Hypothesis: The most common cause of palliative resection and recurrence in gastric cancer is peritoneal seeding. This study evaluates the efficacy of intraperitoneal chemohyperthermia after cytoreductive surgery in patients with peritoneal carcinomatosis arising from gastric cancer.

Design: Prospective clinical trial.

Setting: Surgical department at a university academic hospital.


Interventions: All patients underwent intraperitoneal chemohyperthermia with mitomycin C (40-60 mg); 21 patients had previously undergone extensive cytoreductive surgery.

Main Outcome Measures: Clinicopathologic factors that affect overall survival rates.

Results: With median follow-up of 99 months, overall median survival was 10.3 months. Two factors were significant independent predictors of survival by multivariate analysis: preoperative ascites (P=.04) and completeness of cancer resection (CCR) by cytoreductive surgery (P<.001). Median survival was 21.3 months for patients with CCR-0 (macroscopic complete resection) or CCR-1 (diameter of residual nodules <5 mm) and 6.1 months for patients with CCR-2 (diameter of residual nodules ≥5 mm) (P<.001). Four patients survived longer than 5 years.

Conclusions: An aggressive management strategy combining intraperitoneal chemohyperthermia with cytoreductive surgery is effective for patients with peritoneal carcinomatosis arising from gastric cancer. In highly selected patients (good general status, resectable primary tumor, resectable peritoneal carcinomatosis), this therapy may result in long-term survival.

Arch Surg. 2004;139:20-26

Primary gastric seeding from primary gastric cancer occurs in 5% to 20% of patients being explored for potentially curative resection.1 Historically, it has been regarded as a lethal clinical condition. A multicenter prospective study2 reported that patients with peritoneal carcinomatosis (PC) of gastric origin survived a mean of 6.5 months and a median of 3.1 months. Research protocols using palliative systemic chemotherapy have been conducted but with no improvement in survival rates.3,4 However, during the past decade, there has been renewed interest in PC, and new therapeutic approaches have been proposed, including intraperitoneal injection of anticaner drugs such as OK4325 and mitomycin C adsorbed on activated charcoal.5 The effectiveness of these approaches has not been well established. Most current aggressive treatment regimens include immediate postoperative intraperitoneal chemotherapy,6 extended peritonectomy,7 and intraperitoneal chemohyperthermia (IPCH).8 After an experimental study in dogs,9 IPCH with limited cytoreductive surgery has been used since 1989 (published in 1992) in Centre Hospitalier Lyon-Sud. In a phase 2 study to evaluate IPCH in patients with PC arising from gastric cancer,10 IPCH was most effective for PC with malignant nodules measuring less than 5 mm (stages I and II), whereas PC with malignant nodules measuring 5 mm or greater (stages III and IV) did not benefit from IPCH (Table 1).

In light of the poor survival rates in our early patients with stage III or IV PC, we began to perform more extensive cytoreductive surgery in the hope of improving survival. A feasibility study for the treatment of abdominal cancers with PC has...
already been published.13 The aim of this study is to assess the clinicopathologic factors that affect overall survival rates using this new approach combining IPCH with surgery in patients with PC arising from gastric cancer.

METHODS

PROTOCOL

Before treatment, all patients underwent a physical examination, blood tests, serum electrolyte measurements, serum creatine measurements, and coagulation studies. Diagnostic tests included cardiac ultrasound, spirometry, cerebral and thoracic computed tomography (CT), abdominal ultrasonography of the liver, and abdominal CT for PC assessment.

The inclusion criteria were (1) age younger than 70 years, (2) gastric adenocarcinoma, (3) PC confirmed by cytologic or pathological examination, (4) synchronous or metachronous PC, (5) absence of extra-abdominal metastases, (6) no liver metastases on preoperative explorations, (7) satisfactory cardiorespiratory and renal status, and (8) signed informed consent. The exclusion criteria were (1) esophageal adenocarcinoma, (2) renal or myocardial failures, (3) administration of systemic chemotherapy 1 month before inclusion, (4) central nervous system disease (vascular or neoplastic), and (5) World Health Organization index score greater than 2.

