

Hepatobiliary Procedures in Patients Undergoing Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

Gabriel Glockzin, MD, Philipp Renner, MD, Felix C. Popp, MD, Marc H. Dahlke, MD, PhD, Philipp von Breitenbuch, MD, Hans J. Schlitt, MD, and Pompiliu Piso, MD

Department of Surgery, University Medical Center Regensburg, Regensburg, Germany

ABSTRACT

Background. The long-term prognosis of patients with peritoneal malignancies has greatly improved since the introduction of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Nevertheless, CRS can be associated with high postoperative morbidity. In this retrospective study, we analyzed the influence of hepatobiliary surgery as part of CRS on postoperative short-term patient outcome.

Methods. Between 2005 and 2008, a total of 63 (25%) of 252 patients with peritoneal surface malignancies undergoing CRS and HIPEC required hepatobiliary surgery. Liver resection was performed in 22, resection of Glisson capsule in 39, and bile duct resection in 2 patients. The mean age of the study population was 49.3 years. Thirty-four patients (54%) were women.

Results. Complete macroscopic cytoreduction (CC-0/1) was reached in 59 patients (93.7%). The median hospital stay was 18 days. Twenty-two patients developed minor complications (35%), such as moderate fever, pain, or secondary wound healing. In 21 patients (33%), severe complications occurred, most commonly pancreatitis and abdominal abscess. Three patients (4.8%) developed a biliary leakage. Of these, 2 had to be reoperated.

Conclusions. In our experience, hepatobiliary procedures have to be performed in up to one-third of patients and are associated with a low rate of specific complications, such as biliary leakages.

Over the last few years, cytoreductive surgery (CRS) in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) has become a promising and successful treatment option in selected patients with otherwise poor prognosis due to peritoneal carcinomatosis. Following a protocol established by Sugarbaker and by Gilly et al., curative treatment strategies can be applied in patients with primary peritoneal cancer (as mesothelioma) or peritoneal carcinomatosis arising from colorectal, appendiceal, or ovarian malignancies.^{1–7} For instance, mean survival rates up to 28 months could be accomplished in patients with peritoneal metastasis derived from colorectal cancer, compared to 5.2-month mean survival as found in the EVOCAPE I study on the natural history of this disease.⁸ However, along with extensive surgical resection and aggressive local chemotherapeutic treatment, the risk of complications has to be taken into account regarding oncological outcome and quality of life.

Overall, postoperative morbidity is considered to be rather high in patients having extensive CRS. For instance, Levine et al. reported an overall complication rate of 43% in patients after CRS and HIPEC. The most common adverse events were wound infection, hematologic toxicity, anastomotic leakage, pneumonia, and sepsis. Occurrence of any complication was associated with decreased survival.⁹

Resections of metastases involving the liver, liver capsule, or bile ducts may lead to postoperative biliary leakage. Indeed, Elias et al. reported a rate of 9% biliary leakage in patients with hepatic malignancies undergoing CRS, including hepatectomy with reconstruction of the biliary tree.¹⁰ In the same study, patients treated with normothermic early postoperative intraperitoneal chemotherapy had an increased risk for biliary leakage of 33%.

One of the most important independent prognostic factors in patients treated with HIPEC is complete macroscopic cytoreduction.¹¹ Considering this, resection of tumor masses involving the liver and/or the biliary system

G. Glockzin and P. Renner contributed equally to this work.

© Society of Surgical Oncology 2010

First Received: 12 March 2010;

Published Online: 3 November 2010

P. Piso, MD

e-mail: pompiliu.piso@klinik.uni-regensburg.de

needs to be performed where curative therapy is possible, despite the risk of biliary complications and the unknown additional effect of HIPEC. Furthermore, complete perihaptic cytoreduction is especially challenging because of the anatomical nature of the hepatic hilum and its fissures, which are prone to harbor tumor masses.¹² Clearance of these structures is necessary to prepare the patient for subsequent HIPEC; it has also been shown that insufficient cytoreduction can lead to recurrence or persistence of disease in these compartments in particular.¹²

Little is currently known about the safety of CRS and HIPEC including hepatobiliary surgical procedures. In this retrospective study, we analyzed data of patients with peritoneal carcinomatosis that affected liver parenchyma, liver capsule, or bile duct system treated with CRS and HIPEC with curative intent. Duration of hospital stay, morbidity, and mortality were assessed to address the safety of the surgical procedures.

