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Phase II study of patients with peritoneal carcinomatosis from gastric cancer treated with preoperative systemic chemotherapy followed by peritonectomy and intraperitoneal chemotherapy

BO HULTMAN[1], PEHR LIND[2], BENGT GLIMELIUS[2,3], MAGNUS SUNDBOM[1], PETER NYGREN[3], ULF HAGLUND[1] & HAILE MAHTEME[1]

[1]*Department of Surgical Sciences, Section of Surgery, Uppsala University, Uppsala, Sweden,* [2]*Department of Oncology and Pathology, Karolinska Institute, Stockholm, Sweden and* [3]*Department of Radiology, Oncology Radiation Sciences, Uppsala University, Uppsala, Sweden*

Abstract

Background. The aim was to evaluate the feasibility and the effectiveness of neoadjuvant systemic chemotherapy followed by cytoreductive surgery (CRS), hyperthermic intraperitoneal chemotherapy (HIPEC) and early postoperative intraperitoneal chemotherapy (EPIC) in patients with peritoneal carcinomatosis (PC) from gastric cancer. *Material and methods*. Eighteen patients (median age 57 years, range 38–74) were scheduled for three months' neoadjuvant systemic chemotherapy followed by CRS + HIPEC + EPIC. *Results*. At the time of surgery, the peritoneal tumor burden was extensive with tumor growth on the entire peritoneal cavity. Only eight patients received the entire treatment and OS was 14.3 months (range 6.1–34.3, 95% CI 6.6–20.3). Six patients had macroscopically radical (CC0) surgery and for this subgroup OS was 19.1 months (range 6.1–34.3, 95% CI 6.9–27.1). Postoperative 90-day mortality was 10% (one patient) and the perioperative grades II–IV adverse events (AE) rate was 62.5%. *Discussion*. Neoadjuvant chemotherapy followed by CRS + HIPEC + EPIC does not seem to be associated with prolonged OS in patients with extensive PC growth from gastric cancer unless macroscopically radical surgery is achieved. However, morbidity from this treatment is considerable and it cannot be recommended for routine care until a prospective randomized trial has been performed.

Metastatic gastric cancer is regarded as a terminal stage and in the absence of more effective therapeutic options, systemic chemotherapy is used in patients with a median overall survival (OS) of 11 months [1]. Peritoneal carcinomatosis (PC) from gastric cancer implies a very poor prognosis, with median OS of approximately three months [2] and no survival at five years [3]. In these patients, cytoreductive surgery (CRS) followed by intraperitoneal chemotherapy, e.g. as hyperthermic intraperitoneal chemotherapy (HIPEC) and/or early postoperative intraperitoneal chemotherapy (EPIC), has demonstrated a median OS ranging from 8.0 to 11.5 months [4–10]. Postoperative 30-day mortality in these studies was 0–11% and perioperative morbidity was 14–67%. Neoadjuvant chemotherapy in combination with CRS + HIPEC was used in one of the studies [7]. EPIC was given only to patients in Farma's [9] study and to a few patients in Glehen's study [7]. However, data is still lacking on the possible benefit from a multimodal treatment approach in patients with PC from gastric cancer.

The aims of this study were to investigate whether multimodal treatment consisting of neoadjuvant systemic chemotherapy followed by CRS + HIPEC + EPIC in patients with PC from gastric cancer is feasible and appears effective.

Material and methods

Between January 2005 and March 2009, 18 consecutive patients with PC from gastric cancer were scheduled for neoadjuvant systemic chemotherapy followed by CRS + HIPEC + EPIC at Uppsala University Hospital, Uppsala, Sweden. The regional ethics committee approved the study and informed

Correspondence: B. Hultman, Department of Surgical Sciences, Section of Surgery, Uppsala University, SE-751 85 Uppsala, Sweden. Tel: + 46 18 6114607. Fax: + 46 18 6114508. E-mail: bo.hultman@surgsci.uu.se

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consent was obtained from each patient and the study was registered in ClinicalTrials.gov, with identifier NCT01379482. The eligibility requirements for treatment were: histologically confirmed diagnosis of primary gastric adenocarcinoma; histologically and radiologically confirmed PC diagnosis; no distant metastases; adequate renal, hematopoietic and liver functions, and Karnofsky performance status (KPS) of > 70. Table I summarizes demographic and basic clinical patient data.

