**Adjuvant Hyperthermic Intraperitoneal Peroperative Chemotherapy (HIPEC) Associated with Curative Surgery for Locally Advanced Gastric Carcinoma. An Initial Experience**


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**Key words.** Gastric adenocarcinoma ; hyperthermic intraperitoneal chemotherapy.

**Abstract.** Aim of the study : After macroscopic radical (R0) surgery for advanced gastric carcinoma, 40 to 50% of the tumors recur in the abdomen as locoregional or peritoneal disease. We initiated a protocol in which patients with suspicion of macroscopic serosal, lymphatic or peritoneal invasion, treated with R0 resection, underwent adjuvant HIPEC.

**Methods :** Between June 1998 and January 2003, 16 patients with locally advanced adenocarcinoma of the stomach were included in the study. Surgery consisted of a total gastrectomy with a D2 lymphadenectomy. Splenectomy (n = 1), splenopancreatectomy (n = 4), transverse colectomy (n = 3), left heptectomy (n = 1), localized peritonectomy (n = 3) were associated to obtain a R0 resection. HIPEC protocol consisted of heated (42.5°C) intraperitoneal mitomycin C (15 mg/m2) for a planned duration of 90 minutes.

**Results :** HIPEC median duration was limited to 73(20-90) min because of central hyperthermia recognition in half of the cases. One patient died in the postoperative period of sepsis secondary to a duodenal fistula. Postoperative morbidity included pancreatic fistula (n = 2), pulmonary oedema (n = 1), pulmonary embolus (n = 1) and transient renal failure (n = 1). UICC staging was IB (n = 2), II (n = 2), IIIA (n = 5), IIIB (n = 1), IV (n = 6). None of the 16 patients are alive without recurrence with a median follow-up of 52 months. Four patients developed a recurrence, intraperitoneal (n = 2), systemic (n = 1), or combined (n = 1). Two patients were lost to follow-up.

**Conclusions :** Aggressive surgical therapy and HIPEC might represent the standard of care in a selected population with locoregional disease and for whom a R0 resection can be achieved. This protocol was associated in this study with a 75% 5-year survival with a low peritoneal recurrence rate and an acceptable morbidity.

**Introduction**

One of the main prognostic factors for gastric carcinoma is the ability to achieve a R0 resection. To reach this goal, adequate surgical margins must be obtained usually by total gastrectomy. D2 extended lymphadenectomy also benefits to those patients with locoregional disease (stade II) (1). Even respecting those rules, forty to fifty percent of the tumors will recur in the abdomen as locoregional or peritoneal disease (2). This risk of recurrence is affected by the histology diffuse type, serosal and lymph node invasion, as well as the size of the tumor (3).

Peroperative hyperthermia and intraperitoneal chemotherapy (HIPEC) act in synergy on those free cancer cells resulting from the transection of lymphatics and blood vessels draining the tumor and from the manipulation of a tumor with serosal invasion as well as on microscopic peritoneal carcinomatosis (4, 5). The good results obtained in the Japanese series (7-12) prompted us to initiate a protocol in which patients with suspicion of macroscopic serosal, lymphatic or peritoneal invasion, treated with R0 resection, underwent an adjuvant HIPEC.

**Patients and methods**

Between June 1998 and January 2003, 16 patients (11 Males/5 Females) with adenocarcinoma of the stomach were included in the study. Median age was 67 years (41-74). Median size of the tumor was 4 cm (2.5-10). The tumor originated from the proximal third of the stomach in eight cases, in the middle third in six cases, in the distal third in one patient and infiltrated diffusely the entire organ in one case. Indications for an adjuvant HIPEC were the possibility to achieve a complete R0 resection and the peroperative macroscopic suspicion of serosal invasion (n = 12), lymph node invasion (n = 7) or peritoneal nodules (n = 3).

