JBUON 2017; 22(5): 1338-1344
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Hepatobiliary and pancreatic procedures during cytoreductive surgery and HIPEC

Ioannis Kyriazanos[1], Nikolaos Kopanakis[2], Vasileios Kalles[1], Alexios Tzivanakis[3], Georgios Nikolaou[2], Elias Efstathiou[2], John Spiliotis[2]

[1]2nd Department of Surgery, Naval and Veterans Hospital of Athens, Athens, Greece; [2]Department of Surgery, Metaxa Cancer Hospital, Piraeus, Greece; [3]Department of General Surgery, Southampton University Hospitals NHS Trust, United Kingdom

Summary

Purpose: *The combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has been used as locoregional treatment in selected patients with peritoneal malignancy. The purpose of this study was to report on the outcomes of patients undergoing hepatobiliary and pancreatic procedures during CRS and HIPEC.*

Methods: *A prospectively maintained database was used to identify patients that underwent hepatobilliary and/or pancreatic procedures during CRS and HIPEC. Outcome variables included morbidity, 30-day or in-hospital mortality, return to operating theatre, and complications.*

Results: *Sixty eight patients were included in the study, in whom 67 hepatobiliary and 15 pancreatic procedures were performed. Complete cytoreduction (CC-0/1) was achieved in 64 patients (94.8%). Twelve patients underwent liver resections, 50 underwent resection of Glisson's capsule, 5 underwent procedures of the biliary tree and 15 patients underwent pancreatic procedures. Major complications were encountered in 30/68 patients (44.1%). Pancreatic fistulas (PFs) were observed in 42.8% of the patients that underwent distal pancreatectomy. Reoperation rate was 8.8%, while 2.9% of the patients died during their hospital stay.*

Conclusion: *The need for hepatobiliary procedures bears a significant - but acceptable - rate of morbidity. However, it should not represent a definitive contraindication for CRS and HIPEC.*

Key words: *complications, cytoreductive surgery, hepatobiliary, HIPEC, pancreatic, pancreatic fistula*

Introduction

The presence of peritoneal metastases has previously been considered a terminal condition. The use of CRS followed by HIPEC now offers a promising treatment option in carefully selected patients with peritoneal disease of gastrointestinal cancer, ovarian cancer or primary peritoneal malignancies [1-5].

CRS aims to excise all macroscopic disease in the peritoneal cavity and it usually involves long operative times with multi-visceral resections and peritonectomies followed by peritoneal lavage with a heated chemotherapy solution to eradicate any floating tumor cells or macroscopically invisible deposits [6]. As a result, patients undergoing CRS and HIPEC experience high rates of morbidity (12-52%) and mortality (0.5-6%) [6,7]. This remains the basis of the main criticism of CRS and HIPEC in such patients. The extent of disease, as reflected by the number of the resected organs and the duration of surgery, have been repeatedly identified as independent predictors of morbidity [8,9].

In the rare occasion, where the liver parenchyma, porta hepatis, duodenum, aorto-caval groove

Correspondence to: Vasileios Kalles, MSc, PhD. 2nd Department of Surgery, Naval and Veterans Hospital of Athens, Deinokratous 70, Athens, 11521 Greece.
Tel: +30 210 7261000, E-mail: vkalles@med.uoa.gr
Received: : 09/05/2017; Accepted: 23/05/2017

or the pancreas are involved by carcinomatosis, hepatobiliary and/or pancreatic resections are required in order to achieve complete cytoreduction. Such procedures in many cases are challenging, and represent the most difficult part of cytoreduction, being therefore associated with a significant morbidity and mortality rate [10]. The range of such procedures in CRS and HIPEC ranges from the standard addition of routine cholecystectomy in all cases, to more complex hepatobiliary and pancreatic resections.

The aim of this study was to report on the outcomes of patients with peritoneal carcinomatosis involving the liver parenchyma or capsule, the extra hepatic biliary ducts or the pancreas and who were treated with CRS and HIPEC with curative intent.

Methods

Patient population and characteristics

A prospectively maintained and regularly audited for accuracy of data collection database was used to identify patients that underwent hepatobilliary and/or pancreatic procedures (see below for details) as part of their CRS and HIPEC from two participating centres (Metaxa Cancer Hospital, Piraeus and Naval and Veterans Hospital, Athens).

