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ORIGINAL ARTICLE

Re-operations for early postoperative complications after CRS and HIPEC: indication, timing, procedure, and outcome

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Abstract

Purpose Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have become standard of care for many peritoneal malignancies in selected patients. Nevertheless, this aggressive treatment strategy is associated with significant major morbidity. The aim of the present study is to analyze the re-operation rate and clinical outcome following CRS and HIPEC.

Patients and methods In the present study, prospectively documented data of 474 consecutive patients treated with CRS and HIPEC between February 2011 and December 2015 in a high-volume certified reference center for peritoneal malignancies in Germany have been retrospectively analyzed.

Results The re-operation rate was 14.5%. The most frequent reasons for revisional surgery were fascial dehiscence, intraabdominal hemorrhage, and anastomotic leak. Most complications occurred between postoperative day 7 and 9. However, postoperative bleeding was more common within the first 5 days after surgery. The overall in-hospital mortality rate was 2.1% for all patients and 10% after revisional surgery.

Conclusions CRS and HIPEC are associated with an acceptable re-operation rate and low mortality rate. Most frequently, re-operations are performed on 7–9 days after initial surgery due to fascial dehiscence, pancreatitis, or anastomotic leak. Postoperative bleedings are more common within the first 5 days after surgery.

Keywords Re-operation · Cytoreduction · HIPEC · Surgical procedures · Peritoneal metastases

Introduction

The treatment of peritoneal surface malignancies is challenging for all oncologists. Multimodality treatment strategies including cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), however, have changed prognosis in selected patients. A variety of parietal and visceral peritonectomy procedures are usually required in order to attain a complete cytoreduction, which also represents the aim of surgery [1, 2]. While the multimodal treatment is burdened by increased perioperative morbidity with complication rates up to 52%, it is also associated with acceptable mortality rates (0–17%) and significantly better reported rates in tertiary referral centers (0.9–5.8%) as low morbidity and mortality rates are related to the number of operated cases and the learning curve [3–8].

Despite a number of recent publications in this field, detailed data regarding re-operations remains scarce. The few reported revision rates range between 8.4 and 21% [7, 9–11].

Moreover, to our knowledge, an accurate analysis of causes leading to re-operation, timing of revisional surgery, and patient outcome has not been published yet. Therefore, the aim of the present study was to address this special topic of great relevance for oncological surgeons. Knowing when and which postoperative complications may occur could help surgeons reduce the failure to rescue and mortality.

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Patients and methods

Data of 474 consequently treated patients who received CRS and HIPEC between February, 2011, and December, 2015, in a tertiary referral center in Germany was reviewed. The data had been entered in the national HIPEC registry administered by the German Society for General and Visceral Surgery (DGAV). Due to the retrospective nature of this study, no institutional review board approval was necessary. The patients had agreed to data entry during their initial surgery by written informed consent. All patients had undergone treatment based on a prior-to-surgery interdisciplinary tumor board consensus; some patients were included in ongoing trials.

The extent of the peritoneal disease was estimated using the Peritoneal Cancer Index (PCI), which corroborates the size of the peritoneal lesions with the number of affected areas of the parietal and visceral peritoneum and ranges between 0 and 39 [12]. Nevertheless, since the PCI was not thoroughly documented in this cohort, a reliable statistical analysis could not be performed due to incomplete data.

Following surgical exploration, a complete macroscopic cytoreduction was achieved by using parietal and visceral peritonectomy procedures as described by Sugarbaker [1, 13]. A closed HIPEC at 42 °C for 30 or 60 min, depending on the chemotherapeutic agent, was performed. The bidirectional chemotherapy was applied mainly in patients with colorectal or appendiceal peritoneal carcinomatosis from colorectal and appendiceal cancer, and in those with pseudomyxoma peritonei associated with a low-grade mucinous neoplasm of the appendix (LAMN); the patients with non-digestive malignancies as well as the patients with gastric cancer received cisplatin and doxorubicin intraperitoneally for 60 min. Mitomycin C and gemcitabine were used as "reserve" drugs, administered to patients with platinum allergies or renal insufficiency, as well as to patients who experienced an early relapse after platinum-based regimens (Table 1).