PATIENTS AND METHODS

Patients

A total of 252 patients were treated with CRS followed by HIPEC between 2004 and 2009 at the University Medical Center Regensburg. Of these, 63 patients underwent hepatobiliary interventions, including 22 liver resections, 39 resections of the Glisson capsule, and 2 segmental resections of the bile duct.

CRS and HIPEC

Patients underwent thoracoabdominal computed tomography to estimate resectability and extent of peritoneal tumor dissemination using the peritoneal cancer index, and treatment options and prognostic aspects were discussed with the patients before surgery.^{13,14} CRS included parietal and visceral peritonectomy and either liver resection, bile duct resection, or liver decapsulation, as well as resection of one or more of the following organs: diaphragm, omentum, stomach, gallbladder, pancreas, spleen, small and large bowel, and mesentery.¹⁵ Patients with no tumor residuals (completeness of cytoreduction score 0 [CC-0]) or lesions <2.5 mm (CC-1) after CRS were considered to be macroscopically free of tumor. In these patients, HIPEC was performed in closed abdomen technique with the ThermoChem HT-1000 device (Thermasolutions, Breda, The Netherlands) for 60 min, with an intraperitoneal temperature of 42–43°C. Depending on tumor origin and preoperative treatment, different chemotherapeutic agents were used for HIPEC. Typically 75 mg/m² cisplatin in combination with 15 mg/m²

doxorubicin was applied in ovarian cancer and mesothelioma, and 20 mg/m² mitomycin C with 15 mg/m² doxorubicin was applied for colorectal and appendiceal malignancies.^{16–19} When indicated and tolerated, additional early postoperative intraperitoneal chemotherapy was performed in selected patients.

Perioperative care included anticoagulative therapy with enoxaparin (40 mg s.c. per diem) and oral fluid intake from day 1 after surgery. Patients remained under surveillance in our intensive care unit (ICU) until catecholamine therapy and artificial ventilation could be slowly withdrawn.

Hepatobiliary Resections

To enable removal of all visible tumor masses involving the porta hepatis, certain surgical procedures were performed.¹² These included cholecystectomy, lesser omentectomy, and stripping of the omental bursa. The left triangular ligament was detached for exploration of the lateral segment of the upper right liver lobe, and all visceral surface of the liver was examined for metastatic disease. The feasibility of hepatobiliary procedures was assessed before surgery by computed tomographic scan (Fig. 1).

Inclusion criteria for patients with Glisson capsule resection were a depth of tumor infiltration of ≥ 5 mm and a surgical decapsulation of $\geq 25\%$ of the liver.

In the 22 patients who underwent liver resection, the following surgical procedures were performed: 10 patients underwent a single nonanatomic liver resection, with one of these patients undergoing an additional radiofrequency ablation. Two patients underwent three and 3 patients underwent four nonanatomic resections. Left lateral liver resection was performed in 3 patients with two additional nonanatomic resections in 1 of these patients. One patient underwent left hemihepatectomy and 3 patients right hemihepatectomy. In 2 of these 3 patients, an additional nonanatomic resection was performed.

Statistical Analysis

Clinical data of 63 patients was documented and analyzed retrospectively by GraphPadPrism software (La Jolla, CA) and SPSS for Windows version 15.0 (SPSS, Chicago, IL). *P* values were calculated by *t*-test, χ^2 test, and Fisher's exact test where applicable. A *P* value of <0.05 was defined to be statistically significant. 41 of the 63 patients were included in the matched pair analysis and compared to patients underwent CRS and HIPEC without liver surgery. Matching criteria were (1) operating time, (2) age at time of surgery and (3) sex. Operating time was considered to be an appropriate indicator for the extent of surgery.