Cytoreductive surgery and HIPEC

All patients underwent detailed preoperative assessment including radiological and/or laparoscopic staging to estimate the extent of peritoneal dissemination and resectability of the disease. Peritoneal carcinomatosis was quantified according to the peritoneal cancer index (PCI) [10]. The feasibility of liver resections was assessed preoperatively using computed tomography. The patient's performance status was assessed based on the Eastern Cooperative Oncology Group (ECOG) scale [11]. All cases were discussed in a dedicated Multi–Disciplinary Team (MDT) meeting, in which treatment options were discussed, and the MDT results were available to the patients before surgery.

CRS included primary tumor removal (if present), visceral resections and peritonectomies using the technique described by Sugarbaker [11-13]. The completeness of the cytoreduction (CCR) by CRS was assessed by the surgeon at the end of the procedure and was classified into the following 3 categories: CCR-0 (no macroscopic residual cancer remaining), CCR-1 (no residual nodule >2.5 mm), and CCR-2 (residual nodules >2.5mm in the greatest dimension) [12].

Following CRS, HIPEC was performed using either the closed or the open abdomen technique, at a target intraperitoneal temperature of 42.5oC. Depending on the primary tumor origin and/or preoperative systemic chemotherapy data, different chemotherapeutic agents were used for HIPEC (Table 1).

Table 1. Combinations of chemotherapy agents used for HIPEC

Primary tumor site	*Regimen*
Ovarian cancer	Platinum – sensitive: Cisplatin 50 mg/m² Paclitaxel 175 mg/m² Platinum – resistant: Doxorubicin 15 mg/m² Paclitaxel 175 mg/m²
Colorectal cancer	Previous systemic chemotherapy: Mitomycin 15 mg/m² No previous systemic chemotherapy: Oxaliplatin 360 mg/m² Irinotecan 360 mg/m²
Appendiceal cancer / Pseudomyxoma	Mitomycin 15 mg/m²
Mesothelioma	Cisplatin 75 mg/m² Doxorubicin 15 mg/m²
Primary peritoneal cancer	Cisplatin 75 mg/m² Doxorubicin 15 mg/m²

Hepatobiliary procedures and pancreatic resections

In order to achieve complete cytoreduction, certain surgical procedures were performed, including lesser omentectomy, cholecystectomy, liver round ligament excision and stripping of the omental bursa [14]. The mobilization of the liver was performed as recently described by Halkia et al. [15]. Glisson capsule resection was recorded where the depth of tumor infilitration was greater than 5mm and a surgical decapsulation of ≥25% of the liver was performed, as previously described by Glockzin et al. [16].

Distal pancreatectomy (DP) was performed in association with splenectomy in cases of tumor invasion of the pancreas / pancreatic capsule / splenic hilum, or iatrogenic lesions of the pancreas. The pancreatic duct was closed using sutures, staples, or both. Fibrin glue or fibrin adhesive sealant was routinely used in all cases.

Outcome variables and complications grading

Outcome variables included morbidity, 30-day or in-hospital mortality, return to operating theatre, and complications. Postoperative morbidity was graded according to the Clavien-Dindo classification system [17]. Minor morbidity was defined as Clavien-Dindo grade I and II, while major morbidity was defined as Clavien-Dindo grade III and IV.

PFs were characterized following the International Study Group of Pancreatic Fistula (ISGPF) criteria [18]. The diagnosis of pancreatic leak was made in the presence of any measurable volume of fluid on or after postoperative day 3, with an amylase concentration 3-fold higher the upper limit of normal serum value. Computed tomography scans were performed in patients with abdominal pain, fever, and/or persistently high neutrophils on full blood count analysis, or elevated amylase on drain liquid biochemical analysis. However, radiological documentation was not mandatory for diagnosis of a pancreatic leak.

Statistics

Descriptive statistics, including frequencies and percentages for categorical data and means and standard deviations for continuous data, were calculated for the parameters recorded. P values <0.05 were considered statistically significant.

Results

Patient characteristics

In total 260 patients underwent CRS and HIPEC in the study period. A total of 68 patients were included in the present analysis, in whom a total of 67 hepatobiliary and 15 pancreatic procedures were performed. Previous abdominal surgery was reported in 57 patients, while 38 (55.9%) had received systemic chemotherapy prior to the CRS and HIPEC. The ECOG performance status was ≤1 in 76.5% of the patients. The primary tumor origin data is presented in Table 2.