The patients were postoperatively routinely admitted to the intensive care unit for at least 48 h.

Data was analyzed using the chi-squared test, Fisher's exact test, Mann-Whitney-Wilcoxon test, and a logistic regression in the stepwise backward/forward technique, based on the Akaike Information Criterion (open source R-Project for Statistical Computing, version 3.2.3). This study included only grade IIIb, IV, and V complications, according to the Clavien-Dindo classification [14]. A p value < 0.05 was considered to be significant.

Results

A total of 474 patients suffering from various primary or metastatic peritoneal malignancies were treated as summarized in Table 2. Of those, 182 patients were male (38.4%), 292 female (61.6%). The median age was 55 years (range 17–79). All patients received a parietal peritonectomy and/or a visceral procedure of different extent. Operative data on performed procedures is shown in Table 3. In our group, 194 patients (40.9%) received a rectal resection, 106 of which (54.6%) also received a defunctioning loop-ileostomy.

Most patients received a platinum derivative–based HIPEC, while the general use of Mitomycin C in the total patient population was only 11.2%.

A mortality rate of 2.1% and a re-operation rate of 14.5% were observed. A total number of 69 patients required a re-operation, of which seven (10.1%) died during their hospital stay. The median time to re-operation was 9 days (postoperative day 1–28), and 23 patients (33.3%) underwent more than one revisional surgery.

Overall, an anastomotic leak occurred in 18 patients after colorectal or small bowel resections. This represents 3.8% of all patient population, whereas 12 had a small bowel leak due to extended adhesiolysis with seromuscular tears representing 2.5% (Table 4). An anastomotic leak was diagnosed only in five patients with rectal resection and defunctioning ileostomy.

Subgroup of re-operated patients

The median age of the re-operated patients was 55 years (range 22–74). The age did not statistically influence the rate of re-operation ($p = 0.864$). Of all re-operated patients, 27.5% had undergone primary surgery for peritoneal metastatic colorectal

Table 1 HIPEC regimens used in the clinic in the analyzed period

Primary tumor	HIPEC regimen
Colorectal, appendiceal cancer, and Pseudomyxoma peritonei	Oxaliplatin 300 mg/m^2 i.p. for 30 min + 5-FU 400 mg/m^2 i.v. + folinic acid 20 mg/m^2 i.v.
Ovarian and gastric cancer Peritoneal mesothelioma	Cisplatin 75 mg/m^2 i.p. + Doxorubicin 15 mg/m^2 i.p. for 60 min
Reserve drugs	
Mitomycin C	20 mg/m^2 i.p. for 60 min
Gemcitabine	1000 mg/m^2 i.p. for 60 min

Table 2 Distribution of the tumor entities

	N	%
Peritoneal metastatic colorectal cancer	122	25.73
Pseudomyxoma peritonei/appendiceal malignancies	118	24.89
Peritoneal metastatic ovarian cancer	70	14.77
Peritoneal metastatic gastric cancer	56	11.81
Peritoneal mesothelioma	48	10.13
Cancer of unknown primary (CUP), peritoneal sarcomatosis	36	7.59
Others, e.g., small bowel cancer, desmoplastic small round cell tumor	24	5.07

cancer, 18.8% for pseudomyxoma peritonei, and 15.9% for peritoneal metastatic ovarian cancer. There was a mean value of 3.15 procedures per patient in the re-operated group. The majority of the re-operated patients (49.2%) underwent a cisplatin-based protocol, followed by a bidirectional oxaliplatin-based HIPEC regimen (43.4%), respectively.

The indications for revisional surgery are summarized in Table 5.