Adjuvant radiotherapy and postoperative systemic chemotherapy were recommended, depending on the general status of the patient, lymph node involvement, and the completeness of cytoreduction. This protocol was performed in accordance with the Helsinki Declaration and was approved by the Lyon Human Investigation Committee.

SURGICAL PROCEDURES

Under general anesthesia and mechanical ventilation, a median laparotomy was performed to explore the abdominal cavity and obtain cytologic and pathological samples. Resection of the primary gastric tumor was performed whenever possible, as were peritonectomy procedures to maximally reduce the tumor volumes. These peritonectomies were adapted to the location of the malignant PC by the surgeon, exploration, and extemporaneous biopsies (routine, extensive peritonectomies were not performed). They were performed according to the surgical guidelines of Sugarbaker.14 Peritonectomy locations were recorded on a specific form: (1) right diaphragmatic copula, (2) left diaphragmatic copula, (3) greater omentum, (4) lesser omentum, (5) omental bursa, (6) right paracolic gutter, (7) left paracolic gutter, (8) Douglas pouch, (9) anterior wall peritoneum, (10) posterior wall peritoneum, (11) Glisson capsule, and (12) mesenteric peritoneum. Mesenteric peritoneum was not extensively removed, but after acceptable small-bowel resections guided by maximal tumor volume locations, remaining malignant nodules were destroyed using electrosurgical fulguration. Cytoreductive surgery was considered extensive when more than 2 peritonectomy procedures were performed.

Assessment of the completeness of cancer resection (CCR) by cytoreductive surgery was performed by the surgeon at the end of the procedure and classified into 3 categories: CCR-0 indicated that no macroscopic residual cancer remained; CCR-1, that no residual nodule greater than 5 mm in diameter remained; and CCR-2, that the diameter of every residual nodule was greater than 5 mm.

IPCH DEVICE

At the end of each surgical procedure, IPCH perfusion was carried out under general anesthesia and general hypothermia (32°C induced throughout the peritontectomy procedure using cold wraps on both lower extremities and an ice hat). Before closure of the laparotomy, 2 inflow drains were inserted under the left and right diaphragmatic cupulae (30F silicone William Harvey drain; Bard—Cardiopulmonary Division, Boston, Mass), and a third drain (outflow) was inserted into the Douglas pouch (32F). Temperature probes (Cair SA, Lozanne, France) were also inserted into the abdominal cavity (behind the liver pedicle and near the first jejunal loop). Other thermic probes were set up outside the abdominal cavity: (1) on the inflow and outflow drains (8 cm from the skin) and (2) inside the bladder within a Foley catheter. The laparotomy incision was then closed, and inflow and outflow drains were connected to a closed sterile circuit in which a 4- to 6-L perfusate (Travenol Laboratory, Norfolk, England) was circulated using an electromagnetic pump at a flow rate of 500 mL/min. The perfusate contained mitomycin C (10 mg/mL) (Kyowa, Tokyo, Japan). The total mitomycin C dose was 40 to 60 mg. The closed sterile circuit was heated using a thermic exchanger (Dideco, Paris, France) connected to a heating circuit. Intra- and extra-abdominal temperatures were recorded every 10 minutes using a thermic monitor (Cair SA) (Figure 1). Intraperitoneal chemohyperthermia was performed for 90 minutes, with monitoring of respiratory and hemodynamic variables at inflow temperatures between 46°C and 48°C. Samples of blood, urine, and perfusate were collected during IPCH at 45 and 90 minutes, and mitomycin C concentrations were measured using high-performance liquid chromatography.15 Mitomycin C concentrations were measured in blood, urine, and abdominal drainages, 24 hours after IPCH.

PATIENT FOLLOW-UP

All patients included in the study were transferred postoperatively to an intensive care unit for 24 hours and then to the surgical department. Clinical and radiologic follow-up was conducted monthly after discharge from the hospital.