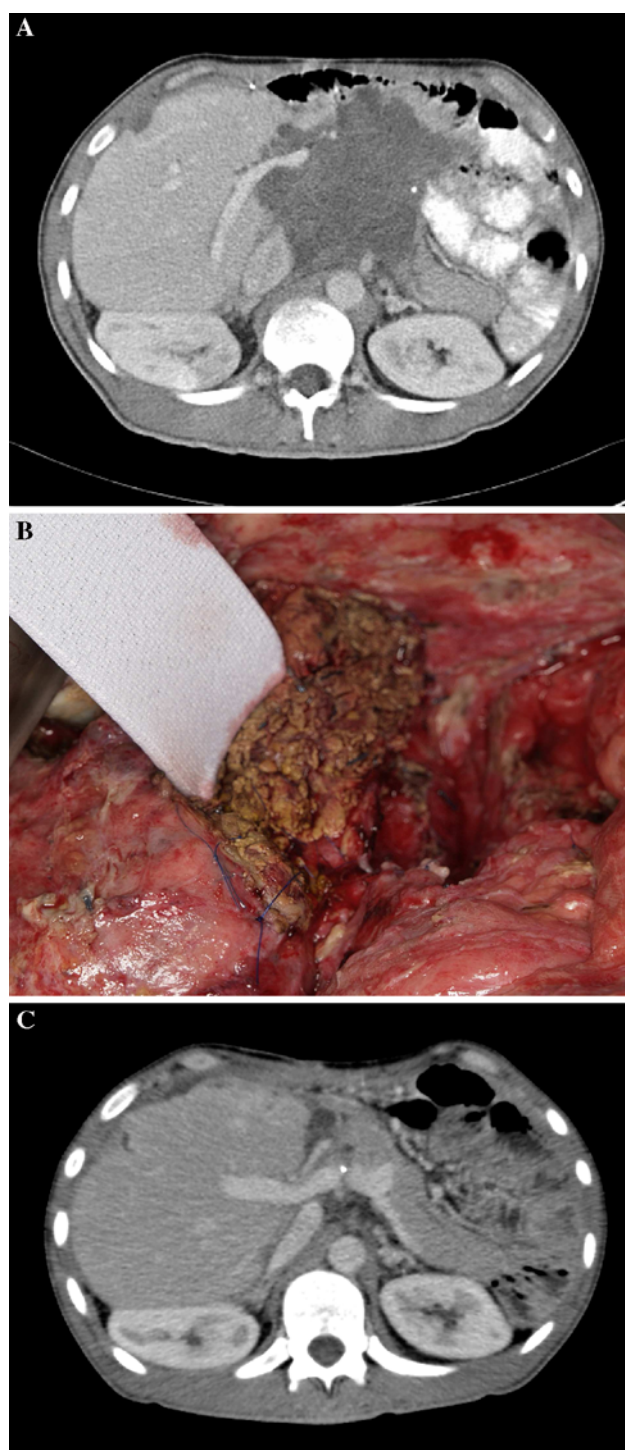


FIG. 1 **a** Preoperative computed tomographic (CT) scan of a patient with local recurrent disease after cytoreductive surgery for peritoneal carcinomatosis. The tumor mass penetrates the left liver lobe. **b** The intraoperative anatomy after resection of the liver segments II and III with dissection of the falciform and round ligament. **c** Postoperative CT scans demonstrating the cleared area of the lesser omentum; a small seroma still persists in the resection site

RESULTS

Patient Characteristics

In total, 63 patients were included in the present study, 22 of whom underwent liver resection, 39 liver decapsulation, and 2 resection of the bile duct. The mean age of the study population was 49.3 years. Thirty-four patients (54%) were women. Previous abdominal surgery was reported in 57 patients (91%). Thirty-one patients received systemic chemotherapy; only 2 patients had been treated with HIPEC.

