experts have recommended full-procedure CS plus HIPEC with PCI \( \leq 15.14 \). In this situation, the probability of complete macroscopic CS is highest. However, we confirm that conventional imaging techniques underestimate the extent of intraperitoneal spread. Indeed, we showed that the presence of an abnormality on CT was not a predictive factor for optimal CS. Similarly, Esquivel et al.\textsuperscript{20} showed that the extent of PC on the basis of CT is inaccurate, and its impact on the management of patients is modest. PET appears to be a promising alternative imaging modality with potentially higher accuracy in identifying peritoneal lesions and the overall extent of PC. Pfannenberg et al.\textsuperscript{21} reported that the combination of PET and CT was accurate in estimating the extent of carcinomatosis. In practice, PET usually fails to detect subcentimeter lesions, whereas the presence of such lesions is conclusive in determining the resectability of patients. In our study, \( ^{18}F \)-fluorodeoxyglucose uptake did not emerge as a predictive factor for optimal CS.

In conclusion, the selection of patients with gastric PC eligible for the complete procedure linking CS with HIPEC...
remains difficult. This study suggests that we must be very careful with malnourished patients with or without the presence of ascites. These 2 factors are an indication of advanced disease and are predictive of nonresectability. Moreover, the present series suggests that optimal CS plus HIPEC may improve survival with acceptable morbidity.

References


