JBUON 2017; 22(5): 1144-1147
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

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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Summary

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. Surgery remains the curative treatment option for GC and the main reason for treatment failure is peritoneal recurrence which, according to the literature, occurs in 40-60% of the cases, despite extensive surgery including D2 lymph node dissection. The hyperthermic intraperitoneal chemotherapy (HIPEC) technique is increasingly used in the treatment of primary and digestive peritoneal carcinomatosis (PC), in association with cytoreductive surgery (CRS). We retrospectively analyzed 14 patients with gastric peritoneal carcinomatosis (GPC) undergoing CRS/HIPEC in the last 10 years. Six patients already had GPC at the time of diagnosis (group A) and 8 developed metachronous GPC (group B). Treatment with CRS and HIPEC didn't seem to confer a survival benefit to patients with synchronous PC from gastric cancer.

Key words: *gastric cancer, cytoreductive surgery, HIPEC, synchronous vs metachronous peritoneal carcinomatosis*

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 5-year survival rate is ~25% for all stages [2]. Peritoneal carcinomatosis (PC) occurs synchronously with the primary tumor in about 14-43% of patients with GC, it accounts for 35% of all synchronous metastases [3] and it is considered a terminal stage of disease.

Surgery remains the curative treatment option for GC and the main reason for treatment failure is peritoneal recurrence which, according to the literature, occurs in 40-60% of the cases, despite extensive surgery including D2 lymph node dissection [4]. Only 40% of GC deaths have hepatic metastases, while in 53–60% the 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 the publication of MAGIC, FNCLCC and FFCD trials [8,9], systemic perioperative chemotherapy is recommended for the curative treatment of GC 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 factor of treatment failure is cancer dissemination within the peritoneal cavity and nodal metastasis. In contrast to lymphatic and haematogeneous dissemination,

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Received: 01/03/2017; Accepted: 17/03/2017

peritoneal spread should be regarded as a locoregional 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 intraperitoneal 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 rational 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 is associated with hyperthermia, the locoregional effects are considerably extended, with an increased penetration up to 3–6mm into malignant nodules and an increased antimitotic effect. Hyperthermia increases the effects of antitumor 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, exerting also a chemotherapeutic effect on the liver [13].

The HIPEC technique is increasingly used in the treatment of primary and digestive peritoneal carcinomatosis, in association with CRS. A growing number of researchers [2,7] has been investigating this procedure and start to test the technique in more aggressive tumors like gastric cancer.

Methods

We retrospectively analyzed 14 patients with gastric peritoneal carcinomatosis (GPC) undergoing CRS/HIPEC in the last 10 years. Six patients already had GPC at the time of diagnosis (group A) and 8 developed metachronous GPC (group B).

Synchronous peritoneal disease was preoperatively diagnosed with CT and MRI. Patients were informed and consented to be treated with extended CRS 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 subjected to cytoreduction and 90 min of HIPEC with cisplatin (50mg/m^2) and doxorubicin (50 mg/m^2).

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%). cc1 cytoreduction was achieved in 3 patients.

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

Statistics

Data were expressed as frequencies and medians. Disease-free survival and overall survival were estimated from the date of CRS and HIPEC, using Kaplan-Meier analysis and multivariate analysis following the Cox multiple regression method. Confidence intervals were calculated at 95%. A $p<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 19.0.

Results

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

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

Therefore, treatment with CRS and HIPEC didn't seem to confer a survival benefit to patients with synchronous PC from GC in comparison with those presented with metachronous PC.

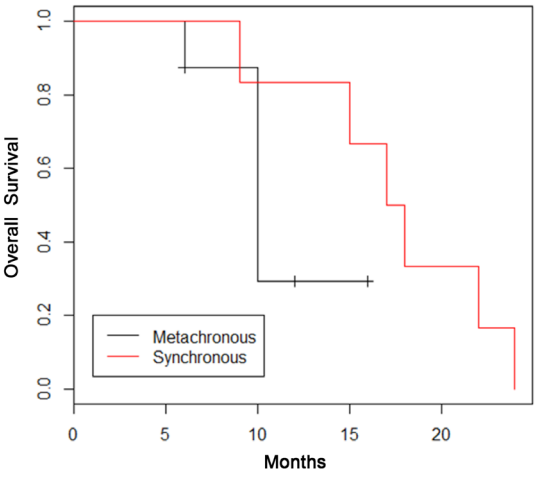

Figure 1. Kaplan-Meier overall survival in the 2 groups (Log rank, p=0.17).

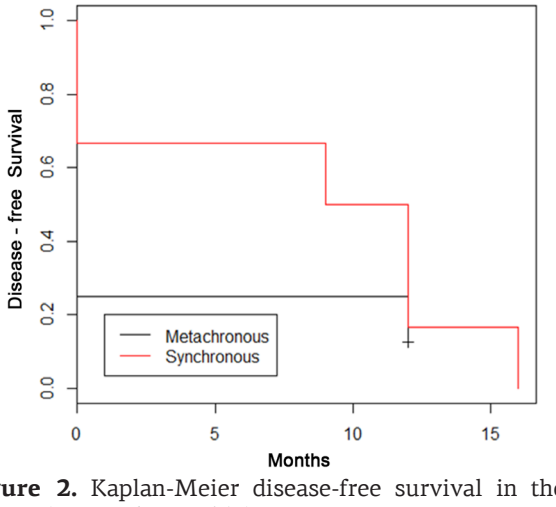

Figure 2. Kaplan-Meier disease-free survival in the 2 groups (Log rank, p=0.463).