Primary tumor was of appendiceal origin in 29 patients, of ovarian origin in 12 patients, and of colorectal origin in 11 patients. Less frequent entities causing peritoneal carcinomatosis were mesothelioma (8%), gastric cancer (3%), primary peritoneal cancer (3%), or other (one patient each with leiomyosarcoma of the uterus and renal-cell carcinoma). Patient characteristics are summarized in Table 1.

CRS and Postoperative Complications

Table 1 provides a detailed overview of the peritonectomy procedures performed. Median operation time was 419.5 min, with a range from 138 to 630 min. Complete macroscopic cytoreduction (CC-0/1) was achieved in 59 patients (93.7%). In 4 patients, HIPEC was performed to reduce malignant ascites for palliative reasons, as recommended by other groups.²⁰ Median hospital stay was 18 days, with 7 days in the ICU in patients with bile duct resection, 2 days in patients with liver resection, and 2 days in patients with decapsulation, respectively. There were no significance differences regarding operating time or hospital stay between the different groups.

In 20 (31.7%) of 63 patients, the postoperative course was without any complications: 32% of liver-resected patients, 31% of patients with decapsulations, and 1 out of 2 patients with bile duct resection. Minor complications such as moderate fever, pain of unknown origin, wound infection, and pleural effusion occurred in 22 (34.9%) of 63 patients. Interestingly, 90% of pleural effusions were found in patients with resected Glisson capsule. Severe complications had to be treated in one-third of all patients (33.3%). Most commonly, patients experienced an episode of pancreatitis (33% of major complications), followed by abdominal abscesses (24%). There was no statistically significant difference regarding overall and major complication rate between the three groups (Table 2).

In 3 patients (one each group, 4.8%), biliary leakage occurred (Table 3). Apart from a longer operation time,

TABLE 1 Patient characteristics

Characteristic	Liver resection	Glisson capsule resection	Bile duct resection	All	<i>P</i> ^a
Number	22	39	2	63	
Mean age (years)	51	48	48	49	0.388
Female sex	13	20	1	34	0.557
Abdominal surgery before CRS (<i>n</i>)	20	35	2	57	0.629
Primary tumor (<i>n</i>)					
Appendix/pseudomyxoma	4	24	1	29	
Ovary	5	7	0	12	
Colorectal cancer	8	3	0	11	
Mesothelioma	1	4	0	5	
Stomach	1	0	1	2	
Primary peritoneal cancer	1	1	0	2	
Other	2	0	0	2	
Completeness of cytoreduction					
CC-0/1	22	36	1	59	0.254
CC-2	0	1	1	2	
CC-3	0	2	0	2	
Operation time (min), median (range)	341 (190–555)	420 (138–609)	418.5 (207–630)	419.5 (138–630)	0.254
Hospital stay (days)					
Median range	18.5 (7–75)	17 (7–53)	28 (15–41)	18 (7–75)	0.420
Median stay in ICU	2 (0–49)	2 (0–10)	7 (1–13)	2 (0–49)	0.154
Parietal peritoneotomies (<i>n</i>)					
Right upper quadrant	11	36	1	48	
Left upper quadrant	6	26	0	32	
Epigastrium	3	0	0	3	
Pelvic region	10	32	1	43	
Organ resections (<i>n</i>)					
Greater omentum	15	33	1	49	
Diaphragm	5	6	0	11	
Small bowel mesentery	6	15	0	21	
Stomach	4	12	0	16	
Small bowel	9	13	2	24	
Large bowel	10	25	1	36	
Sigma/rectum	7	26	1	34	
Pancreas	5	2	1	8	
Gallbladder	14	32	2	48	
Spleen	8	29	1	38	

Clinical, pathological and surgical features and procedures of the 63 patients analyzed. Data is shown separately for each group (liver resection, liver decapsulation, bile duct resection) and summarized for the whole study population. Less frequent resections (as nephrectomy, urinary bladder resection, adrenalectomy) are not listed in the table

CRS cytoreductive surgery, ICU intensive care unit

^a Without bile duct resection

baseline characteristics of these patients did not differ from the study collective.