PATIENTS

Between January 1, 1989, and February 29, 2000, 49 patients underwent 50 IPCH treatments in the surgical department of Centre Hospitalier Lyon-Sud for PC from gastric origin. A variety of selection factors (according to the inclusion and exclusion criteria of the protocol) were used before and after referral and strongly influenced the composition of this patient population: during the study, 200 patients with PC originating from gastric cancer were referred to our department for treatment, and only 49 met the selection criteria and gave their informed consent. No data regarding follow-up of the 151 patients who were excluded were obtained. Exclusions were mainly decided according to age, World Health Organization index score less than 2, unsatisfactory cardiac or renal functions, clear evidence of massive and total abdominal cavity involvement on clinical examination, or the presence of extra-abdominal me-

---

<table>
<thead>
<tr>
<th>Table 1. Peritoneal Carcinomatosis Staging12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
</tbody>
</table>
tastasis. Patients who were excluded were followed up by the referring hospital.

The patient population was composed of 25 women and 24 men (mean [SD] age, 53.7 [11.3] years; range, 27-70 years). The Union Internationale Contre le Cancer TNM staging system16 was used to assess the depth of gastric wall invasion and the extent of lymph node metastasis. Pathologic TNM staging of the gastric tumor was T1 (n=2), T2 (n=2), T3 (n=23), T4 (n=17), and TX (n=5) and N1 (n=10), N2 (n=28), N3 (n=6), and NX (n=5). Ten patients had an unresectable primary tumor, 14 underwent total gastrectomy, 13 underwent subtotal gastrectomy, 9 underwent total gastrectomy with splenectomy, and 3 underwent total gastrectomy combined with splenectomy and distal pancreatectomy. Seventeen patients had surgical down-staging with peritonectomy procedures. Three patients had hepatic metastases, which were discovered at the time of surgery and removed. Primary lesions were well differentiated (n=4), moderately differentiated (n=10), and poorly differentiated (n=35). A specific staging system was used to assess the extent of PC.12 Thirteen patients were stage I, 5 were stage II, 12 were stage III, and 19 were stage IV. Seventeen patients had malignant ascites at the time of surgery. Twenty-eight patients underwent PC at the end of the surgical exploration or at gastric cancer resection, and 21 patients underwent PC at a later time. These 21 patients underwent surgery at a different hospital and postoperatively were referred to Centre Hospitalier Lyon-Sud for surgery and PC treatment (within an average of 30 days). One patient underwent a second PC course (18 months after the first one) because he maintained an excellent performance status. Tumor markers, clinical evidence, and abdominal CT findings were used as indicators of recurrent peritoneal disease. Twenty patients received adjuvant palliative systemic chemotherapy (fluorouracil, cisplatin, and oxaliplatin), and 9 patients received external beam radiotherapy (4400-4600 rad [44-46 Gy]).

DATA ANALYSIS

Data were recorded prospectively. One patient was lost to follow-up 1 month after the surgical procedure was performed. The cutoff date for this analysis was June 1, 2002. Median (SD) follow-up was 99.6 (48.3) months (range, 1-160 months). Data were recorded and analyzed using a commercially available computer program (StatView 4.5; Abacus Inc, Berkeley, Calif) and are expressed as mean (SD) and range. A Kaplan-Meier survival curve was fitted to the data, and the log-rank test was used to identify differences between curves. Logistic regression was used for multiple analysis to discriminate among various effects on survival. A P≤.05 was considered statistically significant.

RESULTS

Thermic and pharmacokinetic results have been published elsewhere.11

SURGICAL RESULTS

Details about peritonectomies and digestive organ resections performed are outlined in Table 2. After the surgical procedures, 5 patients were considered to have
CCR-0, 20 patients CCR-1, and 24 patients CCR-2. Assessment of the CCR of the 49 patients according to the primary PC stage is summarized in Table 3.

**INTROOPERATIVE AND POSTOPERATIVE COURSE**

No intraoperative deaths occurred. Mean (SD) duration of surgery was 5.2 (1.6) hours (range, 1.5-9.5 hours), excluding the duration of IPCH. The 30-day mortality was 4% (2/49): a 51-year-old woman with unresectable pT3 NX gastric adenocarcinoma and stage III PC died of pulmonary embolism 4 days after IPCH, and a 59-year-old woman with pT4 N0 gastric adenocarcinoma and stage III PC treated by total gastrectomy, transverse colectomy, and IPCH died on the fourth postoperative day of multiple organ failure (no autopsy was performed).