Table 2. Patient characteristics

Characteristics	*n*	*%*
Mean age, years (range)	51.2 (29–73)	
Gender		
Male	31	45.6
Female	37	53.4
BMI, mean (range)	26.1 (20.5–31)	
Performance status		
0/1	52	76.5
2+	16	23.5
Primary tumor		
Appendix / Pseudomyxoma	28	41.2
Colorectal cancer	22	32.3
Ovarian cancer	11	16.2
Mesothelioma	5	7.4
Primary peritoneal cancer	2	2.5
Median PCI score (range)	17 (5-32)	

CRS and HPB procedures

Table 2 provides a detailed summary of the organ resections and peritonectomies performed. The median operative time was 360 min, with a range of 160–640 min. Complete cytoreduction (CC-0/1) was achieved in 64 patients (94.8%). In the remaining 4 patients, HIPEC was performed for palliative reasons, as recommended. The mean hospital stay was 18.7 days, with a mean ICU stay 2.9 days.

Twelve patients underwent liver resections (10 non–anatomic resections and 2 left lateral hepatectomy), 50 underwent resection of Glisson's capsule, 4 underwent repair of iatrogenic bile duct injury, while common bile duct resection and reconstruction was performed in one patient. Furthermore, 14 patients underwent distal pancreatectomy and one underwent a Whipple procedure (Table 3).

Table 3. Operative details of patients undergoing HPB procedures as part of CRS and HIPEC

Completeness of cytoreduction	*n*	*%*
CC-0/1	64	94.8
CC-2	4	5.2
Resected organs		
Greater omentum	61	89.7
Salpingoophorectomy	53	77.9
Hysterectomy	43	63.2
Small bowel	21	30.8
Stomach	6	8.8
Large bowel	54	79.4
Rectum	41	60.3
Pancreas	15	22.1
Gallbladder	59	86.8
Spleen	36	52.9
Parietal peritonectomies		
Right upper quadrant	52	76.5
Left upper quadrant	44	64.7
Diaphragm	19	27.9
Epigastrium	7	60.3
Pelvis	49	72.1
Median procedure duration, min (range)	380 (160–640)	
HIPEC technique		
Open	27	39.7
Closed	41	60.3
Median HIPEC duration, min (range)	60 (30–90)	
Median estimated blood loss, ml (range)	850 (250–3.000)	

Postoperative outcomes

An overview of the operative outcomes of the 68 patients included in the study is presented in Table 3. Overall, 16 patients (23.5%) had a completely uneventful postoperative course without any major or minor complications. One or more minor complications such as (but not limited to) fever, postoperative pain, wound infection, delayed wound healing, pleural effusion, chest infection, gastroparesis, urinary tract infection, and deep vein thrombosis were encountered in 38/68 patients (55.8%).

One or more major complications were encountered in 30/68 patients (44.1%). Twelve of the patients experienced more than one major complication. The details of the major postoperative complications (Clavien–Dindo III & IV) are reported cumulatively in Table 4.

Regarding PFs, 6 out of the 14 (42.8%) patients that underwent DP experienced a PF, as per the ISGPF definition. Two patients experienced a grade A PF that was successfully treated without any further intervention. Another 3 patients had a grade B PF, while one patient experienced a grade C PF. These cases were managed with

image–guided percutaneous drainage along with somatostatin analogue, as well as appropriate management in ICU when needed.

Six patients (8.8%) returned to theatre to deal with the complications above (Table 5). Finally, 2 out of the 68 patients died during their hospital stay following CRS that involved HPB procedures and HIPEC, both due to multi–organ failure following sepsis.

Table 4. Short–term outcomes of patients undergoing HPB procedures as part of CRS and HIPEC

Outcomes	*n*	*%*
Minor morbidity [17]	38	55.8
Major morbidity [17]	30	44.1
Abdominal collection / Abscess	12	17.6
Pancreatitis	8	11.8
Pulmonary sepsis	5	7.4
Pancreatic fistula (B&C grade)	4	5.9
Bile leak	3	4.4
Anastomotic leak	2	2.9
Intra–abdominal bleeding	2	2.9
Hematoma	1	1.5
Pulmonary embolism	1	1.5
Renal failure (requiring dialysis)	1	1.5
Wound dehiscence	1	1.5
Pulmonary effusion	1	1.5
Myocardial infarction	1	1.5
Reoperation	6	7.8
30-day or in-hospital mortality	2	2.6
Hospital stay (d), mean (range)	18.7 (8-63)	
ICU stay (d), mean (range)	2.9 (1-17)	

Table 5. Operative management of complications in patients undergoing HPB procedures as part of CRS and HIPEC