Matched-Pair Analysis

To evaluate the effect of liver surgery on morbidity and mortality rate, a matched-pair analysis of 41 patients was

performed. These patients were compared to 41 patients who underwent CRS and HIPEC without hepatic procedures. Because of the matching criteria, the two groups are almost equal regarding operating time, age, and sex. The median hospital stay was 17 vs. 18 days with a stay on ICU of 2 days and 1 day, respectively. Major complications occurred in 14 patients with hepatobiliary procedures

TABLE 2 Morbidity and mortality

Patients with:	Liver (<i>n</i> = 22)	Capsule (<i>n</i> = 39)	Bile duct (<i>n</i> = 2)	Total (<i>n</i> = 63)	<i>P</i>
Any complication (major or minor), <i>n</i> (%)	15 (68%)	27 (69%)	1 (50%)	43 (68%)	0.850
Major complications, <i>n</i> (%)	8 (36%)	12 (31%)	1 (50%)	21 (33%)	0.796
Biliary leakage (<i>n</i>)	1	1	1	3	
Cholestasis (<i>n</i>)	1	0	0	1	
Digestive fistula (<i>n</i>)	1	0	0	1	
Pancreatitis (<i>n</i>)	3	3	1	7	
Bleeding (<i>n</i>)	1	0	0	1	
Abscess in abdominal cavity (<i>n</i>)	2	3	0	5	
Colitis (<i>n</i>)	1	1	0	2	
Transient asystole (<i>n</i>)	1	0	0	1	
Myocardial infarction (<i>n</i>)	1	0	0	1	
Bowel perforation (<i>n</i>)	1	0	0	1	
Esophagitis (<i>n</i>)	0	1	0	1	
Thromboembolism (<i>n</i>)	3	0	1	4	
Ileus (<i>n</i>)	1	2	0	3	
Pneumonia (<i>n</i>)	1	1	0	2	
Ulcer of the stomach (<i>n</i>)	1	0	0	1	
Gastroparesis/gastric dysfunction (<i>n</i>)	1	2	0	3	
Peritonitis (<i>n</i>)	1	1	0	2	
Pneumothorax (<i>n</i>)	0	1	0	1	
Diaphragmatic lesion (<i>n</i>)	0	1	0	1	
Mortality	0	0	0	0	

Patients were subdivided in three groups: one group with no complications at all, one group with minor complications and one with major complications. In contrast to minor complications, major complications led to re-operation or more intensified treatment, which resulted in prolonged hospital stay

TABLE 3 Characteristics of patients with hepatobiliary leakage

Patient	Site of primary tumor	Age (years)	Operation time (min)	No. resections	HIPEC	Other complications	Hospital stay (days) (days in ICU)
1	Adenocarcinoma colon	72	518	9	MMC, DX	Bleeding, myocardial infarction, pancreatitis, anastomotic insufficiency, pneumonia	75 (49)
2	Appendix, mucinoid peritoneal carcinomatosis	64	630	9	5-FU, LOHP	Reinsufficiency of biliodigestive anastomosis, pancreatitis	41 (13)
3	Mesothelioma	57	407	8	MMC, IRI	Pleural effusion	20 (1)

HIPEC hyperthermic intraperitoneal chemotherapy, ICU intensive care unit, MMC mitomycin C, DX doxorubicin, 5-FU 5-fluorouracil, LOHP oxaliplatin, IRI irinotecan

(34.1%) and in 13 patients in the control group (31.7%). The mortality rate was 0% vs. 2.4%. In summary, there were no statistically significant differences between the two groups regarding hospital stay or stay in the ICU, or in morbidity and mortality rates.