Major complications occurred in 13 patients (27%). Five of these complications occurred in patients treated with IPCH without extensive cytoreductive debulking (16% [3/32]) (3 patients had pleuritis, 1 had occlusion, and 1 had parietal collection), and 8 occurred in patients who underwent extensive cytoreductive surgery (47% [8/17]) (2 had occlusion, 2 had ileocolic fistula, and 1 each had pancreatic fistula, biliary peritonitis, peritonitis, and intraperitoneal abscesses) (P=.05). A second operation was necessary in 4 patients (8%). The median (SD) hospital stay was 18.1 (4.9) days (range, 4-31 days). On average, patients treated with IPCH combined with extensive cytoreductive surgery had a longer hospital stay (20 days) than patients treated with IPCH with limited cytoreduction (13 days), but this difference was not significant (P=.60).

**DELAYED COMPLICATIONS**

In the second postoperative month, 8 (47%) of 17 patients with massive malignant ascites were free of ascites on clinical and ultrasound examination. Three delayed complications occurred. One 38-year-old man experienced choledochal stenosis 11 years after total gastrectomy, intraoperative and postoperative radiotherapy (1800 and 4500 rad [18 and 45 Gy], respectively), and IPCH for pT3 N1 disease with stage 1 PC. There was no evidence of recurrence by CT or by biopsies performed by transhepatic choledochoscopy. This complication was attributed to a late adverse effect of irradiation.

**SURVIVAL RESULTS**

Using the Kaplan-Meier method, the overall 1-, 2-, and 5-year survival rates were 48.1%, 19.9%, and 16.0%, respectively. Overall median survival was 10.3 months. For resectable gastric cancer with stage I and II PC, the 1-, 2-, and 5-year survival rates were 71.3%, 37.8%, and 30.2%, respectively, with median survival of 19.0 months, whereas for stage III and IV PC, the 1- and 2-year survival rates were 32.0% and 8.0%, respectively, with median survival of 6.6 months (P=.004) (Figure 2). For patients with CCR-0 or CCR-1, the 1-, 2-, and 5-year survival rates were 74.8%, 36.8%, and 29.4%, respectively, with median survival of 21.3 months, and for patients with CCR-2, the 1-year survival rate was 15.8%, with nobody alive at 2 years and median survival of 6.6 months (P<.001) (Figure 3). Among the different variables tested using univariate analysis, the presence of preoperative ascites, unresectable primary tumor, stage III or IV PC, and CCR-2 had a significant negative effect on survival. Survival rates were higher with adjuvant treatment than without, but this difference was not significant (P=.88). Multivariate analysis using a logistic regression model was performed to determine which clinical variables were most strongly correlated with survival. All clinical variables that were close to significance (P<.10) by univariate analysis were included in the model. The CCR...
category and the presence of preoperative ascites had a significant effect on survival (P<.001 and P=.04, respectively).

During follow-up, 6 patients had prolonged survival (2 patients survived >3 years and 4 survived >5 years): 4 are still alive with no evidence of disease at 140, 108, 107, and 104 months; 1 patient who underwent 2 procedures died of recurrence at 47 months; and 1 patient died of recurrence at 37 months. All four 5-year survivors had stage I PC and were treated by CCR-0 resection. Three of these patients had primary pT3 N1 tumors and 1 had primary pT4N1 tumor.