Patients

Eighteen patients (eight female and 10 male), with a median age of 57 years (range 38–74), were included in the study. Treatment began with three months' (range 2–4.5) neoadjuvant systemic chemotherapy. Four weeks after receiving the last course of chemotherapy, patients with no clinical and radiological signs of tumor progression underwent laparotomy in preparation for CRS + HIPEC followed by EPIC for five days. Patients with clinical and radiological signs of tumor progression during the neoadjuvant systemic chemotherapy did not undergo the planned loco-regional treatment but continued with palliative systemic chemotherapy at the discretion of the physician in charge of the patient.

Neoadjuvant chemotherapy

The intention was to treat the patients with combination chemotherapy for three months. The choice of chemotherapy was individualized, but all patients received optimal drug combinations suitable for good performance patients with metastatic gastric cancer.

Routine clinical controls and blood sampling were done before every treatment cycle. In order to rule out patients with progressive disease and distant metastasis, abdominal and thoracic computed tomography (CT)-scan evaluations were performed prior to surgery.

Surgical treatment

Depending on disease extent, CRS was performed as described by Sugarbaker [11]. Immediately postoperatively, tumor load and completeness of cytoreduction for PC were recorded using the Peritoneal Cancer Index (PCI) [12] and Completeness of Cytoreduction scores (CC) [13] respectively. The PCI (range 1–39) consists of lesion size scores in 13 different regions of the abdomen: 0 = no tumor seen, 1 = tumor up to 0.5 cm, 2 = tumor up to 5 cm and 3 = tumor > 5 cm. The PCI score is calculated by adding together the lesion size scores for the 13 regions. The CC score is based upon the size of tumor left after cytoreduction: CC0 = no peritoneal seeding visible, CC1 = nodules up to 2.5 mm, CC2 = nodules up to 2.5 cm and CC3 = nodules > 2.5 cm.

Table I. Demographic data, basic clinical data and treatment data of 18 patients with peritoneal carcinomatosis from gastric adenocarcinoma enrolled for loco-regional treatment.

Variables	Number of patients
Median age 57 years (38–74)	
Gender	
Female	8
Male	10
Karnofsky performance status	
90–100	14
70	2
MD	2
Tumor grade status	
T3	11
T4	1
MD	6
Lymph node status	
N0	2
N1	3
N2	3
N3	1
MD	9
Signet ring cells	
Yes	13
No	5
Neoadjuvant chemotherapy	
Irinotecan + Nordic FLv	6
EOX	6
FLOX	3
Docetaxel + Irinotecan + 5-FU + LV	1
FOLFIRI	1
ECF	1
Cytoreductive surgery	
Yes	8
No	8
Open and shut	2
Peritoneal Cancer Index for cytoreductive surgery patients	
< 9	3
9–12	1
13–18	2
> 18	2
Completeness of cytoreduction scores for cytoreductive surgery patients	
CC0	6
CC1	1
CC2	1

CC0, no peritoneal seeding visible; CC1, nodules up to 2.5 mm; CC2, nodules up to 2.5 cm; ECF, epirubicin + cisplatin + 5-fluorouracil; EOX, epirubicin + oxaliplatin + capecitabine; 5-FU, 5-fluorouracil; FLOX, 5-fluorouracil + leucovorin + oxaliplatin; FOLFIRI, leucovorin + 5-fluorouracil + irinotecan; LV, leucovorin; MD, missing data; Nordic FLv, bolus 5-fluorouracil + leucovorin.

HIPEC and EPIC

HIPEC was administered according to the Coliseum technique [14] and was combined with EPIC for five days. Before perfusion, the patient's body temperature was lowered to 35°C with a cooling blanket (Allon®). The intra-abdominal temperature during perfusion ranged from 42°C to 44°C. Four intra-abdominal drains were left in place after surgery and EPIC was given daily during the first five postoperative days.

Tumor markers, histopathology and adverse events

Five serum tumor markers (CEA, CA 125, CA 19-9, CA 15-3 and CA 72-4) were taken one to six days before surgery and 10 days after surgery, to analyze the frequency of the impact of gastric cancer with PC on these tumor markers.