DISCUSSION

The development of peritoneal carcinomatosis is characterized by a wide distribution of free tumor cells

throughout the abdominal cavity after the physiological intraperitoneal fluid circulation.^{21,22} Some of these free tumor cells may be trapped in areas where the circulation is of lower intensity, such as in the liver hilum or along the caudate lobe and the inferior caval vein, leading to an infiltration of liver segments III and IVB. The extent of this hepatic and perihepatic tumor distribution is often underestimated by preoperative computed tomography.¹⁴ Clearing this area by surgical procedures may be challenging and in many cases may represent the most difficult

part of the surgical cytoreduction. Consequently, many studies report the right upper abdominal quadrant to be the most common site of recurrent disease after CRS and HIPEC.^{23,24} Moreover, small residual disease left behind during initial surgery or local recurrence may result in tumor cell penetration into the liver parenchyma along the falciform ligament to the left portal branch with infiltration of the left hepatic duct and secondary jaundice.²³

Rarely, in particular in patients with low differentiated or signet-cell carcinoma, the bile duct wall may be infiltrated. This occurred in 2 of our patients, leading to bile duct resection. More frequently, the parietal peritoneum on the diaphragm surface is affected by tumor deposits. A deep tumor infiltration or penetration of the diaphragm is rare. In our series, only 11 (4.4%) of 252 patients required diaphragmatic resection to achieve complete macroscopic cytoreduction.

In contrast, infiltration of the liver capsule is common in patients with peritoneal surface malignancies. However, it may have a variable extent. In some cases, mucinous deposits can be simply wiped off or minor lesions can be electroevaporated by high-voltage cautery or by argon beam. In other cases, tumor penetration of the Glisson capsule demands surgical decapsulation of a limited area or the complete hepatic lobe, most frequently on the right side. At different sites, tumor nodules may deeply infiltrate the liver parenchyma. If so, liver dissection demands careful clipping or suturing of transected peripheral bile ducts to avoid postoperative biliary leakage. Rarely, a complete inclusion of surface nodules into the liver parenchyma may mimic hematogenous liver metastases. However, both kinds of lesions may be treated equally. In our series, almost 10% of the patients required atypical or segmental liver resection up to right hemihepatectomy.

As we now know, CRS and HIPEC procedures are associated with a long learning curve, which may include up to 130 cases.^{25,26} Mortality is low in experienced centers; however, overall morbidity is still high. Major surgical complications include bleeding, digestive fistula, pancreatitis, and abscess formation. It seems that adhesions due to prior surgery and multivisceral resections in the context of cytoreduction increase the risk of complications, rather than HIPEC.^{27–29} However, it remains unclear how this may affect healing processes; some experimental data on mitomycin C suggest impaired wound healing.^{30,31}

Several articles have been published on morbidity rates (Table 4). They include large series of up to 400 patients treated with CRS and HIPEC.⁸ However, just two of them report on the incidence of biliary leakage: 0.5% and 2%.^{32,33} This is in agreement with our experience (1.2%). Including liver capsule resections, surgical procedures on the liver were performed in almost one-third of all our patients, most of them having advanced intraperitoneal

TABLE 4 Reported incidence of morbidity after CRS and HIPEC

Study	Year	<i>n</i>	Morbidity (%)	Bile leak
Stephens et al. ³²	1999	183	27	2%
Glehen et al. ¹⁶	2003	207	25	NR
Smeenk et al. ²⁶	2006	103	54	NR
Kusamura et al. ³³	2006	209	12	0.5%
Levine et al. ⁹	2006	460	43	NR
Elias et al. ³⁴	2007	106	66	NR
Gusani et al. ³⁵	2008	122	57	NR
Present study	2009	252	41	1.2%

CRS cytoreductive surgery, HIPEC hyperthermic intraperitoneal chemotherapy, NR not reported

TABLE 5 Matched pair analysis of 41 patients (*n* = 82)

Characteristic	Hepatobiliary procedures	No. hepatobiliary procedures	<i>P</i>
No. of patients	41	41	
Selection criteria			
Operating time (min), mean (range)	367 (138–609)	365 (153–660)	0.964
Age (years), mean (range)	49 (25–71)	49 (24–73)	0.890
Male sex, <i>n</i> (%)	17 (41.5%)	17 (41.5%)	
Female sex, <i>n</i> (%)	24 (58.5%)	24 (58.5%)	
Primary tumor (<i>n</i>)			
Appendix/pseudomyxoma	18	17	0.823
CRC	8	14	0.135
Gastric cancer	1	3	0.616
Ovarian cancer	7	3	0.177
Mesothelioma	4	2	0.396
Other	3	2	0.644
Hospital stay (days), median (range)	17 (7–45)	18 (6–108)	0.359
Stay in ICU (days), median (range)	2 (0–10)	1 (0–45)	0.211
Minor complications, <i>n</i> (%)	14 (34.1%)	13 (31.7%)	0.815
Major complications, <i>n</i> (%)	11 (26.8%)	13 (31.7%)	0.627
Mortality, <i>n</i> (%)	0 (0%)	1 (2.4%)	0.500

