



Does Upfront Therapy with Cytoreductive Surgery and Hipec Confer a Survival Benefit in Patients with Synchronous Gastric Peritoneal Carcinomatosis when Compared with Patients with Metachronous Gastric Peritoneal Carcinomatosis?

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Abstract

Background: Patients with peritoneal carcinomatosis (PC) of gastric origin have an extremely bad prognosis with a median survival estimate at 1–3 months. Peritoneal carcinomatosis is present at the diagnosis in 5-20% of the patients, and almost 60% of them will present it after curative treatment. Peritoneal carcinomatosis from gastric cancer (GPC) responds poorly to systemic chemotherapy. We studied the efficacy of the upfront treatment with cytoreductive surgery (CRS) and HIPEC in patients with synchronous gastric peritoneal carcinomatosis and in patients with metachronous gastric peritoneal carcinomatosis.

Methods: We retrospectively analyzed 14 patients with GPC undergoing CRS/HIPEC the last 10 years. Six patients already presented GPC at the time of the diagnosis and eight of them presented metachronous GPC.

Results: CRS/HIPEC was performed for synchronous GPC in 6 patients and metachronous GPC in 8 patients. Kaplan-Meier survival curves demonstrated that survival times between two groups were not statistically different.

Conclusion: Upfront treatment with CRS/HIPEC doesn't seem to confer a survival benefit in patients with synchronous gastric peritoneal carcinomatosis.

Keywords: Gastric cancer; Peritoneal carcinomatosis; HIPEC; Upfront therapy

Introduction

Gastric cancer (GC) remains the second leading cause of cancer death worldwide, accounting for 8% of the total cases and 10% of total deaths in 2008 [1]. The five-year survival rate is ~25% for all stages [2]. Peritoneal carcinomatosis (PC) occurs synchronous with the primary tumor in about 14%-43% of patients with GC and accounts for 35% of all synchronous metastasis³ and it is considered a terminal stage of disease.

Surgery remains the curative treatment of choice for stomach cancer and the main reason for treatment failure is peritoneal recurrence which, according to the literature, occurs in 40 to 60% of cases, despite extensive surgery including D2 lymph node dissection [4]. Only 40% of GC deaths have hepatic metastases, while in 53–60% disease evolves through PC [5]. While systemic chemotherapy has shown to marginally improve the survival after curative surgery in GC, it has not shown to significantly lower the rate of distant metastases, including peritoneal recurrence [6] or change the patterns of recurrence [7].

Since MAGIC, FNCLCC and FFCD trials publication [8,9], systemic perioperative chemotherapy is recommended for the curative treatment of stomach cancer in Europe. In these studies the 5-year survival rate was 36% and 38% respectively in the experimental arm, compared to 23% and 24% respectively in the control arm with surgery alone.

The most important component of treatment failure is cancer dissemination within the