The sixth edition of the TNM classification was used. The presence of signet ring cells and the grade of differentiation according to Lauren's classification [15] were reported.

Therapy-related adverse events were graded according to the National Cancer Institute's common toxicity criteria (NCI-CTC) version 3.0 [16]. OS was calculated for all patients from the date of the first neoadjuvant chemotherapy.

Statistical methods

All analyses were performed on the basis of intention-to-treat. OS and disease-free survival (DFS) were analyzed for patients treated with CC0. Results were presented as the median, with a 95% confidence interval (CI). A p-value of less than 0.05 was considered statistically significant. The computer software package STATISTICA AXA version 10.0, StatSoft Scandinavia, Sweden, was used for statistical evaluation of the survival data.

Results

Treatment

All patients had poorly differentiated tumors and 50% (9/18) were of the diffuse type according to Lauren's classification. Signet ring cells were detected in 72% of the patients (13/18).

Eight patients did not undergo CRS+HIPEC due to peritoneal tumor progression during the systemic chemotherapy (4), death during the neo-adjuvant treatment (1), the finding of lung metastasis (2) or due to severe depression (1). Ten of the 18 patients were scheduled for CRS+HIPEC+EPIC: eight patients were treated with CRS+HIPEC+EPIC whereas two patients underwent only laparotomy, i.e. not treated by loco-regional procedure due to extensive tumor growth on the entire small bowel surface. The following CRS procedures were carried out: total (6) or subtotal gastrectomy (1) with D2 lymphadenectomy and greater omentectomy; cholecystectomy (2) and dissection of the duodenal-hepatic ligament (2); splenectomy (6); parietal peritonectomy (3); right (4) and left (3) upper quadrant peritonectomy; colon (4) and small bowel resection (1); pelvic peritonectomy (5); rectosigmoid resection (1) and hysterectomy (1). PCI for the eight patients who received the planned treatment was 12 (range 5–26) and PCI for those who were not treated by loco-regional procedure due to extensive tumor growth on the entire small bowel surface was 19 and 22. CC0 was achieved in six patients, CC1 in one patient and CC2 in one patient. PCI for the CC0 subgroup was 12 (range 5–22). The patients with macroscopically radical surgery (CC0) had a median baseline Karnofsky performance score (KPS) of 100, whereas the patients who did not undergo macroscopically radical surgery ($CC > 0$) had a median KPS of 90. Median follow-up time was 14.3 months (range 2.8–37.2).

During HIPEC, five patients received cisplatin at a dose of 50 mg/m^2 combined with doxorubicin 15 mg/m^2. The carrier solution used for these drugs was low calcium peritoneal dialysis solution PD4 [Dianeal 13.6 mg/ml (Baxter, USA)]. The treatment lasted 90 minutes. Three patients were treated during HIPEC by oxaliplatin 460 mg/m^2 + concomitant intravenous (IV) 5-FU 500 mg/m^2 bolus and intravenous LV 60 mg/m^2 for 30 minutes [17]. The carrier solution for oxaliplatin was 50 mg/ml glucose IV solution.

Six patients received EPIC, five with 5-FU (550 mg/m^2 daily) and intravenous LV (60 mg/m^2 daily) and one with paclitaxel (20 mg/m^2 daily). Two patients did not receive EPIC treatment due to chemotherapy-related toxicity. Five patients received postoperative systemic chemotherapy, three in the adjuvant setting and two in the palliative setting. Median time to start the postoperative systemic chemotherapy was seven weeks (range 6–72).

Morbidity

Fourteen of the 18 patients had AEs of grades II–IV related to the neoadjuvant treatment period and one died in multi-organ failure caused by chemotherapy treatment. Five of the eight patients undergoing CRS+HIPEC+EPIC had AEs grades II–IV related to the in-hospital period of CRS+HIPEC+EPIC. No patients died within 30 days of surgery, but one patient died within 90 days of surgery. Eight of the 10 patients in the palliative setting (not undergoing

CRS + HIPEC + EPIC) had AEs grades II–IV. Table II presents details on morbidity.