**COMMENT**

The management of PC arising from gastric cancer is a major problem because this form of metastasis is the most common cause of death in these patients. In the past, patients with PC were treated with high doses of intraperitoneal or systemic chemotherapy, with no improvement in survival and no long-term survivors. Most patients with PC die within 6 months of diagnosis, and the 5-year survival rate is 0%. During the 1990s, IPCH with its experimental background (direct cytotoxicity of hyperthermia against malignant cells, enhancement of anticancer drug cytotoxicity, and pharmacokinetic advantages of the intraperitoneal route for chemotherapy), cytoreductive surgery with the peritonectomy procedures, and immediate postoperative intraperitoneal chemotherapy were introduced for the management of PC of digestive origin. The first aim of IPCH is to wash out free intraperitoneal cancer cells and to damage peritoneal metastases by simultaneous heating and exposure to anticancer drugs: mitomycin C was demonstrated to have enhanced efficacy when combined with hyperthermia, and it is routinely used in Japan for gastric cancer adjuvant therapy. The authors previously reported the pharmacokinetic results, demonstrating that mitomycin C completely disappeared from blood within 2 hours after the end of IPCH, from urine within 24 hours, and from abdominal drains within 24 hours.

Cytoreductive surgery and peritonectomy procedures affect the reduction of tumor volume, which has always been considered an important factor in achieving a response to chemotherapy. The idea of reducing tumor volume in PC has been reported in the past for ovarian cancer. The combination of peritonectomy and IPCH (with or without hyperthermia) acts as a “dose-intensification device,” leading to better results. Theoretically, cytoreductive surgery is performed to treat the macroscopic disease and IPCH is performed to treat the microscopic residual disease to eradicate disease completely in a single procedure. However, combining 2 aggressive procedures can lead to greater mortality and morbidity rates. We reported morbidity of 16% in patients who underwent IPCH with limited cytoreductive surgery and a considerably higher rate of 47% in patients who underwent IPCH combined with extensive cytoreductive surgery. The number of resections and peritonectomy procedures, the number of anastomoses, and, in particular, the duration of surgery contribute to a significantly higher rate of complications. It would be expected that morbidity would correlate with the magnitude of surgery. Many patients had moderate to extensive surgery before being referred to our care. They required extensive dissection of all adhesions, stripping of peritoneum, and organ resections to maximize the benefits of this treatment. Surgeons must use their judgment to achieve a balance between the postoperative risk of extensive surgery and the potential benefit in survival and quality of life. The risk of postoperative complications also emphasizes the necessity for patient selection using the current strict criteria (young patients with good performance status, acceptable renal and myocardial function, no systemic chemotherapy 1 month before the procedure, no extra-abdominal metastases, no previous abdominal radiation therapy, and PC stage evaluation by abdominal CT).

Intraperitoneal chemohyperthermia was delayed in 21 patients and was performed after the resection of the primary tumor. Delaying IPCH reduces its effectiveness on residual tumor cells within the peritoneal cavity. Adhesions from previous operations entrap tumor cells and allow them to progress. Tumor cells fixed within scar tissue may not be reached by systemic or intraperitoneal chemotherapy. Delay in definitive treatment of carcino-
matosis until disease progression is evident allows superficial seeding to progress into an invasive process that is much more difficult and often impossible to eradicate. It has been suggested that peritonectomy procedures and cytoreductive surgery should remove gross disease and that intraperitoneal chemotherapy used at the same operative setting will eliminate microscopic residual disease. Median survival was shorter in patients who underwent delayed IPCH than in those for whom IPCH and surgical resection were performed as the same time. However, this difference was not statistically significant.

We reported 1-, 2-, and 5-year survival rates of 48.1%, 19.9%, and 16.0%, respectively, and 6 patients had pro-

longed survival (2 patients survived >3 years and 4 survived >5 years). These survival results are similar to those previously reported by Yonemura et al23 (Table 4 and Table 5). They updated their experience in 1996 with 83 patients who had peritonectomy in addition to IPCH with mitomycin C, cisplatin, and etoposide. They were the only researchers who reported 5-year survivors in patients with peritoneal seeding arising from gastric cancer. As we previously reported,23 PC with localized or small tumor nodules (stage I or II) seems to be the best indication for IPCH. Our study shows that the median survival of stage I and II PC was 19 months, whereas it was 6.6 months for stage III and IV PC. All 5-year survivors had stage I PC. Fujimoto et al9 (Table 4) also reported impressive survival in patients with limited PC (P1, peritoneal dissemination limited to the adjacent peritoneum, and P2, several scattered metastases in the distant peritoneum). For P1 and P2 PC, the 5-year survival rates were 55% and 42%, respectively, whereas the 1-year survival rate was only 18% for P3 PC (numerous metastases to the distant peritoneum). As some of our patients with stage III or IV PC are still alive 1 and 2 years after their procedure, we will not exclude them from our further studies.