Case no.	*Complication*	*Procedure*
1	Intra–abdominal bleeding	Re–look laparotomy, washout, hemostasis
2	Intra–abdominal bleeding	Re–look laparotomy, washout, hemostasis
3	Anastomotic leak	Laparotomy, washout, reconstruction of anastomosis
4	Anastomotic leak	Laparotomy, washout, end colostomy formation
5	Bile leak	Laparotomy, repair of biliodigestive anastomosis with sutures
6	Wound dehiscence	Wound debridement, placement of vacuum dressing

Discussion

CRS combined with HIPEC are becoming a standard of care in selected patients with peritoneal carcinomatosis, who would otherwise have had a significantly poor prognosis. Due to the complexity of these procedures (multi-visceral resections and peritonectomies), CRS has been associated with a significant risk of surgical complications [6]. However, complete cytoreduction (CC0 or 1) has been identified as the most important factor leading to the improved survival seen in such patients [19,20].

During the development of peritoneal carcinomatosis, free tumor cells may be entrapped in areas of "low intensity circulation" of the peritoneal fluid, such as the liver hilum, the liver round ligament, the caudate lobe (Arantius ligament) or the aorto-caval groove [16,21]. As a result, segments III and IVb of the liver tend to be more frequently involved. In addition, among patients with colorectal cancer metastatic disease, about 8% experience concomitant peritoneal carcinomatosis and liver metastases. This combination has always been considered a bad prognostic factor with a significantly low survival, however more recent studies have shown that CRS and HIPEC in the presence of simultaneous peritoneal and liver metastases is feasible and produces a better survival outcome than systemic chemotherapy alone [22-25]. Finally, infiltration of the liver capsule is commonly seen in patients with peritoneal surface malignancies, however the extent of its involvement varies significantly. Minor lesions can usually be electroevaporated safely with high-voltage electrocautery, while tumor penetration of the Glisson's capsule demands surgical decapsulation. The tumor nodules may also infiltrate the liver parenchyma, mimicking hematogeneous metastases and thus requiring surgical resection [16]. Thus, it is evident that in order to achieve complete cytoreduction and therefore improve survival in patients with peritoneal carcinomatosis, CRS and HIPEC operation may require hepatobiliary and/or pancreatic procedures.

Recent studies report that, although hepatobiliary procedures represent a significantly challenging part of cytoreduction, they are not associated with an increase in morbidity or mortality [16]. In more detail, previously published studies reporting cumulative outcomes of patients undergoing CRS and HIPEC, bile leaks have been reported to occur in 0.5–2% of the patients [9,26]. Stephens et al. suggested that duration of surgery, intraoperative blood loss, duration of HIPEC, dose of Mitomycin–C and intra-abdominal temperature were associated with increased risk of bile leaks [26]. On the other hand, Elias et al. reported a bile leak rate of 9% in patients with hepatic malignancies undergoing CRS, including hepatectomy with reconstruction of the biliary tree combined with early postoperative intra-abdominal chemotherapy (EPIC) [10].

In our study bile leaks occurred in 4.4% of the patients, which is comparable to similar subgroups of patient series from Glockzin et al. (4.8%) [16].

Although not supported by their data, Glockzin et al. suggest an endoscopic retrograde cholangiopancreatography (ERCP) with additional sphincterotomy or stenting as the standard first therapeutic step in patients with bile leaks [16], followed by appropriate surgical management in case of failure. In our series, surgical management was required in only one case, following failure of a biliodigestive anastomosis, with the remaining cases being managed endoscopically as indicated.

Distal pancreatectomy during CRS is indicated in cases of iatrogenic injury of the pancreas or tumor involvement of the splenic hilum/pancreatic capsule or the pancreas itself [27]. In these cases, splenectomy alone is neither oncologically nor technically safe. Performing DP during CRS has been reported to associate with a significant increase in patient morbidity, but not mortality [28]. This can be explained, as patients that require DP present with significantly increased volume of disease and require more extensive operations, as reflected from the longer operative time, higher blood loss and greater number of resected organs, meaning that it is the extent of cytoreduction rather than the procedure of DP itself that contributes to the overall worse perioperative outcomes [28].