Survival

The median OS for the CRS + HIPEC + EPIC group was 10.2 months (range 1.2–34.3, 95% CI 6.9–13.7). For the eight patients undergoing all treatment as planned, OS was 14.3 months (range 6.1–34.3, 95% CI 6.6–20.3). Six of the eight patients had macroscopically radical surgery (CC0) and for this subgroup OS was 19.1 months (range 6.1–34.3, 95% CI 6.9–27.1) with a DFS of 9.0 months (range 2.2–16.1, 95% CI 3.2–12.6).

Tumor markers

Tumor markers were normal in three of the eight patients who had CRS + HIPEC + EPIC and in five of the eight patients at least one tumor marker was elevated. In contrast, all 10 patients without CRS + HIPEC + EPIC treatment had at least one elevated tumor marker.

Discussion

This is the first prospective study testing combined treatment with neoadjuvant systemic chemotherapy followed by CRS, HIPEC and EPIC, in patients with PC from gastric cancer. Our objectives were to investigate whether this multimodal treatment of PC from gastric cancer is feasible and to evaluate the clinical outcomes.

In patients with operable, non-metastatic gastric cancer, a perioperative regimen of ECF (epirubicin, cisplatin and 5-FU) decreases tumor size and staging and improves survival [18]. Patients with PC from gastric cancer are mostly treated with systemic chemotherapy [2,19]. A growing treatment option for PC is CRS + HIPEC + EPIC, with promising results in colorectal cancer [20] and pseudomyxoma [13]. There is no technical difference in the performance of CRS for PC from gastric cancer compared to PC from colorectal cancer [21–23], but the prognosis is worse for patients with PC from gastric cancer [24]. This could presumably result from different tumor biology and HIPEC's lower efficacy in PC from gastric cancer, compared to PC from colorectal cancer. However, data are still lacking on the possible benefits from such an approach in patients with PC from gastric cancer and there is debate as to whether this treatment should be applied in this disease [19].

Seven studies have been published testing various combinations of CRS + HIPEC + EPIC in patients with gastric cancer and PC (see Table III): one randomized clinical trial [10], two prospective [4,8], one non-randomized with case control patients [5], and three retrospective [6,7,9]. OS for our CRS + HIPEC + EPIC group was in line with these seven studies, and so was OS for the subgroup CC0 (19.1 months in this study and 8.0–36.3 for the comparable studies). Signet ring cell carcinoma is a major and independent factor of poor prognosis in gastric cancer [25] and to some extent this is also true for cancer with diffuse histo-clinical type according to Lauren´s classification [26], as well as poorly differentiated tumors [27]. In our study, the patients' tumor histopathology was less favorable than in the comparable studies. All our patients had poorly differentiated tumors: 50% were of the diffuse type, and signet ring cells were detected in 72% of the patients. In comparable studies [4,6–8,10,28] 56% of patients had poorly differentiated tumors (range 33–82) and only one group reported in two studies [8,10] the presence of signet ring cells, in 4–11.8% of the patients. There has been speculation that histopathologically, signet cell type cancers could also be an exclusion criterion. In a study by Fanelli et al. [29], there was a significant correlation between signet cell type cancers and the presence of PC at diagnosis, but signet cell type cancers were not a predictor of poor survival. In addition, patients in our study were treated with extensive CRS, even if tumor involvement was found in more than seven regions, and we refrained from surgery only if PC was widespread on the small bowel [30]. Careful patient selection seems essential for good results from loco-regional treatment for patients with PC from gastric cancer [4–7] and baseline performance status seems to be an important tool in the selection process [7]. Our current study supported those opinions concerning

Table II. Adverse events (AEs) of grades II–IV in relation to neoadjuvant period; cytoreductive surgery (CRS) + hyperthermic intraperitoneal chemotherapy (HIPEC) + early intraperitoneal chemotherapy (EPIC) period; and late period (postoperative in-hospital until death).

	Neoadjuvant	CRS/HIPEC/EPIC	Late period
Thromboembolism		2	1
Intracranial haemorrhage			2
Anastomotic leakage		3	
Bowel perforation		1	1
Intra-abdominal abscess	1	1	1
Septicemia	1		
GI-function disturbance	19	2	6
Psychiatric/psychological	3	1	3
Neurological	11		5
Hematogenic	2	1	1
Dermatological			2
Variety of symptoms	10	2	7

GI-function disturbance, AEs related to gastrointestinal function such as diarrhea, nausea, vomiting, obstipation and dysphagia; Psychiatric/psychological, depression, anxiety, insomnia.

