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Feasibility of adjuvant laparoscopic hyperthermic intraperitoneal chemotherapy in a short stay setting in patients with colorectal cancer at high risk of peritoneal carcinomatosis

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Abstract

Introduction: Treatment of peritoneal carcinomatosis (PC) of colorectal cancer (CRC) origin is relatively ineffective and associated with morbidity. This raises the question whether we should focus on prevention of the development of PC. We determined the feasibility of adjuvant laparoscopic hyperthermic intraperitoneal chemotherapy (HIPEC) in a short stay setting.
Methods: A prospective single centre pilot study was conducted between January 2011 and July 2012. Ten patients at risk of developing PC of CRC origin were included. Laparoscopic HIPEC using Mitomycin-C (90 min; inflow temperature 42–43 °C) was performed within several weeks after primary resection of CRC and was considered feasible when postoperative hospital stay was three days or shorter in at least six patients, and if a maximum of one conversion and one re-admission within 30 days occurred.
Results: HIPEC was performed after a median of 6 weeks (range 3–9 weeks). Postoperatively, five patients were discharged at day one, four patients at day two and one patient at day three. Laparoscopic adhesiolysis resulted in small bowel injury in one patient, but no conversion to open surgery and no postoperative complications were observed. One patient was readmitted within 30 days due to a clostridium infection. The postoperative course was uneventful for the remaining patients.
Conclusion: Adjuvant laparoscopic HIPEC appeared to be feasible in a short stay setting based on this small pilot study. The necessity of adhesiolysis determines the complexity of the procedure and requires an operating team with experience in minimally invasive abdominal surgery.

Keywords: Colorectal neoplasms; Peritoneal neoplasms; Chemotherapy; Adjuvant; Laparoscopy; Peritoneal lavage

Introduction

Peritoneal carcinomatosis (PC) from colorectal cancer (CRC) is most often associated with a dismal prognosis. The only curative option for PC is cytoreductive surgery (CR) combined with hyperthermic intraperitoneal chemotherapy (HIPEC).[1] Five-year survival rates around 30% have been reported after CR/HIPEC for CRC in large multicentre observational studies, but at the cost of substantial morbidity.[2,3] However, the majority of patients with PC is not suitable for CR/HIPEC, due to the extensiveness of PC at presentation, the presence of distant metastases and/or the patients' clinical condition. Palliative treatment in these patients consists of systemic therapy and interventions to reduce associated symptoms such as bowel obstruction and

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ascites.[4] There seems to be a relative resistance of PC to systemic treatment, even if modern combination chemotherapy with targeted agents is used.[5,6] Reported median survival with palliative chemotherapy ranges between 5 and 15 months.[6,7]

The relative ineffectiveness and associated morbidity of current treatment of PC of CRC origin raises the question whether we should focus on prevention of development of PC in an adjuvant setting. The need for effective adjuvant treatment is also underlined by the difficulty to detect PC during follow-up by imaging modalities.[8] Risk factors for the development of PC have been identified, such as pT4 stage, tumour perforation, positive cytology of abdominal lavage, and ovarian metastasis.[9–11] Based on the proven efficacy of HIPEC in combination with CR for macroscopic disease, a few studies explored the use of HIPEC to treat PC at a clinically occult stage in these high risk patients with promising results.[11–13] Adjuvant HIPEC may be performed simultaneous with resection of the primary tumour, however this requires pre- or intraoperative selection of high risk patients and the availability of HIPEC facilities in any potential candidate.[13] Therefore, adjuvant HIPEC has been delayed for several weeks to more than one year after primary resection. Chouillard et al. performed laparoscopic adjuvant HIPEC in 16 CRC patients after a median period of 5 weeks (range 0–8), with 19% major and 52% minor complications, and a median hospital stay of 11 days (range 7–22).[14] Elias et al. performed second look surgery after 11 months (±7) using laparotomy in 43 patients, of whom 18 underwent prophylactic HIPEC with 11% severe morbidity and a mean hospital stay of 20 days (range 14–42).[11] Morbidity and hospital stay should be minimized before HIPEC becomes an acceptable treatment modality in the adjuvant setting. Therefore, the purpose of this study was to determine the feasibility of adjuvant laparoscopic HIPEC in a short stay setting within several weeks after primary resection of CRC.

Methods

Patients

Between January 2011 and July 2012, patients diagnosed with adenocarcinoma of the colon and proximal rectum and at least one of the following risk factors for PC were considered for inclusion: pT4, (resected) local peritoneal nodules in the close proximity of the primary tumour, primary tumour presenting with obstruction and/or perforation, positive cytology in peritoneal lavage, ovarian metastasis or omental metastasis. A group of ten patients was included in this prospective single centre pilot study. Adjuvant laparoscopic HIPEC was considered feasible in a short stay setting if postoperative hospital stay was three days or shorter in at least six patients, and if a maximum of one conversion and one re-admission within 30 days occurred.

Eligibility criteria were age between 18 and 75 years, ECOG performance status of 0 or 2, written informed consent obtained prior to any study specific screening procedure, white blood cell count of at least 3000/mm3, platelet count at least 100.000/mm3, no bleeding diathesis or coagulopathy, normal creatinine or creatinine clearance of at least 50 ml/min. Exclusion criteria were liver and/or lung metastases, pregnant or lactating women, unstable or uncompensated respiratory or cardiac disease, serious active infections, and other concurrent chemotherapy.

Procedure

Included patients were planned to undergo a laparoscopic HIPEC procedure within 4–8 weeks after resection of the primary tumour. After intravenous injection of prophylactic antibiotics (1 g Cefazoline and 500 mg Metronidazole), laparoscopic HIPEC started with open introduction of a 12 mm trocar in the left upper quadrant of the abdomen. After induction of a CO_2 pneumoperitoneum, additional trocars of 5 or 12 mm were placed under direction vision in order to enable complete dissection of adhesions and thorough inspection of the abdominal cavity, including the Douglas pouch, the sub diaphragmatic spaces, the paracolonic gutters, and the entire small bowel. One multiperforated inflow catheter was placed through a right lower quadrant port and positioned with its tip in Douglas pouch, and one outflow catheter was positioned through the left upper quadrant trocar and positioned in the right subphrenic space. The patient's body temperature was monitored in the oesophagus. The intra-abdominal pressure was monitored by connecting an arterial line system to one of the trocars. All trocars were tightly fixed to the skin in order to avoid fluid leakage during the procedure. Perfusion by an operator controlled pump system was started with a minimum of 2l isotonic dialysis fluid at a flow rate of 1–2 l/min and an inflow temperature of 42–43 °C. As soon as the temperature in the abdomen was stable above 40 °C, Mitomycin C in a start dose of 17.5 mg/m^2 was added to the circuit, followed by two additional doses of 8.8 mg/m^2 after 30 and 60 min from the start dose. The operating table was rotated and tilted every 10 min, and abdominal movement was induced throughout the infusion to allow homogeneous exposure of the peritoneal surfaces to the heated chemotherapy. After 90 min perfusion time, the peritoneal fluid was removed through suction and the abdomen was examined for evidence of tissue injury or bleeding. The inflow catheter was left in the Douglas pouch for 24 h to drain remaining intraperitoneal fluid. The other port sites were closed in a standard fashion.

Post-operative management

Nasogastric tubes were removed at the end of surgery, and intravenous lines and intra-abdominal drains were removed at post-operative day one. The criteria for