An anastomotic leak was noticed in nine patients who underwent rectal resection without defunctioning ostomy; all of these patients were re-operated. The anastomotic leak after colonic resections was treated with a discontinuity resection (Hartmann's procedure). The fascial dehiscence was treated by implanting a Vicryl® mesh and vacuum wound therapy, followed by secondary skin closure. Bile leaks that occurred following extended resection in the hepato-duodenal ligament were treated with sutures and T-drain placement. The postoperative peritonitis usually benefited from an extensive lavage of the peritoneal cavity; the postoperative intraabdominal hemorrhage was mainly due to diffuse bleeding, only two cases presented with active bleeding and required surgical hemostasis and packing; in all the other cases, a peritoneal lavage and drain placement were performed.

Most bleedings reported in our data occurred early in the postoperative course, in one case as a consequence of a CT-guided drain, and in three cases associated with a pancreatic resection. All other bleedings were due to an extended wound surface.

Complications noted after the first week included fascial dehiscence, anastomotic leaks, and pancreatitis. Fascial dehiscence usually occurred later in the postoperative course (day 6–22), with the highest incidence between the 6th and 7th day. Thus, this complication and timing should be considered during the intermediate postoperative course.

Correlation among clinical parameter and the risk of re-operation

There was no statistically significant correlation between re-operation and colonic resection ($p = 0.116$, 16.9% vs. 11.8%; OR = 5.11 for the patients who received a colonic resection (95% CI 1.17–11.39)).

There was, however, a significant difference in re-operation rate for patients who received a splenectomy ($N = 108$), compared with those who did not ($N = 366$) ($p = 0.01$). The odds of being re-operated were 9.93 times higher (95% CI 1.4–18.46) in those who underwent a splenectomy as compared with those who did not (Table 6). Surprisingly, we found no statistical correlation between the probability of being re-operated and the pancreatic procedures (20% vs. 14.2%, $p = 0.389$) or gastric resections (20% vs. 13.4%, $p = 0.13$), respectively. The univariate analysis showed that splenectomy significantly influenced the re-operation rate.

Mitomycin C was used in only 2.1% of the patients requiring re-operation, and there was no statistical association between its use and pancreatic complications. In addition, there was no significant association between pancreatic complications and the use of hyperthermic intraperitoneal mitomycin C versus platinum derivatives (2.1% vs. 97.8%, $p = 0.607$) or between anastomotic leak and the type of HIPEC regimen (mitomycin C

Table 3 Surgical procedures

Procedure	N (%)
Parietal peritonectomy and omentectomy	266 (56.12)
Colonic resection	254 (53.59)
Low anterior rectal resection	194 (40.93)
Hysterectomy	110 (23.21)
Splenectomy	108 (22.78)
Gastrectomy	80 (16.88)
Pancreatic resection	25 (5.27)

Table 4 Postoperative complications in the general population

	N (%)
Pancreatitis (yes vs. no)	9/474 (1.9)
Fistula (yes vs. no)	12/474 (2.53)
Anastomotic leak (yes vs. no)	18/474 (3.8)
Pulmonary embolism (yes vs. no)	8/474 (1.69)
Deep vein thrombosis (yes vs. no)	8/474 (1.69)
Re-operation (yes vs. no)	69/474 (14.56)
Hematological (yes vs. no)	6/474 (1.27)

Table 5 Indications for revisional surgery in the re-operated patients

No.	Indication for re-operation	*N* (%)
1	Fascial dehiscence	13 (18.84%)
2	Hemorrhage	13 (18.84%)
3	Anastomotic leak	9 (13.04%)
4	Bile leak	5 (7.24%)
5	Surgical site infection	5 (7.24%)
6	Planned second-look	5 (7.24%)
7	Small bowel leak	4 (5.79%)
8	Pancreatitis/pancreatic fistula	4 (3/1) (5.79%)
9	Prolonged ileus	2 (2.89%)
10	Peritonitis	2 (2.89%)
11	Hematothorax/pleural empyema	2 (1/1) (2.89%)
12	Knee empyema	1 (1.45%)
13	Ureteral leak	1 (1.45%)
14	Gastric perforation	1 (1.45%)
15	Gastric ulcer	1 (1.45%)
16	Coecal perforation	1 (1.45%)
	Total	69 (100%)