Table III. Data from trials on CRS + HIPEC in patients with PC from GC.

Author	Publication year	No of patients	Chemo EPIC	Mortality (%)	Morbidity (%)	OS (months)	1-year survival (%)	2-year survival (%)	3-year survival (%)
Rossi [40]	2003	13	No	0	26	15	MD	MD	MD
Glehen [4]	2004	49	No	4	27	10.3	39	14	10
Hall [5]	2004	34	No	0	35	8.0	36	26	23
Yonemura [6]	2005	42	No	7	43	11.5	31	14	MD
Farma [9]	2005	9	Yes	11	67	9.0	22	11	11
Gusani [41]	2007	2	No	MD	MD	MD	MD	MD	MD
Spiliotis [42]	2008	3	No	MD	MD	10	33	0	0
Yang [28]	2009	12	No	MD	MD	29	>75	MD	MD
Yang [8]	2010	28	No	0	14.3	9.2	28	14	7
Glehen [7]	2010	150	Yes/No	6.5	27.8	9.2	43	23	18
Yang [10]	2011	34	No	0	14.7	11.0	42	15	6
Present study	-	8	Yes	0	62.5	14.3	62.5	37.5	0

EPIC, early postoperative intraperitoneal chemotherapy; MD, missing data; OS, overall survival.

gastric cancer with PC: all the patients who had macroscopically radical surgery had a very good performance status, while one of the patients who had no macroscopically radical surgery had a reduced performance status.

Over the past two decades, many studies have revealed that tumor markers are useful as a means of checking the prognosis, predicting a favorable outcome after treatment, and predicting recurrence and risk of death for patients with advanced GC [31–39]. Tumor markers could also be potential tools in the selection process. Thus, of the 10 patients in the subgroup that received no CRS + HIPEC + EPIC, none had normal tumor marker levels in contrast to three of the eight patients receiving the entire planned treatment. However, due to the small number of patients, conclusions about the value of tumor markers must be made with care.

Postoperative 30-day mortality in our study was at the low end (0%) compared with patients in previously published studies (range 0–11%). However, the perioperative morbidity rate in our study was at the high end (62.5%) compared with patients in previously published studies (Table III). In this study, grades II–IV morbidity were reported, not just grades III and IV toxicity, as presented in some other studies. Interestingly, Glehen et al. [7] noted that the complication rate was higher (60%) in the EPIC subgroup, well in line with the complication rate in the study by Farma et al. [9], including patients receiving EPIC (67%). A learning curve is not a plausible reason for the morbidity rate, as dedicated surgeons have performed CRS with HIPEC/EPIC with good results at our center for the past two decades [21]. Moreover, higher morbidity could be expected with the use of platinum-based HIPEC [21], and this could be one reason for higher morbidity in our cohort [21], as both Glehen et al. [4] and Hall et al. [5] used only Mitomycin C, and Yang et al. [8,10] used relatively low doses of cisplatin. The value of each intraperitoneal chemotherapy treatment (HIPEC or EPIC) on survival could not be addressed by our study. However, due to the increased morbidity rate that is observed when EPIC treatment is applied [7], perioperative morbidity could be reduced in the future if the EPIC regimen is excluded.

In conclusion, the results of this study support previous reports [4–10] that PC from gastric cancer has a dismal prognosis regardless of treatment. If feasible, CRS + HIPEC + EPIC treatment seems to give a slightly prolonged survival, even though it is associated with a rather high degree of morbidity. Before this treatment can be recommended for routine care in patients with gastric cancer with PC, further studies, preferably a prospective randomized trial must be performed.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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References

[1] Gubanski M, Johnsson A, Fernebro E, Kadar L, Karlberg I, Flygare P, et al. Randomized phase II study of sequential docetaxel and irinotecan with 5-fluorouracil/folinic acid (leucovorin) in patients with advanced gastric cancer: The GATAC trial. Gastric Cancer 2010;13:155–61.