One of the most devastating complications of DP during CRS and HIPEC is the development of PFs, as it has been associated with increased morbidity rates, a higher rate of reoperation and prolonged hospital stay [28,29]. Interestingly, evidence on the effect of PF on mortality rates is equivocal: although Schwarz et al. report no effect of the development of a PF on mortality [29], Doud et al. report a 23% PF-specific mortality rate [28]. However, this estimate has to be interpreted carefully, as the number of patients included in the latter study is rather small, and 2 of the 3 mortality cases also had concurrent enteric leaks [28]. A PCI score greater than 20 and prolonged duration of surgery are risk factors that consistently appear to correlate with the occurrence of PFs, and both indicate a high burden of disease and a need for extensive cytoreduction [29,30].

Various pancreatic resection methods and pancreatic stump closure techniques have been evaluated over the years in order to reduce the incidence of PF after DP. These include transection with the use of energy or stapling devices, hand-sewn suture or stapled closure, reinforcement of the stump with a seromuscular patch or pancreaticoenteric anastomosis, sealing with fibrin sealants, pancreatic stent placement, and administration of octreotide, all in various combinations [29,31].

In our study, we routinely used stapling devices for the resection of the pancreas along with fibrin glue/fibrin adhesive sealant. Despite this, almost half out of the 14 patients that underwent DP experienced a PF, with the rate of Grade B/C PFs being 28.5%, slightly higher than the rate of PFs reported by Doud et al. [28], but comparable to the results of the single biggest multicenter study published to date [29]. All patients were managed using interventional radiology drainage or prolonged maintenance of an extra drain in the area of the pancreatic stump that was routinely placed intraoperatively in all cases requiring splenectomy (for possible occult iatrogenic injury of the pancreas) or DP, as also suggested by Doud et al. [28]. We found this practice very useful in the early identification of failure of the pancreatic stump, by measuring amylase levels postoperatively. As proposed by Schwarz et al., early detection and aggressive management of PFs with appropriate techniques is crucial, and can possibly lead to better patient outcomes [29].

The present retrospective study does not come without limitations: first of all, although every effort was made to make the patient sample homogeneous, the data come from two different centers, with the majority of the patients being registered from one of the two institutes. Both surgical teams had a learning curve which occurred in a different time period, however the patient results were studied cumulatively and not grouped by surgical team or year of surgery. Moreover, the data were collected in a 11-year period, throughout which the perioperative management as well as the clinical practices have significantly changed. Finally, this study represents an observational study and is limited to the report of outcomes of patients undergoing HPB procedures as part of CRS and HIPEC.

Complete cytoreduction is the primary objective in patients undergoing CRS and HIPEC, as it is the single most important factor that determines the survival benefit. In certain cases, a variety of hepatobiliary and/or pancreatic procedures are necessary in order to achieve a CC-0/1 resection. In the present retrospective analysis of the outcomes of patients undergoing HPB procedures as part of CRS and HIPEC, major complications were encountered in 44.1% of the patient sample, with a 8.8% reoperation and 2.9% mortality rate. Of the patients that underwent DP 28.5% developed a Grade B/C PFs, with all cases being successfully managed without surgical intervention. Although the need for HPB procedures bears a significant - but acceptable - rate of morbidity, it should not represent a definitive contraindication for CRS and HIPEC.

Conflict of interests

The authors declare no confict of interests.