The most important prognostic indicator seems to be the completeness of cytoreduction. Intraperitoneal chemohyperthermia seems to be most effective when cytoreduction achieves a complete or nearly complete resection, with the intent to cure. In patients with CCR-0 or CCR-1, median survival was 21.3 months, but it was only 6.1 months for patients with CCR-2. The same observations have been reported by other peritoneal surface malignancy centers for PC arising from gastric cancer (5-year survival rates in patients treated with complete cytoreduction and IPCH of 11%-31%).23 Similar results for PC arising from other origins have been reported.20,23,26 An aggressive attempt at complete resection, including surgical excision of all sites of macroscopic

Table 4. Median Survival in Different Subgroups by Univariate Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Median Survival, mo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metachronous</td>
<td>9.9</td>
<td>.40</td>
</tr>
<tr>
<td>Synchronous</td>
<td>12.6</td>
<td></td>
</tr>
<tr>
<td>Preoperative ascites</td>
<td>5.0</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>No preoperative ascites</td>
<td>15.6</td>
<td></td>
</tr>
<tr>
<td>Resectable tumor</td>
<td>13.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Unresectable tumor</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>pH1 involvement</td>
<td>10.3</td>
<td>.96</td>
</tr>
<tr>
<td>pH2-N3 involvement</td>
<td>9.5</td>
<td></td>
</tr>
<tr>
<td>Stage I-II PC</td>
<td>19.0</td>
<td>.004</td>
</tr>
<tr>
<td>Stage III-IV PC</td>
<td>6.6</td>
<td></td>
</tr>
<tr>
<td>CCR-0 or CCR-1</td>
<td>21.3</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>CCR-2</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>Delayed IPCH</td>
<td>9.6</td>
<td>.31</td>
</tr>
<tr>
<td>No delayed IPCH</td>
<td>13.9</td>
<td></td>
</tr>
<tr>
<td>Adjuvant treatment</td>
<td>15.2</td>
<td>.88</td>
</tr>
<tr>
<td>No adjuvant treatment</td>
<td>9.5</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CCR, completeness of cancer resection; IPCH, intraperitoneal chemohyperthermia; PC, peritoneal carcinomatosis. *These variables have a significant effect on survival in the multivariate analysis.