versus platinum derivatives, 3.3% vs. 96.6%, $p = 0.131$). Moreover, no statistical significance based on the chi-squared test was found between the probability of being re-operated and the type of chemotherapy applied (mitomycin C versus platinum derivatives, $p = 0.259$; OR 1.72 (95% CI 0.65–5.76)).

Re-operation led to a significant prolongation of the hospital stay (95% CI 14–21, $p < 0.001$) as well as of the ICU stay (95% CI 2–4, $p < 0.001$).

Subgroup of mortality patients

Of our cohort, ten patients died during the hospital stay; seven of them had undergone revisional surgery, thus representing a 10% mortality rate in the re-operated group of patients. The odds of death showed a statistically significant correlation with the re-operation rate (OR 14.98, 95% CI 3.31–92.12; $p < 0.01$). Two deceased patients (one suffering from malignant peritoneal mesothelioma and the other suffering from LAMN) died as a consequence of extended mesenterial ischemia 3 and 5 days after surgery, respectively. One patient suffering from ovarian cancer was re-operated 19 days after the initial surgery due to a leak of the jejunal anastomosis and died following the second re-operation on postoperative day 51. One patient suffering from malignant peritoneal mesothelioma was re-operated on day 1 due to an acute arterial diaphragmal hemorrhage and re-operated again 1 day later due to a diffuse intraperitoneal hemorrhage. Three other patients were re-operated because of a septic multiorgan dysfunction on postoperative days 1, 2, and 3, respectively, however without finding a surgical correspondent intraoperatively.

Table 6 Odds ratio regarding revisional surgery

9.93 times higher (95% CI 1.4–18.46) after splenectomy
5.11 times higher (95% CI 1.17–11.39) after colonic resection
5.75 (95% CI − 10.26–21.76) after pancreatic resection
6.55 (95% CI − 2.84–15.94) after gastrectomy
2 (95% CI − 4.85–9.62) after hysterectomy

The death causes in patients who died without prior re-operation were meningiosis carcinomatosa (exitus on day 18), septic multiple organ dysfunction syndrome (exitus on day 11), and large infarction in the medial cerebral artery territory with secondary herniation (exitus on day 6).

Discussion

General considerations on morbidity and mortality after CRS and HIPEC

CRS and HIPEC are associated with a significant morbidity; the rate may reach 20% when considering only grade III and IV complications. A comprehensive retrospective analysis on 1200 patients from a reference center from England revealed a major morbidity rate ranging between 6.7 and 13.7%, as well as a mortality rate of 0.7–3.0% [6]. Data from another tertiary center from the USA showed an overall morbidity of 32.9% and a 30-day mortality of 2.3% [7]. Despite the relatively high morbidity rates that have been reported, the hospital mortality rates remain acceptable and the mortality rates observed in experienced centers are low [15–23]. This may be explained by the higher likelihood to rescue patients that have surgical complications by timely operative revision, before the general condition has deteriorated or sepsis has occurred. Therefore, the data was reviewed with respect to re-operations to find out when they were indicated, how long after initial surgery–specific problems occurred, and what the outcomes were. To our knowledge, this is the first publication of detailed data regarding the indication and timing of the re-operation coming from a high-volume center.

Frequent causes for re-operations

Our reported results regarding morbidity and re-operation rate were comparable with those from other high-volume centers. There was no association between the number of peritonectomy procedures and postoperative complications, which may be related to the learning curve that builds for the first one hundred patients, whereas we present here almost 500 patients. Also, there was no association between the oxaliplatin doses and major complications, probably due to the lower dosage administered as compared with previous reports. Lower doses of oxaliplatin were applied in the closed HIPEC technique, as well as in the reported cohort. [24] Oxaliplatin seems to increase the risk of postoperative bleeding, mostly at least 1 week after surgery, particularly if used in high doses [25].