Matching criteria were operating time, age at time of surgery, and sex
CRC colorectal cancer, ICU intensive care unit

disease with extended and long-lasting surgical procedures. However, the matched-pair analysis indicates that hepatobiliary procedures in the context of CRS and HIPEC do not increase the morbidity or mortality rates (Table 5). As expected, there was no bile leak in the control group

without liver resections, although patients with cholecystectomy as a common part of cytoreduction were not excluded.

Because of the small number of events, the results of the present study do not qualify for evidence-based recommendations concerning the treatment of biliary leakages after CRS and HIPEC. However, in our opinion, an endoscopic retrograde cholangiopancreatography with additional sphincterotomy or stenting should be performed first. This procedure was successful in one of our patients. In our second case, conservative treatment was unsuccessful. Therefore, repeat operation with suture of a peripheral leak at liver segment II was performed. Thus, in case of larger liver resections or creation of deep surgical fissures, a T drain may be placed intraoperatively to prevent bile leakage. The third patient had a leak of the biliodigestive anastomosis. This patient had to undergo repeat operation and the anastomosis had to be redone; a transhepatic bile drain was placed to facilitate the healing without further intervention.

Considering all the aspects discussed, procedures of the right upper quadrant are common and may be performed to different extents in patients with peritoneal surface malignancies during CRS and HIPEC. However, specific complications, such as bile leakages, are rare. Additional liver resection seem to be feasible without impairment of the perioperative outcome.

CONFLICT OF INTEREST All authors have no competing interests to declare.

REFERENCES

1. Sugarbaker PH, Cunliffe WJ, Belliveau J, et al. Rationale for integrating early postoperative intraperitoneal chemotherapy into the surgical treatment of gastrointestinal cancer. *Semin Oncol.* 1989;16:83–97.
2. Gilly FN, Carry PY, Sayag AC, et al. Treatment of peritoneal carcinomatosis by intraperitoneal chemo-hyperthermia with mitomycin C. Initial experience. *Ann Chir.* 1990;44:545–51.
3. Yan TD, Deraco M, Baratti D, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. *J Clin Oncol.* 2009;27:6237–42.
4. Verwaal VJ, Bruin S, Boot H, et al. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol.* 2008;15:2426–32.
5. Verwaal VJ, van Ruth S, de Bree E, 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.
6. Omohwo C, Nieroda CA, Studeman KD, et al. Complete cytoreduction offers longterm survival in patients with peritoneal carcinomatosis from appendiceal tumors of unfavorable histology. *J Am Coll Surg.* 2009;209:308–12.
7. Sugarbaker PH. Cytoreductive surgery and perioperative intraperitoneal chemotherapy for the treatment of advanced primary and recurrent ovarian cancer. *Curr Opin Obstet Gynecol.* 2009;21:15–24.
8. Glockzin G, Schlitt HJ, Piso P. Peritoneal carcinomatosis: patients selection, perioperative complications and quality of life related to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *World J Surg Oncol.* 2009;7:5.
9. Levine EA, Stewart JHT, Russell GB, et al. Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy for peritoneal surface malignancy: experience with 501 procedures. *J Am Coll Surg.* 2007;204:943–53.
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. Piso P, Glockzin G, von Breitenbuch P, et al. Patient selection for a curative approach to carcinomatosis. *Cancer J.* 2009;15:236–42.
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. 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;35:1299–305.
14. Koh JL, Yan TD, Glenn D, Morris DL. Evaluation of preoperative computed tomography in estimating peritoneal cancer index in colorectal peritoneal carcinomatosis. *Ann Surg Oncol.* 2009;16:327–33.
15. Sugarbaker PH. Peritonectomy procedures. *Surg Oncol Clin N Am.* 2003;12:703–27.
16. 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.
17. Glehen O, Cotte E, Kusamura S, et al. Hyperthermic intraperitoneal chemotherapy: nomenclature and modalities of perfusion. *J Surg Oncol.* 2008;98:242–6.
18. Sugarbaker PH. Laboratory and clinical basis for hyperthermia as a component of intracavitary chemotherapy. *Int J Hyperthermia.* 2007;23:431–42.
19. Elias D, Benizri E, Di Pietrantonio D, et al. Comparison of two kinds of intraperitoneal chemotherapy following complete cytoreductive surgery of colorectal peritoneal carcinomatosis. *Ann Surg Oncol.* 2007;14:509–14.
20. Younan R, Kusamura S, Baratti D, et al. Morbidity, toxicity, and mortality classification systems in the local regional treatment of peritoneal surface malignancy. *J Surg Oncol.* 2008;98:253–7.
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. Ceelen WP, Bracke ME. Peritoneal minimal residual disease in colorectal cancer: mechanisms, prevention, and treatment. *Lancet Oncol.* 2009;10:72–9.
23. Smeenk RM, Verwaal VJ, Antonini N, Zoetmulder FA. Survival analysis of pseudomyxoma peritonei patients treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg.* 2007;245:104–9.
24. Sugarbaker PH, Bijelic L. The porta hepatis as a site of recurrence of mucinous appendiceal neoplasms treated by cytoreductive surgery and perioperative intraperitoneal chemotherapy. *Tumori.* 2008;94:694–700.
25. Yan TD, Links M, Fransi S, et al. Learning curve for cytoreductive surgery and perioperative intraperitoneal chemotherapy