Table 5. Treatment of PC With Cytoreductive Surgery Combined With IPCH

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, No.</th>
<th>Follow-up, mo</th>
<th>Treatment</th>
<th>Median Survival, mo</th>
<th>1-y Survival, %</th>
<th>5-y Survival, %</th>
<th>5-y Survivors, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yonemura et al,25 1996</td>
<td>83</td>
<td>46</td>
<td>CC+IPCH (mitomycin C, cisplatin, etoposide)</td>
<td>NA</td>
<td>43</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>R0</td>
<td>28</td>
<td></td>
<td>CC+IPCH (mitomycin C)</td>
<td>13.9</td>
<td>61</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>R2</td>
<td>55</td>
<td></td>
<td>CC+IPCH (mitomycin C)</td>
<td>6.8</td>
<td>30</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Fujimoto et al,3 1997</td>
<td>48</td>
<td>NA</td>
<td>CC+IPCH (mitomycin C)</td>
<td>16.5</td>
<td>54</td>
<td>31</td>
<td>NA</td>
</tr>
<tr>
<td>P1 PC</td>
<td>21</td>
<td></td>
<td></td>
<td>NA</td>
<td>73</td>
<td>55</td>
<td>NA</td>
</tr>
<tr>
<td>P2 PC</td>
<td>8</td>
<td></td>
<td></td>
<td>52.8</td>
<td>62</td>
<td>42</td>
<td>NA</td>
</tr>
<tr>
<td>P3 PC</td>
<td>19</td>
<td></td>
<td></td>
<td>8.3</td>
<td>18</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hirose et al,14 1999</td>
<td>17</td>
<td>14.6</td>
<td>CC+IPCH (mitomycin C, cisplatin, etoposide)</td>
<td>11.0</td>
<td>44</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Loggie et al,24 2000</td>
<td>17</td>
<td>NA</td>
<td>CC+IPCH (mitomycin C)</td>
<td>10.1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Present study</td>
<td>49</td>
<td>99</td>
<td>CC+IPCH (mitomycin C)</td>
<td>10.3</td>
<td>48</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Stage I-II PC</td>
<td>18</td>
<td></td>
<td></td>
<td>19.0</td>
<td>71</td>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td>Stage III-IV PC</td>
<td>31</td>
<td></td>
<td></td>
<td>6.6</td>
<td>32</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CCR-0 or 1</td>
<td>25</td>
<td></td>
<td></td>
<td>21.3</td>
<td>75</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>CCR-2</td>
<td>24</td>
<td></td>
<td></td>
<td>6.1</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: CC, cytoreductive surgery; CCR, completeness of cancer resection; IPCH, intraperitoneal chemohyperthermia; NA, not assessed; PC, peritoneal carcinomatosis; P1, PC limited to the adjacent peritoneum; P2, several scattered metastases in the distant peritoneum; P3, numerous metastases to the distant peritoneum; R0, complete cytoreduction; R2, residual disease.

©2004 American Medical Association. All rights reserved.
disease, may add to the efficacy of IPCH. When cytoreductive surgery does not allow sufficient down-staging, the survival benefit of IPCH remains extremely low, and median survival does not exceed 6 to 8 months. In light of the risk of postoperative complications, IPCH may be not indicated in patients with CCR-2. These patients will be excluded from our further studies.

For many Korean and Japanese researchers, IPCH has been performed prophylactically or in an adjuvant setting. They report encouraging survival results in pT3 gastric adenocarcinoma. Yonemura et al recently conducted a randomized controlled study of 139 patients with T3 or T4 gastric tumor allocated to 3 groups: IPCH plus surgery, intraperitoneal normothermic chemotherapy plus surgery, and surgery alone. After median follow-up greater than 5 years, the 3-year survival rate of patients treated by the combination of IPCH and surgery was significantly higher at 60% than those of the other 2 groups, with similar morbidity rates. But these promising results were not confirmed by all Japanese studies. In Western countries, only one German study reported the use of IPCH for the prevention of PC recurrence in advanced gastric cancer. Nine patients were included in the study, with a median survival of >5 years, the 3-year survival rate of patients treated with IPCH in earlier stages of PC disease. Positive peritoneal cytologic examination is a risk factor for the development of PC and may be indicative of a poor prognosis. We are currently conducting a prospective multicenter study, EVOCAPE 2, to evaluate whether patients with positive peritoneal cytologic examination are at risk of PC disease. This study could define a group of patients at risk for PC development for whom IPCH would be indicated.

In conclusion, our results confirm that IPCH combined with cytoreductive surgery may improve survival results in gastric cancer with PC and may result in some long-term survivors among highly selected patients. The best indications are PC from resectable primary tumor, with localized, small tumor nodules, without preoperative ascites, or PC for which the cytoreductive surgery leads to sufficient down-staging. Because of high morbidity rates, strict patient selection is vital. The standardization of surgical procedures and IPCH techniques coupled with new anticancer drugs in a neoadjuvant setting may further improve the results of this promising treatment strategy.

Accepted for publication June 6, 2003.

This study was supported by grants from the French National League Against Cancer (Sàône-et-Loire, France) and the Lyon University of Sciences (Lyon). We thank Faheez Mohamed, MD, for reviewing the English editing.

Corresponding author and reprint: François Noel Gilly, MD, PhD, Surgical Department, Centre Hospitalier Lyon-Sud, 69495, Pierre Bénite CEDEX, France (e-mail: francogi@lyon-sud.univ-lyon1.fr).

REFERENCES