Another problem that challenges surgeons during the postoperative course of patients treated with loco-regional approaches as presented is the anastomotic leak. In the present study, an incidence of 13% anastomotic leaks was found in the re-operated patients' group, while in the full cohort, this incidence was of 3.8%, which was slightly higher than that reported by Chua et al. and by Jafari et al. [4, 7] and may be explained by the higher number of anterior rectal resections. In our clinic, we tend to generously recommend CT scans for all patients presenting postoperative prolonged paralysis and/or inadequate increase of the CRP value, and thus enable the early diagnosis of anastomotic leaks.

Another challenging complication is pancreatitis with or without peripancreatitis. This occurred in patients with large volume disease in the left upper quadrant. In such cases, the pancreatic tail was traumatized, and the pancreatic capsule partially removed during resection including splenectomy. The need for pancreatic resections in the present cohort was similar to that reported in other cohorts. In our group, pancreatic resection was avoided whenever possible as the combination with HIPEC is known to increase the severity of pancreatic fistula [26, 27]. Splenectomy was identified as a major risk factor for pancreatitis because patients warranting the procedure usually had a bulky disease in the lesser sac afflicting the spleen hilum and thus requiring splenectomy with or without distal pancreatectomy in order to achieve a complete macroscopical cytoreduction.

Last but not the least, fascial dehiscence occurred in most cases associated with other intraabdominal complications—particularly in patients who had to be re-operated multiple times. Vicryl® mesh placement and vacuum wound therapy, followed by secondary skin closure for fascial dehiscence, were performed in most cases, followed by secondary skin closure for fascial dehiscence.

Timing of re-operation

Our data shows a re-operation rate comparable with that of other published series following CRS and HIPEC or similar extended visceral resections. Moreover, the complication rate in specialized centers is similar for these groups of patients, especially when comparing complex pancreatic or esophageal resections with parietal and visceral peritonectomies plus HIPEC. Our own (unpublished) data on re-operation rate and the postoperative mortality were similar to those reported by other certified centers for pancreatic and for esophageal resections. As expected, most re-operations were performed within the first 10 days following surgery with a peak noted on postoperative day 8. Whereas bleeding was the most frequent cause for a re-operation during the first 5 days after CRS and HIPEC, anastomotic leak, pancreatitis, or fascial dehiscence were the reasons for re-operations between postoperative day 5 and 10. These findings should be kept in mind during the postoperative treatment of CRS and HIPEC patients.

Recommendations for the management of surgical complications

As clinical examination is limited in patients following CRS and HIPEC, timely CT scans should be considered to exclude the aforementioned causes that may require revision.

Early diagnostic and aggressive treatment may reduce the lethal outcome for patients with severe surgical complications.

Limitations and conclusions

This study is limited by its retrospective and single-center nature. The cohort had many indications and different surgical procedures as well as HIPEC regimens. This reduces the internal validity of the results. Also for several outcomes or measurements, the present study shows imprecision, e.g., for the relation between death and re-operation, thus limiting conclusions. Nevertheless, the study includes a large number of CRS and HIPEC patients treated in a referral center.

Another limitation—although extrapolated to the present situation—after the presentation of the French multicenter RCT is a decrease in the number of patients with peritoneal carcinomatosis and colorectal cancer.

In conclusion, the present study may guide surgeons in the early detection of specific complications and help indicate re-operations and reduce the failure to rescue and consequently the postoperative mortality following CRS and HIPEC.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval/informed consent This study includes anonymized prospectively gathered patients data. Informed consent was obtained from all participants included in this study.