- for peritoneal surface malignancy—a journey to becoming a nationally funded peritonectomy center. *Ann Surg Oncol*. 2007;14:2270–80.
26. Smeenk RM, Verwaal VJ, Zoetmulder FA. Learning curve of combined modality treatment in peritoneal surface disease. *Br J Surg*. 2007;94:1408–14.
27. Yan TD, Edwards G, Alderman R, et al. Morbidity and mortality assessment of cytoreductive surgery and perioperative intraperitoneal chemotherapy for diffuse malignant peritoneal mesothelioma—a prospective study of 70 consecutive cases. *Ann Surg Oncol*. 2007;14:515–25.
28. Franko J, Gusani NJ, Holtzman MP, et al. Multivisceral resection does not affect morbidity and survival after cytoreductive surgery and chemoperfusion for carcinomatosis from colorectal cancer. *Ann Surg Oncol*. 2008;15:3065–72.
29. Hansson J, Graf W, Pahlman L, et al. Postoperative adverse events and long-term survival after cytoreductive surgery and intraperitoneal chemotherapy. *Eur J Surg Oncol*. 2008;35:202–8.
30. Aarts F, Bleichrodt RP, de Man B, et al. The effects of adjuvant experimental radioimmunotherapy and hyperthermic intraperitoneal chemotherapy on intestinal and abdominal healing after cytoreductive surgery for peritoneal carcinomatosis in the rat. *Ann Surg Oncol*. 2008;15:3299–307.
31. Pelz JO, Doerfer J, Decker M, et al. Hyperthermic intraperitoneal chemoperfusion (HIPEC) decrease wound strength of colonic anastomosis in a rat model. *Int J Colorectal Dis*. 2007;22:941–7.
32. 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.
33. 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.
34. Elias D, Goere D, Blot F, et al. Optimization of hyperthermic intraperitoneal chemotherapy with oxaliplatin plus irinotecan at 43 degrees C after complete cytoreductive surgery: mortality and morbidity in 106 consecutive patients. *Ann Surg Oncol*. 2007;14:1818–24.
35. Gusani NJ, Cho SW, Colovos C, 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.