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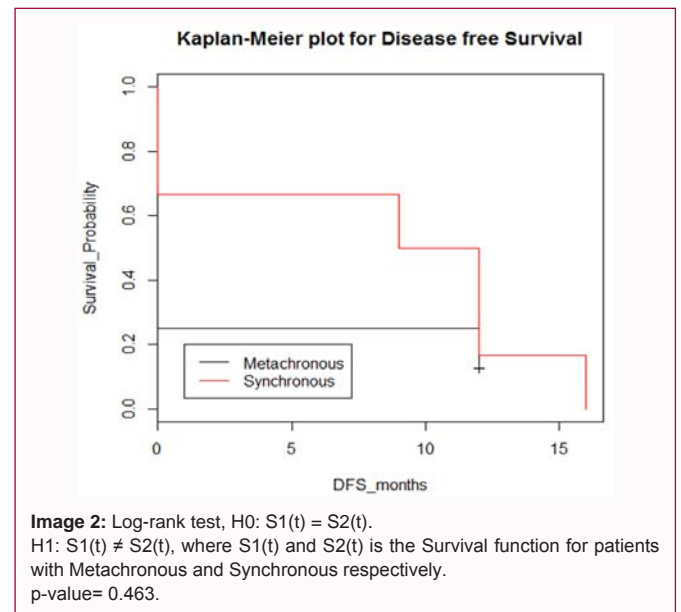
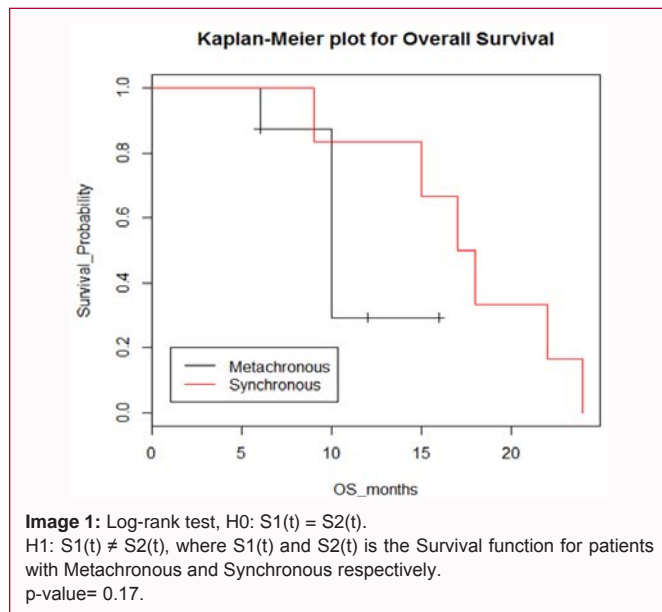
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peritoneal cavity and nodal metastasis. In contrast to lymphatic and haematogenous dissemination, peritoneal spread should be regarded as a loco-regional disease extension rather than systemic metastasis [10]. The poor response of PC to systemic chemotherapy is mainly due to the presence of the “plasma-peritoneal barrier” which isolates the peritoneal cavity from the effects of intravenous chemotherapy. Furthermore, the poor intra-peritoneal blood supply and oxygenation of cancer cells and the low apoptotic potential of such hypoxic tumor cells are also thought to be responsible for the poor response to chemotherapy [11].

The rationale for a regional perfusion is that local administration of chemotherapy in the peritoneum increases the local effects of the drugs and reduces the systemic toxicity [5]. When chemotherapy treatment is associated with hyperthermia, the loco-regional effects are considerably extended, with an increased penetration up to 3–6 mm into malignant nodules and an increased antimetastatic effect. Hyperthermia increases the effects of antitumoral drugs, especially of oxaliplatin, mitomycin C, doxorubicin, cisplatin, paclitaxel, and irinotecan, also increasing the chemosensitivity of neoplastic cells [12]. Drugs absorbed through the peritoneum enter the portal vein, and also have a chemotherapeutic effect on the liver [13].

The HIPEC technique is increasingly used in the curative treatment of primary and digestive peritoneal carcinomatosis, in association with cytoreductive surgery. A growing number of authors have been investigating this procedure and start to test the technique in more aggressive tumours like gastric cancer.

Patients and Methods

We retrospectively analyzed 14 patients with GPC undergoing CRS/HIPEC the last 10 years. Six patients already presented GPC at the time of the diagnosis (group A) and eight of them presented metachronous GPC (group B).

Synchronous peritoneal disease was preoperatively diagnosed with CT and MRI. Patients were informed and consented to be treated with extended cytoreductive surgery and HIPEC. Patients of group B were treated initially with gastrectomy in our and in others centers. They all received adjuvant systemic chemotherapy after surgery. The

diagnosis of peritoneal recurrence was again made by CT scan and MRI.

All patients were offered a complete cytoreduction and 90 minutes of HIPEC with cis-platinum (50mg/m²) and doxorubicine (50 mgr/m²).

Median PCI was 15 for both groups and complete cytoreduction (cc0) was achieved in 5 patients of group A (83, 3%) and in 6 patients of group B (75%). Cytoreduction cc1 was achieved in 3 patients.

Morbidity and mortality were similar in both groups and patients were followed-up for 4 years.

Results

Patient’s demographics were similar in both groups and morbidity and mortality were not statistically different between groups.

We analyzed the results in both groups in terms of long term survival and disease free survival. Kaplan-Meier survival curves (Image 1 and 2) demonstrated that survival times between two groups were not statistically different.