References

1. Sugarbaker PH (1995) Peritonectomy procedures. Ann Surg 221(1):29–42
2. Sugarbaker PH (2003) Peritonectomy procedures. Surg Oncol Clin N Am 12(3):703–727 xiii
3. Stewart JH, Shen P, Levine EA (2005) Intraperitoneal hyperthermic chemotherapy for peritoneal surface malignancy: current status and future directions. Ann Surg Oncol 12(10):765–777. https://doi.org/10.1245/ASO.2005.12.001
4. Chua TC, Yan TD, Saxena A, Morris DL (2009) 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 249(6):900–907
5. Baratti D, Kusamura S, Mingrone E, Balestra MR, Laterza B, Deraco M (2012) Identification of a subgroup of patients at highest risk for complications after surgical cytoreduction and hyperthermic intraperitoneal chemotherapy. Ann Surg 256(2):334–341. https://doi.org/10.1097/SLA.0b013e31825704e3
6. Moran B, Cecil T, Chandrakumaran K, Arnold S, Mohamed F, Venkatasubramaniam A (2015) The results of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in 1200 patients with peritoneal malignancy. Color Dis 17(9):772–778. https://doi.org/10.1111/codi.12975
7. Jafari MD, Halabi WJ, Stamos MJ, Nguyen VQ, Carmichael JC, Mills SD, Pigazzi A (2014) Surgical outcomes of hyperthermic intraperitoneal chemotherapy: analysis of the American college of surgeons national surgical quality improvement program. JAMA Surg 149(2):170–175. https://doi.org/10.1001/jamasurg.2013.3640
8. Tabrizian P, Shrager B, Jibara G, Yang MJ, Romanoff A, Hiotis S, Sarpel U, Labow DM (2014) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis: outcomes from a single tertiary institution. J Gastrointest Surg 18(5):1024–1031. https://doi.org/10.1007/s11605-014-2477-5
9. Jimenez W, Sardi A, Nieroda C, Sittig M, Milovanov V, Nunez M, Aydin N, Gushchin V (2014) Predictive and prognostic survival factors in peritoneal carcinomatosis from appendiceal cancer after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol 21(13):4218–4225. https://doi.org/10.1245/s10434-014-3869-1
10. Konigsrainer I, Horvath P, Struller F, Grischke EM, Wallwiener D, Konigsrainer A, Beckert S (2014) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in recurrent epithelial ovarian cancer with peritoneal metastases: a single center experience. Langenbeck's Arch Surg 399(5):589–594. https://doi.org/10.1007/s00423-014-1207-5
11. Konigsrainer I, Zieker D, Glatzle J, Lauk O, Klimek J, Symons S, Brucher B, Beckert S, Konigsrainer A (2012) Experience after 100 patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. World J Gastroenterol 18(17):2061–2066. https://doi.org/10.3748/wjg.v18.i17.2061
12. Jacquet P, Sugarbaker PH (1996) Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res 82:359–374
13. Glehen O, Gilly FN (2003) Quantitative prognostic indicators of peritoneal surface malignancy: carcinomatosis, sarcomatosis, and peritoneal mesothelioma. Surg Oncol Clin N Am 12(3):649–671
14. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240(2):205–213
15. Mizumoto A, Canbay E, Hirano M, Takao N, Matsuda T, Ichinose M, Yonemura Y (2012) Morbidity and mortality outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy at a single institution in Japan. Gastroenterol Res Pract 2012: 836425–836425. https://doi.org/10.1155/2012/836425
16. Froysnes IS, Larsen SG, Spasojevic M, Dueland S, Flatmark K (2016) Complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal peritoneal metastasis in Norway: prognostic factors and oncologic outcome in a national patient cohort. J Surg Oncol 114(2):222–227. https://doi.org/10.1002/jso.24290