[2] Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: Results of the EVOCAPE 1 multicentric prospective study. Cancer 2000;88:358–63.

[3] Yonemura Y, Fujimura T, Nishimura G, Falla R, Sawa T, Katayama K, et al. Effects of intraoperative chemohyperthermia in patients with gastric cancer with peritoneal dissemination. Surgery 1996;119:437–44.

[4] 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;139:20–6.
[5] Hall JJ, Loggie BW, Shen P, Beamer S, Douglas Case L, McQuellon R, et al. Cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for advanced gastric cancer. J Gastrointest Surg 2004;8:454–63.
[6] Yonemura Y, Kawamura T, Bandou E, Takahashi S, Sawa T, Matsuki N. Treatment of peritoneal dissemination from gastric cancer by peritonectomy and chemohyperthermic peritoneal perfusion. Br J Surg 2005;92:370–5.
[7] 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 Surg Oncol 2010;17:2370–7.
[8] Yang XJ, Li Y, Yonemura Y. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy to treat gastric cancer with ascites and/or peritoneal carcinomatosis: Results from a Chinese center. J Surg Oncol 2010;101:457–64.
[9] Farma JM, Pingpank JF, Libutti SK, Bartlett DL, Ohl S, Beresneva T, et al. Limited survival in patients with carcinomatosis from foregut malignancies after cytoreduction and continuous hyperthermic peritoneal perfusion. J Gastrointest Surg 2005;9:1346–53.
[10] 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; 18:1575–81.
[11] Sugarbaker PH. Peritonectomy procedures. Ann Surg 1995;221:29–42.
[12] Vazquez Vde L, Sugarbaker PH. Cholecystectomy, lesser omentectomy, and stripping of the omental bursa: A peritonectomy procedure. J Surg Oncol 2003;84:45–9.
[13] Sugarbaker PH, Chang D. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. Ann Surg Oncol 1999;6:727–31.
[14] Sugarbaker PH, Averbach AM, Jacquet P, Stephens AD, Stuart OA. A simplified approach to hyperthermic intraoperative intraperitoneal chemotherapy (HIIC) using a self retaining retractor. Cancer Treat Res 1996;82:415–21.
[15] Lauren P. The two histological main types of gastric carcinoma: Diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand 1965;64:31–49.
[16] NCI NIH DHHS. DTCD, Common terminology criteria for adverse events v3.0 (CTAE). Cancer Therapy Evaluation Program, 2006. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf
[17] Elias D, Bonnay M, Puizillou JM, Antoun S, Demirdjian S, El OA, et al. Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: Pharmacokinetics and tissue distribution. Ann Oncol 2002; 13:267–72.
[18] Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Participants, perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. New Engl J Med 2006;355:11–20.
[19] Bozzetti F, Yu W, Baratti D, Kusamura S, Deraco M. Locoregional treatment of peritoneal carcinomatosis from gastric cancer. J Surg Oncol 2008;98:273–6.
[20] Cashin PH, Graf W, Nygren P, Mahteme H. Cytoreductive surgery and intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis: Prognosis and treatment of recurrences in a cohort study. Eur J Surg Oncol 2012;38: 509–15.
[21] van Leeuwen BL, Graf W, Pahlman L, Mahteme H. Swedish experience with peritonectomy and HIPEC. HIPEC in peritoneal carcinomatosis. Ann Surg Oncol 2008;15: 745–53.
[22] Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De Simone M, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: A multi-institutional study. J Clin Oncol 2004;22: 3284–92.
[23] Elias D, Benizri E, Di Pietrantonio D, Menegon P, Malka D, Raynard B. Comparison of two kinds of intraperitoneal chemotherapy following complete cytoreductive surgery of colorectal peritoneal carcinomatosis. Ann Surg Oncol 2007; 14:509–14.
[24] Glehen O, Gilly FN, Boutitie F, Bereder JM, Quenet F, Sideris L, et al. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: A multi-institutional study of 1,290 patients. Cancer 2009; 116:5608–18.
[25] Piessen G, Messager M, Leteurtre E, Jean-Pierre T, Mariette C. Signet ring cell histology is an independent predictor of poor prognosis in gastric adenocarcinoma regardless of tumoral clinical presentation. Ann Surg 2009;250: 878–87.
[26] Sun Z, Xu YY, Wang ZN, Zhu Z, Zhang H, Huang BJ, et al. Macroscopic serosal classification predicts peritoneal recurrence for patients with gastric cancer underwent potentially curative surgery. Ann Surg Oncol 2011;18:1068–80.
[27] Greene F, Page DL, Fleming ID, Fritz A, Balch CM, Haller DG, et al. AJCC cancer staging manual. New York: Springer; 2002.
[28] Yang XJ, Li Y, al-shammaa Hassan AH, Yang GL, Liu SY, Lu YL, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy improves survival in selected patients with peritoneal carcinomatosis from abdominal and pelvic malignancies: Results of 21 cases. Ann Surg Oncol 2009; 16:345–51.
[29] Fanelli MF, Silva MJ, de Paiva TF, Jr., Chinen LT, Guimaraes AP, Gimenes DL, et al. Factors correlated with peritoneal carcinomatosis and survival in patients with gastric cancer treated at a single institution in Brazil. Int J Clin Oncol 2009;14:326–31.
[30] Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003;21:3737–43.
[31] Takahashi Y, Takeuchi T, Sakamoto J, Touge T, Mai M, Ohkura H, et al. The usefulness of CEA and/or CA19-9 in monitoring for recurrence in gastric cancer patients: A prospective clinical study. Gastric Cancer 2003;6: 142–5.
[32] Kodama I, Koufuji K, Kawabata S, Tetsu S, Tsuji Y, Takeda J, et al. The clinical efficacy of CA 72-4 as serum marker for gastric cancer in comparison with CA19-9 and CEA. Int Surg 1995;80:45–8.
[33] Safi F, Kuhns V, Beger HG. Comparison of CA 72-4, CA 19-9 and CEA in the diagnosis and monitoring of gastric cancer. Int J Biol Markers 1995;10:100–6.
[34] Yamao T, Kai S, Kazami A, Koizumi K, Handa T, Takemoto N, et al. Tumor markers CEA, CA19-9 and CA125 in monitoring of response to systemic chemotherapy in patients with advanced gastric cancer. Jpn J Clin Oncol 1999;29:550–5.