The upfront treatment with cytoreductive surgery and HIPEC didn’t seem to confer a survival benefit to patients with synchronous peritoneal carcinomatosis from gastric cancer.

Discussion

The percentage of patients with gastric cancer who presents with synchronous peritoneal carcinomatosis varies from 14% to 43% according to literature. Peritoneal recurrence after curative surgery is seen in 10%-46% of patients [3,14]. Recent studies show that peritoneal dissemination is more frequent than hematogenous metastases. Only 40% of deaths from gastric cancer have hepatic metastases, while in 53–60% disease evolves through PC [5].

While systemic chemotherapy has shown to marginally improve the survival after curative surgery in gastric cancer, it hasn’t shown to significantly lower the rate of distant metastases, including peritoneal recurrence [9,15].

The need for new methods of preventing and treating PC from

GC was obvious. Furthermore, the belief that PC is more of a loco-regional than a systemic disease has led to a resurgence of interest in regional therapies like cytoreductive surgery (CRS) and hyperthermic intra-peritoneal chemotherapy (HIPEC) [7].

Fujimoto et al. [16] in 1988 was the first to report the use of CRS and HIPEC in patients with gastric cancer and peritoneal carcinomatosis. Out of 15 patients, 9 had synchronous PC. They were all offered extensive resection of the disease and HIPEC with mitomycin C. The median survival at the time of the report was 7.2±4.6 mo. They concluded that extensive surgery with IPHP was a safe and well tolerated treatment for GCPC.

In 1996, Yonemura et al. [17], for the first time, reported a 5 year survival of 11% in a group of 83 patients who underwent cytoreductive surgery with HIPEC. Glehen et al. [18] reported a prospective study of 49 patients of GC with PC from the same institution. In 51% of the patients, the cytoreduction was either complete or the size of the residual nodules were <5 mm. The overall median survival was 10.3 mo and the 5-year survival rates was 16%. A complete cytoreduction (CCRO) and a smaller volume of tumor were associated with a better survival. In patients who underwent a CCR 0/1 resection, the 5-year survival was 29.4% and the median survival was 21.3 mo.

A multi-institutional study from 15 centres in France and Belgium published a large series of CRS and HIPEC in 159 patients. The 5 year survival was 13% and median survival was 9.2 mo.

Yang et al. [19] from China published a randomized phase 3 study of CRS and HIPEC in patients with peritoneal carcinomatosis from gastric cancer. He enrolled 68 patients that received CRS and HIPEC either CRS alone. The 3-year survival in the CRS with HIPEC arm was 5.9% compared to 0% in the CRS alone arm. CRS with HIPEC was associated with a significantly higher median survival compared to CRS alone (11 mo vs. 6.5 mo, P = 0.04). The authors concluded that compared to CRS alone, CRS with HIPEC is likely to increase survival by 2.6 times.

Various factors have been reported to be associated with a good outcome following CRS and HIPEC for GCPC. Completeness of cytoreduction [18,20] seems to be the most important one. The extent of peritoneal carcinomatosis, the presence of preoperative ascites, the response to neoadjuvant chemotherapy and the institution where the procedure is done are other independent prognostic factors [18,20,21]. Furthermore Yang [19] has reported that synchronous peritoneal carcinomatosis from gastric cancer is an independent predictor for better survival after CRS and HIPEC.

In our study we tried to verify if Yang's experience was reproducible in the western world. Even if both groups' characteristics were similar to each other, in terms of PCI index and CC score, non-statistically difference in overall survival and disease free survival was reported. Tumors different biologic behavior and genetic factors may play an important role for these different results between eastern and western world.

More patients need to be enrolled in our study in order to be able to report safe conclusions about the necessity of CRS and HIPEC as upfront therapy in gastric cancer with synchronous peritoneal carcinomatosis.

References

- Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin.* 2011; 61: 69-90.