17. Jacquet P, Stephens AD, Averbach AM, Chang D, Ettinghausen SE, Dalton RR, Steves MA, Sugarbaker PH (1996) Analysis of morbidity and mortality in 60 patients with peritoneal carcinomatosis treated by cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy. Cancer 77(12):2622–2629. https://doi.org/10.1002/(SICI)1097-0142(19960615)77:12<2622::AID-CNCR28>3.0.CO;2-T
18. Stephens AD, Alderman R, Chang D, Edwards GD, Esquivel J, Sebbag G, Steves MA, Sugarbaker PH (1999) Morbidity and mortality analysis of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the coliseum technique. Ann Surg Oncol 6(8):790–796
19. Sugarbaker PH, Alderman R, Edwards G, Marquardt CE, Gushchin V, Esquivel J, Chang D (2006) Prospective morbidity and mortality assessment of cytoreductive surgery plus perioperative intraperitoneal chemotherapy to treat peritoneal dissemination of appendiceal mucinous malignancy. Ann Surg Oncol 13(5):635–644. https://doi.org/10.1245/ASO.2006.03.079
20. Roviello F, Marrelli D, Neri A, Cerretani D, de Manzoni G, Pedrazzani C, Cioppa T, Nastri G, Giorgi G, Pinto E (2006) Treatment of peritoneal carcinomatosis by cytoreductive surgery and intraperitoneal hyperthermic chemoperfusion (IHCP): postoperative outcome and risk factors for morbidity. World J Surg 30(11): 2033–2040; discussion 2041-2032. https://doi.org/10.1007/s00268-006-0038-0
21. Kusamura S, Younan R, Baratti D, Costanzo P, Favaro M, Gavazzi C, Deraco M (2006) Cytoreductive surgery followed by intraperitoneal hyperthermic perfusion: analysis of morbidity and mortality in 209 peritoneal surface malignancies treated with closed abdomen technique. Cancer 106(5):1144–1153. https://doi.org/10.1002/cncr.21708
22. Smeenk RM, Verwaal VJ, Zoetmulder FA (2006) Toxicity and mortality of cytoreduction and intraoperative hyperthermic intraperitoneal chemotherapy in pseudomyxoma peritonei—a report of 103 procedures. Eur J Surg Oncol 32 (2):186- 190. doi:https://doi.org/10.1016/j.ejso.2005.08.009
23. Elias D, Goere D, Blot F, Billard V, Pocard M, Kohneh-Shahri N, Raynard B (2007) Optimization of hyperthermic intraperitoneal chemotherapy with oxaliplatin plus irinotecan at 43 degrees C after compete cytoreductive surgery: mortality and morbidity in 106 consecutive patients. Ann Surg Oncol 14(6):1818–1824. https://doi.org/10.1245/s10434-007-9348-1
24. Verhulst J (2013) Hyperthermic intraperitoneal chemoperfusion with high dose oxaliplatin: influence of perfusion temperature on postoperative outcome and survival. F1000Res 2:179. https://doi.org/10.12688/f1000research.2-179.v2
25. Quenet F, Elias D, Roca L, Goere D, Ghouti L, Pocard M, Facy O, Arvieux C, Lorimier G, Pezet D, Marchal F, Loi V, Meeus P, De Forges H, Stanbury T, Paineau J, Glehen O, UNICANCER-GI Group and the French BIG-Renape Group (2018) A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. J Clin Oncol 36(18_suppl):LBA3503–LBA3503
26. Doud AN, Randle RW, Clark CJ, Levine EA, Swett KR, Shen P, Stewart JH, Votanopoulos KI (2015) Impact of distal pancreatectomy on outcomes of peritoneal surface disease treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol 22(5):1645–1650. https://doi.org/10.1245/s10434-014-3976-z
27. Downs-Canner S, Ding Y, Magge DR, Jones H, Ramalingam L, Zureikat A, Holtzman M, Ahrendt S, Pingpank J, Zeh HJ, Bartlett DL, Choudry HA (2015) A comparative analysis of postoperative pancreatic fistulas after surgery with and without hyperthermic intraperitoneal chemoperfusion. Ann Surg Oncol 22(5):1651–1657. https://doi.org/10.1245/s10434-014-4186-4