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ORIGINAL ARTICLE

Validation of clinical risk score for colorectal liver metastases resected in a contemporary multicenter cohort

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Abstract

Background: Recent advances in care for colorectal liver metastases (CRLM) have lengthened 5-year survival. In this new era, prognostic tools such as the clinical risk score (CRS) for colorectal liver metastases require reevaluation.

Methods: Patients undergoing resection for CRLM between 2008 and 2012 at 4 specialty hepatobiliary centers in Canada (N = 740) were stratified by CRS and analyzed in Kaplan–Meier survival curves. Primary outcome of overall survival (OS) and secondary outcome of recurrence-free survival (RFS). Multivariate Cox regression compared CRS to patient factors.

Results: Median OS not reached (>60 months), median RFS 16 months. Original CRS strata was a significant ($p < 0.001$) predictor of both OS (5-year OS: 0; 75%, 1; 71%, 2; 57%, 3; 57%, 4; 46%) and RFS (5-year RFS: 0; 39%, 1; 33%, 2; 21%, 3; 21%, 4; 8%). The presence of extrahepatic colorectal metastatic disease increased recurrence risk (RFS hazard ratio of 1.32 (1.06–1.65)), and the use of intraoperative portal pedicle clamping reduced recurrence risk (RFS hazard ratio of 0.78 (0.61–0.99)).

Conclusions: The CRS remains a relevant tool for predicting long-term outcomes for patients undergoing resection of CRLM. Additional factors such as the presence of extrahepatic colorectal metastatic disease and the use of intraoperative portal pedicle clamping may improve the prognostic power of the CRS.

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Introduction

Colorectal cancer remains a significant contributor to the worldwide cancer burden, with its incidence in men only behind that of lung and prostate cancers, and incidence in women led only by breast cancer.[1] While the colorectal primary lesion causes significant morbidity and mortality alone, colorectal liver metastases (CRLM) occur in approximately 50% of all patients with colorectal cancer with half of these metastases present upon diagnosis of the primary.[2–5] With recent advances in oncologic care, the resection and attenuation of these metastases has led to significant increases in 5-year survival with estimates reaching 60%.[2–7] Intraoperative technical improvements have led to a dropping rate of intra-operative mortality approaching 1%, while advances in chemotherapy, preoperative radiological imaging and patient selection, and perioperative care have all helped reduce the rates of mortality and recurrence overall.[4,5,7,8]

Despite these improvements in care, surgeons must make patient-dependent decisions on the appropriateness of a surgical resection. While surgeons' anecdotal experiences with similar patients can help guide their decision-making, a more rigorous and evidence-based methodology is needed to ensure that

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surgeons and patients are informed of their likely post-surgical outcomes. At the turn of the millennium, a clinical risk score (CRS) for predicting survival following resection of CRLM[9] was published that stratified patients into five risk categories dependent on the presence or absence of five patient factors. Although other risk scores for this population exist, the CRS has seen longstanding and pervasive use in surgical practice. While a clinical risk score of this kind was important for the accurate care of colorectal cancer patients, the interim improvements in clinical care may have influenced the accuracy of this scoring system, yielding some factors no longer important or others to become relevant. For example, allogeneic red blood cell transfusions (RBCT) and their transfusion-related immunomodulation effects have been recently suggested as a cause for early cancer recurrence and worse overall outcomes.[10–12] Portal pedicle clamping has also been recently employed in regular hepatobiliary practice with its effects on survival and recurrence being investigated.[13] Due to this changing stage for CRLM care, this study aims to reassess the value of the clinical scoring system within a contemporary cohort of colorectal liver metastatic patients.

Methods

This was a retrospective cohort study of all colorectal metastatic liver resections occurring in four major hepatobiliary units in Canada: Sunnybrook Health Sciences Centre in Toronto, London Health Sciences Centre in London, The Ottawa Hospital in Ottawa, and Foothills Medical Centre in Calgary between 2008 and 2012.

Selection of participants

Patients receiving liver resection for CRLM at one of the four aforementioned tertiary care hepatobiliary surgery care centers were the target population for this study. Patients ≥18 years of age were included.

Outcomes and data collection

Data from each site was collected from patients' electronic medical records according to a distributed study guideline and within a standard format.

Overall survival (OS), and recurrence-free survival (RFS) were used as primary and secondary outcomes, respectively. OS was calculated as the time from CRLM resection to the date of death, with all remaining alive patients being censored at the time of their last known survival status. RFS was calculated as the time from CRLM resection to either date of death, or date of recurrence of colorectal metastases at any location, whichever occurred first, with patients being censored at the date of last known recurrence assessment ending July, 2016. Recurrence was defined as any biopsy-proven or "suspicious" lesions on imaging that were not present prior to CRLM resection.

Clinical risk score (CRS) was used as the stratifying factor for this study, calculated as 1 point per criterion met: node positive primary, >1 preoperative liver lesions, largest preoperative liver lesion >5 cm, preoperative CEA >200 pg/L, and time between removal of primary and appearance of liver metastases <12 months. A CRS of 5 only occurred in 3 patients (0.4%), and was therefore excluded from individual analyses. Following statistical and visual analysis of the CRS, a low risk group (score <2), and a high risk group (score ≥2) were created.

Dates of death for Sunnybrook patients were extracted in August of 2015 from the Ontario Cancer Registry (OCR), a provincial database that collects intra-provincial hospital records and death certificates for all Ontario residents diagnosed with cancer. Date of death for Sunnybrook, Ottawa, London, and Foothills patients were collected or supplemented by medical records or online obituaries.

Major operation was defined as any operation that resected ≥4 liver segments or partial segments[14] (wedge resections were not counted as segments). Blood loss during liver resection surgeries at each of the four participating sites was minimized by aiming for low central venous pressure. Estimated blood loss (EBL) was extracted from anaesthetic records in liters, as well as operative time (OR Time) in hours. Portal pedicle clamping was recorded as any use of intraoperative portal pedicle clamp maneuver for any amount of time, and collected from patient's medical records.

As per operative guidelines, non-bleeding patients were administered RBCT if their hemoglobin dropped below 70 mg/ml intraoperatively, or if the patient experienced symptoms of anemia. Bleeding patients were administered RBCT in order to maintain their hemoglobin within 70–80 mg/ml. All blood products were provided by Canadian Blood Services. Preoperative anemia was defined in accordance with the World Health Organization (WHO) definition of a measured hemoglobin <130 mg/ml. Receipt of perioperative red blood cell transfusion was defined as reception of any number of units of allogeneic blood during or within 30 days of CRLM resection.

Age-adjusted Charlson comorbidity index (CCI)[15] was summated from patient's medical records. Extrahepatic disease was defined as the presence of colorectal cancer found in situ at any site other than the liver (including the colorectal primary if in situ) upon date of CRLM resection, as derived from patient's medical records. Colorectal metastases at any site resected prior to CRLM resection were not counted as extrahepatic disease.

Statistical analysis

Characteristics of all study participants were analyzed prior to stratification. Categorical variables were reported as absolute numbers (n) and percentages of the whole (%), while non-parametric continuous variables were reported as medians with interquartile ranges (IQR).

The Kaplan–Meier protocol was used in univariate analysis to create survival curves. OS or RFS were used as the endpoints (time and event variables), with study participants stratified by CRS or within CRS risk groups (factor variables). As a sensitivity

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