[35] Ychou M, Duffour J, Kramar A, Gourgou S, Grenier J. Clinical significance and prognostic value of CA72-4 compared with CEA and CA19-9 in patients with gastric cancer. Dis Markers 2000;16:105–10.
[36] Gaspar MJ, Arribas I, Coca MC, Diez-Alonso M. Prognostic value of carcinoembryonic antigen, CA 19-9 and CA 72-4 in gastric carcinoma. Tumour Biol 2001;22:318–22.
[37] Lai IR, Lee WJ, Huang MT, Lin HH. Comparison of serum CA72-4, CEA, TPA, CA19-9 and CA125 levels in gastric cancer patients and correlation with recurrence. Hepatogastroenterology 2002;49:1157–60.
[38] Marrelli D, Roviello F, De Stefano A, Farnetani M, Garosi L, Messano A, et al. Prognostic significance of CEA, CA 19-9 and CA 72-4 preoperative serum levels in gastric carcinoma. Oncology 1999;57:55–62.
[39] Bystrom P, Berglund A, Nygren P, Wernroth L, Johansson B, Larsson A, et al. An explorative study on the clinical utility of baseline and serial serum tumour marker measurements in advanced upper gastrointestinal cancer. Oncol Rep 2010;24:1645–52.
[40] Rossi CR, Pilati P, Mocellin S, Foletto M, Ori C, Innocente F, et al. Hyperthermic intraperitoneal intraoperative chemotherapy for peritoneal carcinomatosis arising from gastric adenocarcinoma. Suppl Tumori 2003;2:S54–7.
[41] Gusani NJ, Cho SW, Colovos C, Seo S, Franko J, Richard SD, et al. Aggressive surgical management of peritoneal carcinomatosis with low mortality in a high-volume tertiary cancer center. Ann Surg Oncol 2008;15:754–63.
[42] Spiliotis J, Tentes AA, Vaxevanidou A, Korakianitis OS, Rogdakis A, Mirelis CG, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal carcinomatosis. Preliminary results and cost from two centers in Greece. J Buon 2008;13:205–10.