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Safety and efficacy of combined resection of colorectal peritoneal and liver metastases

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ABSTRACT

Background: To determine if a select subgroup of patients with combined liver and peritoneal colorectal metastases would derive oncologic benefit from surgical resection as a component of multimodality treatment.

Materials and methods: We retrospectively compared 32 patients with combined colorectal peritoneal and liver metastases (CRLM) and 173 patients with peritoneal metastases only (CRPM) undergoing cytoreductive surgery with hyperthermic intraperitoneal chemoperfusion (CRS-HIPEC). Kaplan-Meier survival curves and multivariate Cox-regression models identified prognostic factors affecting survival.

Results: Major postoperative complications (Clavien-Dindo grades 3-5) occurred in 32% (CRLM) and 17% (CRPM) of patients ($P = 0.08$). After an estimated median follow-up from surgery of 57 mo, propensity score–adjusted median progression-free survival was 5.1 mo (CRLM) and 7.6 mo (CRPM), whereas median overall survival was 13 mo (CRLM) and 21 mo (CRPM). Multivariate Cox-regression analysis of the CRLM group identified number of liver metastases to be the only independent predictor of poor survival (hazard ratio: 2.3, $P = 0.03$), with a dramatic decrease in survival in patients with more than three liver metastases.

Conclusions: Simultaneous resection of colorectal liver metastases at the time of cytoreductive surgery with hyperthermic intraperitoneal chemoperfusion for peritoneal metastases may be associated with worse survival, especially in patients with more than three liver metastases.

Introduction

The peritoneum is the third most common site of colorectal metastases, following hepatic and pulmonary sites of dissemination.[1-6] A prospective analysis of 32 phase II/III North Central Cancer Treatment Group (NCCTG) clinical trials of patients with metastatic colorectal cancer receiving "non-modern era" systemic chemotherapy demonstrated median survival of 9-12 mo and 5-year survival of 1.1%.[7] A significant improvement in median survival (15-30 mo) has been

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achieved with the addition of "modern era" chemotherapy and targeted agents. However, 5 year survival remains low (~10%), even with "modern era" chemotherapy regimens, predominantly related to low complete response rates (~5%).[8-12]

The addition of surgical resection to systemic chemotherapy has been advocated to improve long-term survival in a larger subset of well-selected patients with colorectal metastases by achieving "mechanical complete response". The success of this combined approach has been demonstrated in well-selected patients with isolated colorectal liver or lung metastases, with 5-year survival rates of 30%-40% and 20%-30%, respectively.[13,14] This rationale has also been applied to patients with colorectal peritoneal metastases. A randomized controlled trial, a well-matched case-control study and numerous institutional case series have demonstrated improved median survival (22-63 mo) and 5-year survival (20%-51%) following cytoreductive surgery—hyperthermic intraperitoneal chemoperfusion (CRS-HIPEC) in well-selected patients with isolated colorectal peritoneal metastases.[15-20] However, certain prognostic factors have been attributed to poor survival following CRS-HIPEC, including the presence of synchronous liver metastases.[19,21-23]

Combined surgical resection of liver metastases at the time of CRS-HIPEC for colorectal peritoneal metastases is controversial.[24] Maggiori *et al*. published a prospective, matched case-control study comparing CRS-HIPEC in patients with colorectal peritoneal metastases with and without synchronous liver metastases. Although they demonstrated worse survival in patients with synchronous liver disease, patients with <3 liver lesions and limited peritoneal disease (peritoneal cancer index < 12) demonstrated 40 month median survival and 3 year survival over 60%, suggesting that long-term survival could be achieved in appropriately selected patients.[25]

We evaluated perioperative and oncologic outcomes following CRS-HIPEC for concurrent colorectal peritoneal and liver metastases (CRLM) in selected patients at a high-volume center.

Materials and methods

We performed a retrospective review of a prospectively maintained database of patients undergoing curative CRS-HIPEC for colorectal peritoneal metastases between 2005 and 2013. We identified a subgroup of patients with synchronous CRLM group ($n = 32$) who underwent concurrent liver resection and/or radiofrequency ablation (RFA) at the time of CRS-HIPEC. We compared the CRLM group to the larger subset of patients undergoing CRS-HIPEC for colorectal peritoneal metastases alone (CRPM group; $n = 173$). This study was approved by the Institutional Review Board at the University of Pittsburgh.

Patients were excluded from undergoing CRS-HIPEC if they had extraabdominal metastatic disease, poor performance status (ECOG 3-5), unresectable disease on preoperative imaging or intraoperative assessment, and "significant" (as opposed to "limited") progressive disease while on preoperative systemic chemotherapy (disease progression on imaging was defined as any increase in disease burden reported by the radiologist reviewing the imaging, while the distinction between "limited" *versus* "significant" disease progression was determined by the clinical judgment of the multidisciplinary team managing the patient based on whether the degree of progression was enough to preclude surgery). All patients in the CRLM group had pathologically confirmed parenchymal metastases; we excluded patients with extrinsic disease invading the liver or capsular disease only. Intraoperatively, volume of peritoneal disease was quantified by the peritoneal carcinomatosis index (PCI).[26] Cytoreductive surgery (CRS) was performed in accordance with techniques described by Bao and Bartlett to achieve CC-0 (no residual macroscopic disease) or CC-1 (residual tumor nodule < 2.5 mm) resection.[27] Patients undergoing ≥ 3 organ resections or ≥ 2 visceral anastomoses were defined as having "extensive CRS" as opposed to "limited CRS." A standard institutional protocol for HIPEC was initiated after CRS, with the closed technique and target intraperitoneal tissue temperature of 42°C. Mitomycin C 30 mg was added to the perfusate initially for 60 minutes followed by an additional 10 mg for a further 40 minutes. Postoperative morbidity was classified according to the Dindo-Clavien grading system.[28] For the purpose of analysis, grades 3-5 were considered major complications.

Statistical analysis

Clinicopathologic, perioperative, and oncologic outcomes between CRLM and CRPM groups were examined using Wilcoxon two-sample test or Fisher's exact test when appropriate. Overall survival (OS) was calculated from the date of diagnosis of peritoneal metastases and also the date of surgery to the date of death. For patients presumably still alive at the time of analysis, follow-up was censored as of the date of last contact. Progression-free survival (PFS) was calculated from the date of diagnosis of peritoneal metastases and also the date of surgery to the date of recurrence or progression or death. Kaplan-Meier method was used to estimate the survival distributions, and Log-rank test was used to assess the difference. Survival function estimates and comparisons were also adjusted by propensity score weighting method to account for differences in confounding variables between the CRLM and CRPM groups. Variables in the propensity-scored model included, in order or importance, intraoperative PCI, preoperative body mass index (BMI), and gender. The relationship of overall survival to patients' characteristics was further assessed by Cox proportional hazards regression. The corresponding relative mortality rates are summarized as hazard ratios (HRs), with HR > 1.0 corresponding to increased mortality. A significance level was set at 0.05, and all P values reported were two-sided. Statistical analyses were performed using SAS v9.4 (SAS Institute, Cary, NC).

Results

CRLM group

Thirty-two patients underwent CRS-HIPEC and concurrent liver resection and/or RFA for synchronous colorectal liver and peritoneal metastases (Table 1). The majority of patients had a