Discussion

The percentage of patients with GC who present with synchronous PC varies from 14 to 43% according to the literature [3]. Peritoneal recurrence after curative surgery for GC is seen in 10-46% of the patients [3,4]. Recent studies [3,4,7] show that peritoneal dissemination is more frequent than hematogeneous metastases. Only 40% of patients dying of GC have hepatic metastases, while in 53–60% of the disease evolves through PC [5].

While systemic chemotherapy has shown to marginally improve the survival after curative surgery in GC, it hasn't shown to significantly lower the rate of distant metastases, including peritoneal recurrence [15,16].

The need for new methods of preventing and treating PC from GC is obvious. Furthermore, the belief that PC is more a locoregional than a metastatic disease has led to a resurgence of interest in regional therapies like CRS and HIPEC [17].

Fujimoto et al. [18] in 1988 were the first to report the use of CRS and HIPEC in patients with GC and PC. Out of 15 patients, 9 had synchronous PC. They were all subjected to extensive disease resection and HIPEC with mitomycin C. The median survival at the time of the report was 7.2±4.6 months and the authors concluded that extensive surgery with HIPEC was a safe and well tolerated treatment for PC of GC.

In 1996, Yonemura et al. [19] reported for the first time a 5-year survival of 11% in a group of 83 patients who underwent CRS with HIPEC. Glehen et al. [22] 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 median overall survival was 10.3 months and the 5-year survival 16%. Complete cytoreduction (CCR0) and a smaller volume of tumor were associated with better survival. In patients who underwent a CCR 0/1 resection, the 5-year survival was 29.4% and the median survival 21.3 months.

The authors of a multi-institutional study from 15 centres in France and Belgium [21] published a large series of CRS and HIPEC for PC from GC in 159 patients. The 5-year survival was 13% and the median survival 9.2 months.

Yang et al. [22] from China published a randomized phase 3 study of CRS and HIPEC in patients with PC from GC. They enrolled 68 patients that received CRS and HIPEC or 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 vs 6.5 months, 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 PC of GC and completeness of cytoreduction [20,21] seems to be the most important one. The extent of PC, the presence of preoperative ascites, the response to neoadjuvant chemotherapy and the institution where the procedure is done are other independent prognostic factors [20,21,23]. Furthermore, Yang et al. [22] has reported that synchronous PC from GC is an independent predictor of better survival after CRS and HIPEC.

In our study we tried to verify whether Yang's experience was reproducible in a western population. Even if both groups' characteristics were similar to each other in terms of PCI and CC score, no statistically significance difference in overall survival and disease-free survival was noticed. Different biological behaviors and genetic factors may play an important role for the different results between eastern and western patients.

In studies like the present one more patients should be enrolled in order to be able to report safe conclusions about the necessity of CRS and HIPEC as upfront therapy in GC with synchronous PC.

Conflict of interests

The authors declare no confict of interests.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D: Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2. Berretta M, Fisichella R, Borsatti E et al. Feasibility of intraperitoneal trastuzumab treatment in a patient with peritoneal carcinomatosis from gastric cancer. Eur Rev Med Pharmacol Sci 2014;18:689-92.
3. Thomassen I, van Gestel YR, van Ramshorst B et al. Peritoneal carcinomatosis of gastric origin: a population-based study on incidence, survival and risk factors. Int J Cancer 2014;134:622-628.
4. Yoo CH, Noh SH, Shin DW, Choi SH, Min JS. Recur-

rence following curative resection for gastric carcinoma. Br J Surg 2000;87:236-42.

5. Okines A, Verheij M, Allum W, Cunningham D, Cervantes A. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21:v50-v54.
6. 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;40:1614-21.
7. 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;21:233-48.
8. Cunningham D, Allum WH, Stenning SP et al. MAGIC Trial Participants: Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.
9. Ychou M, Boige V, Pignon JP et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715-21.
10. Yan TD, Black D, Sugarbaker PH 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;14:2702-13.
11. Jacquet P, Sugarbaker PH. Peritoneal-plasma barrier. Cancer Treat Res 1996;82:53-63.
12. Roviello F, Caruso S, Marrelli D 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.
13. Speyer JL, Sugarbaker PH, Collins JM et al. Portal levels and hepatic clearance of 5-fluorouracil after intraperitoneal administration in humans. Cancer Res 1981;41:1916-22.
14. 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;4:122-7.
15. Sakuramoto S, Sasako M, Yamaguchi T et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007;357:1810-20.
16. Ducourtieux M, Bedenne L, Fabre JM et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715-21.
17. 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: 233-48.
18. Fujimoto S, Shrestha RD, Kokubun M et al. Intraperitoneal hyperthermic perfusion combined with surgery effective for gastric cancer patients with peritoneal seeding. Ann Surg 1988;208:36-41.
19. Yonemura Y, Fujimura T, Nishimura G et al. Effects of intraoperative chemohyperthermia in patients with gastric cancer with peritoneal dissemination. Surgery 1996;119:437-44.
20. Glehen O, Schreiber V, Cotte E et al. Cytoreductive surgery and intraperitoneal chemohyperthermia for peritoneal carcinomatosis arising from gastric cancer. Arch Surg 2004;139:20-6.
21. Glehen O, Gilly FN, Arvieux C et al. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. Ann Surg Oncol 2010;17:2370-77.
22. Yang XJ, Huang CQ, Suo T 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;18:1575-81.
23. Fujimoto S, Takahashi M, Mutou T et al. Improved mortality rate of gastric carcinoma patients with peritoneal carcinomatosis treated with intraperitoneal hyperthermic chemoperfusion combined with surgery. Cancer 1997;79:884-91.