**Surgical procedure**

Surgery consisted in total gastrectomy in all cases combined in one case with a subtotal oesophagectomy for a gastric tumor invading the distal oesophagus. A D2
lymphadenectomy was done in all cases except that the lymph node dissection was not routinely associated with a resection of the splenic vessels. Splenectomy alone and spleno-pancreatectomy were associated respectively in one and four cases, because of the localization and extension of the gastric tumor. A transverse colectomy was performed in three cases dictated by the invasion or the proximity of the mesocolon. A left hepatectomy was associated in the removal of a 10 cm tumor of the fundus. In three cases a macroscopic peritoneal invasion was evidenced as a localized nodule, respectively, on the left diaphragm, the transverse mesocolon and the Douglas pouch. The nodules were resected with the underlying peritoneum.

**Hyperthermic intraperitoneal chemotherapy**

The intraperitoneal chemotherapy consisted of mitomycin C (MMC) at a dose of 15 mg/m² for a planned duration of 90 min. The effective median duration of the treatment was however only 73 min (20-90) because in half of the cases, the duration had to be shortened for central hyperthermia (above 39°C). HIPEC was started after tumor resection and before completion of the gastrointestinal anastomoses. The abdominal edges were suspended according to the Coliseum technique (13) and the abdominal fluid was continuously stirred to ensure adequate contact of the peritoneal and visceral surfaces including the abdominal wall. The temperature was continuously monitored to stay between 42 and 43°C in all compartments of the abdomen (5).

**Postoperative complications**

One patient developed a duodenal fistula complicated by sepsis and renal failure. Although he underwent a new laparotomy and closure of the fistula, he progressed to multi-organ failure and died. Two patients developed a pancreatic leak after distal splenopancreatectomy, one responsible for a temporary external fistula, the other leading to a subphrenic abscess, drained percutaneously. One patient developed a pulmonary oedema shortly after the operation, which responded promptly to fluid restriction and diuretics. Other complications are listed in table I.

**Histopathological grading and staging**

All tumors were adenocarcinoma, poorly differentiated in 12 cases (with signet ring cells identified in seven cases), and moderately differentiated in four cases. Staging was performed according to the UICC(6) guidelines (Table II). Two patients T2N0 (Stage IB) were included in the study because of suspicion of macroscopic invasion of the serosa that was not confirmed by histology.
prognosis remains poor. Reported survival after curative surgery varies with reports between 10 and 40% at 5 years (2, 14). Epidemiologic variables, tumor stage and surgical technique explain the discrepancy between series. Obtaining a R0 resection by adequate surgical margins and extended lymphadenectomy seems to be important to improve patient survival and reduce the locoregional recurrence rate (15). The 70% locoregional recurrence rate reported in the US Intergroup Trial (INT-116) was suspected to reflect the limited extent of lymphadenectomy performed with only 10% of D2 lymphadenectomy (16). This would be substantiated by the 38% recurrence observed after D1 lymphadenectomy compared to 28% with D2 dissections in the Dutch Gastric Cancer Group study (17). The increase in surgical morbidity and mortality by the D2 resection may conceal the positive oncological effect, explaining the similar results obtained after D1 and D2 resections, published by the surgical Co-operative Group (18).

A macroscopic complete resection is however not sufficient to prevent intraabdominal recurrence. After R0 D2 resections, recurrence is still limited to the abdomen as loco-regional or peritoneal carcinomatosis in 40 to 50% of the cases (2). This can be explained by the frequent microinvolvement of lymph nodes (19) and the microscopic peritoneal involvement, both appearing as independent prognostic factors in multivariate analysis. In the study of Bando (20), five percent of patients without macroscopic peritoneal carcinomatosis had a positive peritoneal cytology at operation. The occurrence of positive peritoneal cytology is dependent on the tumor stage and the histology type (poorly differentiated, signet ring cell and mucinous carcinomas). The association of diffuse type histology and serosal invasion translated in a 69% rate of peritoneal recurrence in the study of ROVIELLO et al. (3).

