ORIGINAL ARTICLE

The impact of portal pedicle clamping on survival from colorectal liver metastases in the contemporary era of liver resection: a matched cohort study

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Abstract

Introduction: Portal pedicle clamping (PPC) may impact micro-metastases' growth. This study examined the association between PPC and survival after a hepatectomy for colorectal liver metastases (CRLM).

Methods: A matched cohort study was conducted on hepatectomies for CRLM at a single institution (2003–2012). Cohorts were selected based on PPC use, with 1:1 matching for age, time period and the Clinical Risk Score. Outcomes were overall and recurrence-free survival (OS and RFS). Cox regression was performed to assess the association between PPC and survival.

Results: Of 481 hepatectomies, 26.9% used PPC. One hundred and ten pairs of patients were matched in the cohorts. There was no significant difference in OS [hazard ratio (HR) 1.18; 95% confidence interval (CI): 0.76–1.83], with a 5-year OS of 57.8% (95%CI: 52.4–63.2%) with PPC versus 62.3% (95%CI: 57.1–67.5%) without. Five-year RFS did not differ (HR 0.98; 95%CI: 0.71–1.35) with 29.7% (95%CI: 24.9–34.5%) with PPC versus 28.0% (95%CI: 23.2–32.8%) without. When adjusting for extent of resection, transfusion, operative time and surgeon, there was no difference in OS (HR 0.91; 95%CI: 0.52–1.60) or RFS (HR: 0.86; 95%CI: 0.57–1.30).

Conclusions: PPC was not associated with a significant difference in OS or RFS in a hepatectomy for CRLM. PPC remains a safe technique during hepatectomy.

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Introduction

Hepatectomy has become the standard of care for curative intent treatment of colorectal liver metastases (CRLM). With broader patient selection and effective multimodal approaches, overall survival (OS) ranges from 30% to 60% at 5 years.[1] However, recurrence remains common and occurs in up to 60% of patients following initial hepatectomy.[2]

This study was presented at the Annual Meeting of the AHPBA, 11-15 March 2015, Miami, Florida and has been accepted for podium presentation at the Canadian Surgery Forum to be held in Québec City, QC, in September 2015.

Due to advances in surgical techniques and peri-operative care, the morbidity profile of hepatectomy has improved significantly, with current peri-operative mortality now nearing 1% in high-volume centres.[3,4] However, blood loss and need for a transfusion remain a significant concern that can impact both immediate and long-term outcomes.[5–7] Numerous intra-operative strategies have been developed to limit blood loss.[8–10] Of these, portal pedicle clamping (PPC), first described by Hogarth Pringle for liver trauma,[11] is one of the only strategies proven effective to reduce intra-operative blood loss in randomized controlled trials.[12,13]

Despite evidence of the efficacy and safety of PPC with regards to post-operative morbidity and liver failure, the

uptake of PPC is highly variable. While 30% of Canadian hepato-pancreatico-biliary surgeons use PPC, 40% do so in the United Kingdom, 50% in Japan and 70% in Continental Europe.[14–17] Concerns remain regarding the long-term oncological effects of PPC due to ischemia–reperfusion injury to the liver remnant.[18,19] Current evidence defining the precise effect of PPC on oncological outcomes in a CRLM resection is restricted to studies with small sample sizes from individual hospitals and cohorts spanning the introduction of modern patient selection and multi-modal therapy.[20–23]

The purpose of this study was to ascertain the effect of PPC on long-term oncological outcomes in a contemporary cohort of patients undergoing hepatectomy for CRLM.

Patients and methods

A retrospective matched cohort study of a prospectively maintained database was conducted. This study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board.

Patient selection

Patients were identified from a prospectively maintained institutional database at a tertiary care hepato-pancreatico-biliary surgery academic centre (Sunnybrook Health Sciences Centre – Odette Cancer Centre). Adult patients (≥18 years of age) undergoing an elective liver resection for CRLM from 2003 to 2012 were included.

Patients who underwent PPC were identified and then matched 1:1 with patients who did not undergo PPC. Matching criteria were age (≤40 years old, 5-year increments, and ≥70 years old), time period of operation (2003–2007, 2008–2012) and clinical risk score (one-point increments from 0 to 5). The clinical risk score was computed with one point assigned for each of: node-positive primary malignancy, disease-free interval < 12 months, more than one hepatic metastasis, largest hepatic metastasis measuring more than 5 cm and pre-hepatectomy carcinoembryonic antigen >200 ng/ml.[24] The time period cut-off of 2008 was selected to correspond with the routine introduction of peri-operative systemic treatment of CRLM at our institution.[25] Patients were categorized according to the matching criteria and a random number generator used to match corresponding pairs within the same categories. All PPC patients with a matched control available were included in the analysis to optimize the sample size. Post-hoc power calculation was conducted.

Outcomes and data collection

The primary outcome was overall survival (OS), defined as date of hepatectomy to date of death. The secondary outcome was recurrence-free survival (RFS), defined as date of hepatectomy to date of recurrence.

The database was queried for data on baseline demographics, pre-operative systemic treatment, pre-operative biochemical parameters, intra-operative factors and post-operative clinical course, including recurrence. Major liver resection was defined as a resection of 3 or more liver segments. Major morbidity included grade 3 to 5 Clavien–Dindo complications.[26] Recurrence was defined as intra- or extra-hepatic biopsy-proven recurrent adenocarcinoma or lesion deemed suspicious on cross-sectional imaging. Death data were obtained from the Ontario Cancer Registry (OCR), a provincial administrative database of Ontario residents diagnosed with cancer since 1964, receiving hospital discharge records, pathology reports, death certificates and reports from regional cancer centres in the province of Ontario.[27]

Technical considerations

Liver resections were performed aiming for low central venous pressure. Intermittent PPC was used at the discretion of the operating surgeon (no longer than 15 min clamped with 5–10 min unclamped). Hepatic pre-conditioning is not routinely used. After hepatectomy for CRLM, patients are initially followed every 3–6 months clinically and radiologically with cross-sectional imaging of the chest, abdomen and pelvis, for 5 years.

Statistical analysis

Descriptive analysis was performed to compare the characteristics of patients who underwent PPC with those who did not. Categorical variables were reported as absolute number (n) with proportion (%), and continuous variables as the median with interquartile range (IQR). Groups were compared using Pearson's chi-square test, Fisher's exact test and ANOVA, as appropriate.

Survival analysis was performed using the Kaplan–Meier method.[28] Dates of death from the OCR as of August 8th, 2014 were used, providing a minimum of 24 months of follow-up data for all patients in the cohort. The end of follow-up for OS analysis was considered as date of death or August 8th, 2014. For RFS, date of first recurrence was used, with end of the last follow-up defined as date of recurrence, date of death or date of the last clinical encounter. A sensitivity analysis was conducted for OS and RFS in patients alive 90 days after a hepatectomy. Differences in OS and RFS were calculated using the log-rank test.[28] The association between PPC and survival was assessed with Cox regression analysis. Multi-variable Cox regression was used to adjust for relevant clinico-therapeutic variables identified *a priori*: operative time (continuous, in hours), receipt of a red blood cell transfusion (categorical), major liver resection defined as ≥3 segments (categorical) and surgeon (categorical). Results of Cox regression were reported as hazard ratios (HR) with 95% confidence interval (95% CI). Statistical significance was set at $P < 0.05$. All analyses were conducted with SPSS 22.0 (IBM Corp., Amon, NY, USA).