References

1. Halkia E, Gavriel S, Spiliotis J. Management of peritoneal surface malignancy: a review of the recent literature. J BUON 2014;19:618-26.
2. Yan TD, Black D, Savady R, Sugarbaker PH. Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. J Clin Oncol 2006;24:4011-9.
3. Yan TD, Black D, Savady R, Sugarbaker PH. A systematic review on the efficacy of cytoreductive surgery and perioperative intraperitoneal chemotherapy for pseudomyxoma peritonei. Ann Surg Oncol 2007;14:484-92.
4. Yan TD, Welch L, Black D, Sugarbaker PH. A systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for diffuse malignancy peritoneal mesothelioma. Ann Oncol 2007;18:827-34.
5. Spiliotis J, Halkia E, de Bree E. Treatment of peritoneal surface malignancies with hyperthermic intraperitoneal chemotherapy-current perspectives. Curr Oncol 2016;23:e266-75.
6. Chua TC, Yan TD, Saxena A, Morris DL. Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure?: a systematic review of morbidity and mortality. Ann Surg 2009;249:900-7.
7. Moran B, Cecil T, Chandrakumaran K, Arnold S, Mohamed F, Venkatasubramaniam A. The results of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in 1200 patients with peritoneal malignancy. Colorectal Dis 2015;17:772-8.
8. Glehen O, Osinsky D, Cotte E et al. Intraperitoneal chemohyperthermia using a closed abdominal procedure and cytoreductive surgery for the treatment of peritoneal carcinomatosis: morbidity and mortality analysis of 216 consecutive procedures. Ann Surg Oncol 2003;10:863-9.
9. Kusamura S, Younan R, Baratti D et al. Cytoreductive surgery followed by intraperitoneal hyperthermic perfusion: analysis of morbidity and mortality in 209 peritoneal surface malignancies treated with closed abdomen technique. Cancer 2006;106:1144-53.
10. Elias D, Dube P, Bonvalot S et al. Treatment of liver metastases with moderate peritoneal carcinomatosis by hepatectomy and cytoreductive surgery followed by immediate post-operative intraperitoneal chemotherapy: feasibility and preliminary results. Hepatogastroenterology 1999;46:360-3.
11. Sugarbaker PH. Peritonectomy procedures. Ann Surg 1995;221:29-42.
12. Sugarbaker PH. Intraperitoneal chemotherapy and cytoreductive surgery for the prevention and treatment of peritoneal carcinomatosis and sarcomatosis. Semin Surg Oncol 1998;14:254-61.
13. Sugarbaker PH. Technical handbook for the integration of cytoreductive surgery and perioperative intraperitoneal chemotherapy into the surgical management of gastrointestinal and gynecologic malignancy. 4th ed. Grand Rapids (MI): The Ludann Company; 2005.
14. Vazquez Vde L, Sugarbaker PH. Cholecystectomy, lesser omentectomy, and stripping of the omental bursa: a peritonectomy procedure. J Surg Oncol 2003;84:45-9.
15. Halkia E, Efstathiou E, Spiliotis J, Romanidis K, Salmas M. Management of diaphragmatic peritoneal carcinomatosis: surgical anatomy guidelines and results. JBUON 2014;19:29-33.
16. Glockzin G, Renner P, Popp FC et al. Hepatobiliary procedures in patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol 2011;18:1052-1109.
17. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
18. Bassi C, Dervenis C, Butturini G et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138:8-13.
19. Elias D, Gilly F, Boutitie F et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol 2010;28:63-8.
20. Glehen O, Gilly FN, Boutitie F 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 2010;116:5608-18.
21. Sugarbaker PH. Observations concerning cancer spread within the peritoneal cavity and concepts supporting an ordered pathophysiology. Cancer Treat Res 1996;82:79-100.
22. Elias D, Benizri E, Pocard M, Ducreux M, Boige V, Lasser P. Treatment of synchronous peritoneal carcinomatosis and liver metastases from colorectal cancer. Eur J Surg Oncol 2006;32:632-6.
23. Chua TC, Yan TD, Zhao J, Morris DL. Peritoneal carcinomatosis and liver metastases from colorectal cancer treated with cytoreductive surgery perioperative intraperitoneal chemotherapy and liver resection. Eur J Surg Oncol 2009;35:1299-1305.
24. Maggiori L, Goere D, Viana B et al. Should patients with peritoneal carcinomatosis of colorectal origin with synchronous liver metastases be treated with a curative intent? A case-control study. Ann Surg 2013;258:116-21.
25. Esquivel J, Sticca R, Sugarbaker P et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement. Society of Surgical Oncology. Ann Surg Oncol 2007;14:128-33.
26. Stephens AD, Alderman R, Chang D et al. Morbidity and mortality analysis of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the coliseum technique. Ann Surg Oncol 1999;6:790-6.

27. Kehoe SM, Eisenhauer EL, Abu-Rustum NR et al. Incidence and management of pancreatic leaks after splenectomy with distal pancreatectomy performed during primary cytoreductive surgery for advanced ovarian, peritoneal and fallopian tube cancer. Gynecol Oncol 2009;112:496-500.
28. Doud AN, Randle RW, Clark CJ et al. Impact of distal pancreatectomy on outcomes of peritoneal surface disease treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol 2015;22:1645-50.
29. Schwarz L, Votanopoulos K, Morris D et al. Is the Combination of Distal Pancreatectomy and Cytoreductive Surgery With HIPEC Reasonable?: Results of an International Multicenter Study. Ann Surgery 2016;263:369-75.
30. Kusamura S, Baratti D, Antonucci A et al. Incidence of postoperative pancreatic fistula and hyperamylasemia after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol 2007;14:3443-52.
31. Makino I, Kitagawa H, Nakagawara H et al. Management of remnant pancreatic stump to prevent the development of postoperative pancreatic fistulas after distal pancreatectomy: current evidence and our strategy. Surg Today 2013;43:595-602.