Intraperitoneal chemotherapy places intraperitoneal cells and tissues in contact with high levels of cytotoxic drugs. Using a cytotoxic drug with elevated peritoneoplasmatic gradient will limit systemic toxicity. Hyperthermia per se has a temperature-dependent cytotoxic effect in vitro but also a synergistic effect with cytotoxic drugs (4, 21-23). These results were confirmed in the clinical setting. The prognosis of digestive carcinomatosis is poor, with a median survival below 6 months (25), enhanced at best by 3 to 6 months by systemic chemotherapy (26). In colo-rectal carcinomatosis, ELIAS et al. reported 3 and 5-year survival of 47 and 27%
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after RO cytoreduction (27). A prospective randomized trial of cytoreductive surgery and HIPEC vs systemic chemotherapy alone for the treatment of colorectal peritoneal carcinomatosis showed a 2-fold increase in survival in the combined arm, further magnified if cytoreduction was macroscopically complete (28). The results obtained in gastric carcinomatosis are also in favour of HIPEC, with long survivors after complete cytoreduction and significant increase of survival, compared to historical controls (29, 30).

Another step was the prophylactic use of HIPEC in cancers with high risk of recurrence (serosal or lymph node involvement). The results of several Japanese randomized trials demonstrated a significant reduction in peritoneal recurrence but also an increase in survival. Fujimoto et al. randomized 141 patients with gastric cancer invading the serosa to standard surgical resection with or without HIPEC with MMC (8). The peritoneal recurrence rate was significantly decreased while the 8-year survival rate was 62% for the patients receiving HIPEC versus 49% for the control group (p = 0.036). Yonemura et al. also demonstrated a statistically significant advantage in survival with HIPEC combining MMC and cisplatin in a 139 patients study, with a 5-year survival rate of 61% vs. 42% for surgery alone (9). Huang et al. (10) reported 72% 2-year survival in patients randomized to surgery and hyperthermic hypoorosmolar infusion combined with MMC bound to activated carbon vs 45.5% in patients treated with surgery alone (p = 0.035). In those studies, noticeable differences existed with the procedure described in this paper regarding drug and dosing regimen, as well as duration of HIPEC (from 60 to 120 min). The timing and modality of HIPEC also varied, being applied with the abdomen open or closed, before or after restoration of digestive continuity. A closed technique has been associated with an impaired distribution of heat and antineoplastic drugs (31). Furthermore, completion of digestive anastomoses before HIPEC exposes to the risk of tumor cells entrapment in the suture line. This might help to explain the non-significant increase of 5-year survival reported by Hamazoe et al. (64.2% with HIPEC vs 52.5% without) (11) and later by Ikekuchi et al. (51% with HIPEC vs 46% without) (12) who performed HIPEC with MMC after closure of the abdomen.

The dose of MMC (15 mg/m2) used in our study was adopted from the protocol of the Sugarbaker group (24). A temperature of 42-43°C appeared from experimental and clinical experiences as a compromise between antitumoral activity and morbidity to the patient (5). In this study, HIPEC duration had to be shortened for central hyperthermia. This has led us to adopt with experience a “cooling protocol” in which patient’s central temperature is decreased peroperatively, one hour before HIPEC is carried out. During HIPEC, cooling packs are placed around the head of the patient. The air temperature of the heat-exchange blankets covering the body parts excluded from the surgical field is decreased to room temperature. With this technique, HIPEC could be carried out for the planned duration in our ulterior experience. We did not encounter complications that we would consider a side effect of HIPEC. No haematological abnormalities were observed and the surgical complications were related to the importance of the procedures. This experience is shared by the Japanese groups who reported no increase of morbidity associated with HIPEC or a low
incidence of complications that were associated to the magnitude of hyperthermia (> 43°C) or to the specific side effects of the chemotherapy chosen.

Our report seems thus to confirm the promising results from the Japanese series. The limited size of our series and its retrospective character do not allow us to draw firm conclusions. However, this population represented a subset of patients with high risk for abdominal recurrence because of tumor stage, size and histology type. Aggressive surgical therapy with R0 resection and adjuvant HIPEC was carried out in selected patients with locally advanced gastric adenocarcinoma. It permitted to obtain 75% 5-year survival with an acceptable mortality and morbidity. Accumulating evidence from the literature suggests that HIPEC has a role in the treatment of locally advanced gastric carcinoma and warrants the validation of those results in a western randomized trial.

References