- Berretta M, Fischella R, Borsatti E, Lleshi A, Loffredo S, Menequzzo N, et al. Feasibility of intraperitoneal Trastuzumab treatment in a patient with peritoneal carcinomatosis from gastric cancer. *Eur Rev Med Pharmacol Sci.* 2014; 18: 689-692.
- Thomassen I, van Gestel YR, van Ramshorst B, Luyer MD, Bosscha K, Nienhuijs SW, et al. Peritoneal carcinomatosis of gastric origin: a population-based study on incidence, survival and risk factors. *Int J Cancer.* 2014; 134: 622-628.
- Yoo CH, Noh SH, Shin DW, Choi SH, Min JS. Recurrence following curative resection for gastric carcinoma. *Br J Surg.* 2000; 87: 236-242.
- Okines A, Verheij M, Allum W, Cunningham D, Cervantes A; ESMO Guidelines Working group. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology.* 2010; 21: v50-v54.
- Liang JW, Zheng ZC, Yu T, Wang X, Zhang JJ. Is postoperative adjuvant chemoradiotherapy efficacious and safe for gastric cancer patients with D2 lymphadenectomy? A meta-analysis of the literature. *Eur J Surg Oncol.* 2014; 40: 1614-1621.
- Sugarbaker PH, Yu W, Yonemura Y. Gastrectomy, peritonectomy, and perioperative intraperitoneal chemotherapy: the evolution of treatment strategies for advanced gastric cancer. *Semin Surg Oncol.* 2003; 21: 233-248.
- Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. MAGIC Trial Participants: Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med.* 2006; 355: 11-20.
- Ychou M, Boige V, Pignon JP, Conroy T, Bouche O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol.* 2011; 29: 1715-1721.
- Yan TD, Black D, Sugarbaker PH, Zhu J, Petrou G, Morris DL, et al. A systematic review and meta-analysis of the randomized controlled trials on adjuvant intraperitoneal chemotherapy for resectable gastric cancer. *Ann Surg Oncol.* 2007; 14: 2702-2713.
- Jacquet P, Sugarbaker PH. Peritoneal-plasma barrier. *Cancer Treat Res.* 1996; 82: 53-63.
- Roviello F, Caruso S, Marrelli D, Pedrazzani C, Neri A, De Stefano A, et al. Treatment of peritoneal carcinomatosis with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: state of the art and future developments. *Surg Oncol.* 2011; 20: e38-e54.
- Speyer JL, Sugarbaker PH, Collins JM, Dedrick RL, Klecker RW Jr, Mayers CE. Portal levels and hepatic clearance of 5-fluorouracil after intraperitoneal administration in humans. *Cancer Res.* 1981; 41: 1916-1922.
- Abbasi SY, Taani HE, Saad A, Badheeb A, Addasi A. Advanced gastric cancer in Jordan from 2004 to 2008: a study of epidemiology and outcomes. *Gastrointest Cancer Res.* 2011; 4: 122-127.
- Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med.* 2007; 357: 1810-1820.
- Fujimoto S, Shrestha RD, Kokubun M, Ohta M, Takahashi M, Kobayashi K, et al. Intraperitoneal hyperthermic perfusion combined with surgery effective for gastric cancer patients with peritoneal seeding. *Ann Surg.* 1988; 208: 36-41.
- Yonemura Y, Fujimura T, Nishimura G, Falla R T, Katayama K, Tsugawa K, et al. Effects of intraoperative chemohyperthermia in patients with gastric cancer with peritoneal dissemination. *Surgery.* 1996; 119: 437-444.
- Glehen O, Schreiber V, Cotte E, Sayag-Beaujard AC, Osinsky D, Freyer G, et al. Cytoreductive surgery and intraperitoneal chemohyperthermia for peritoneal carcinomatosis arising from gastric cancer. *Arch Surg.* 2004; 139: 20-26.

19. Yang XJ, Huang CQ, Suo T, Mei LJ, Yang GL, Cheng FL, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. *Ann Surg Oncol.* 2011; 18: 1575-1581.
20. Glehen O, Gilly FN, Arvieux C, Cotte E, Boutitie F, Mansvelt B, et al. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. *Ann Sur Oncol.* 2010; 17: 2370-2377.
21. Fujimoto S, Takahashi M, Mutou T, Kobayashi K, Toyosawa, T, Isawa E, et al. Improved mortality rate of gastric carcinoma patients with peritoneal carcinomatosis treated with intraperitoneal hyperthermic chemoperfusion combined with surgery. *Cancer.* 1997; 79: 884-891.