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ORIGINAL ARTICLE

Complications following liver resection for colorectal metastases do not impact on longterm outcome

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Abstract

Background: It has been suggested that adverse postoperative outcomes may have a negative impact on longterm survival in patients with colorectal liver metastases.

Objectives: This study was conducted to evaluate the prognostic impact of postoperative complications in patients submitted to a potentially curative resection of colorectal liver metastases.

Methods: A retrospective analysis of outcomes in 199 patients submitted to hepatic resection with curative intent for metastatic colorectal cancer during 1999–2008 was conducted.

Results: The overall complication rate was 38% ($n = 75$). Of all complications, 79% were minor (Grades I or II). There were five deaths (3%). The median length of follow-up was 39 months. Rates of 5-year overall and disease-free survival were 44% and 27%, respectively. Univariate analysis demonstrated that an elevated preoperative level of carcinoembryonic antigen (CEA), intraoperative blood loss of >300 ml, multiple metastases, large (≥35 mm) metastases and resection margins of <1 mm were associated with poor overall and disease-free survival. In addition, male sex and synchronous metastases were associated with poor disease-free survival. Postoperative complications did not have an impact on either survival measure. The multivariate model did not include complications as a predictive factor.

Conclusions: Postoperative complications were not found to influence overall or disease-free survival in the present series. The number and size of liver metastases were confirmed as significant prognostic factors.

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Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related death in Australia, where approximately 4000 patients die from this disease each year (age-standardized mortality is approximately 18%).[1] The liver is the most common site for metastatic disease, and resection of isolated metastases prolongs survival and achieves cure in selected patients.[2–4] Operative mortality following liver resection is <5% in high-volume centres,[5–8] but postoperative morbidity rates remain as high as 56%.[9–11]

Numerous preoperative factors have been shown to predict poor longterm outcomes following the resection of colorectal liver metastases. These include an elevated serum carcinoembryonic antigen (CEA) level, poor primary tumour differentiation and primary tumour lymph node involvement.[9] It has also been suggested that postoperative complications following liver resection may have a negative impact on longterm survival.[11] However, the mechanisms of this putative relationship are unclear.

The purpose of this study was to evaluate the prognostic impact of postoperative complications, as defined by the Clavien–Dindo system for grading complications,[12] in patients submitted to resection for colorectal liver metastases. A secondary aim was to determine additional factors that might predict poor longterm survival in these patients.

Materials and methods

A retrospective analysis of prospectively collected data was performed. The study sample consisted of consecutive patients submitted to first-time liver resection with curative intent for

colorectal liver metastases at Royal North Shore Hospital and associated campuses during the study period of 1999–2008. Ethics approval for the study was provided by the Human Research Ethics Committee of the Northern Sydney Area Health Service.

Data collection and definitions

All data were collected prospectively and extracted from the departmental liver database for retrospective analysis. Additional information was obtained from the hospital or the consulting surgeon's records. A range of demographic, clinical, radiological, pathological and follow-up variables were assessed.

Synchronous liver metastases were defined as those presenting within 4 months of the primary CRC diagnosis; metachronous liver metastases were defined as those identified at >4 months after the primary CRC diagnosis.

Intraoperative data collected included the total duration of inflow occlusion (Pringle manoeuvre), the estimated volume of blood loss, and the transfusion of blood products. Liver resection nomenclature was documented as per the Brisbane terminology.[13] Minor liver resections were defined as those in which up to two Couinaud liver segments were removed and major liver resections were defined as those in which three or more Couinaud liver segments were removed.

All perioperative morbidity was recorded in a prospective manner. All complications recorded were reviewed weekly at the unit meeting. These complications were categorized using the Clavien–Dindo system of classification.[12] The highest grade complication was recorded for each patient. Postoperative liver failure, postoperative bleeding and postoperative bile leakage were documented using standard definitions as per the International Study Group of Liver Surgery.[14–16]

Perioperative mortality referred to death during the same admission (in-hospital) or within 90 days of surgery. For survival analyses, patients were divided into two groups consisting of: (i) those patients requiring intervention (complications of Clavien–Dindo Grade II or higher), and (ii) those patients who either had no postoperative complications or had complications that did not require intervention (Clavien–Dindo Grade I). Specifically, patients who died in the perioperative period (Clavien–Dindo Grade V complication) were excluded from the survival analyses because otherwise death would represent both a predictor and an outcome measure in this group. Overall survival (OS) was defined as the time from hepatic surgery to the date of death (all-cause mortality). Disease-free survival (DFS) was defined as the time from hepatic surgery to the date of either death or the first evidence of recurrence (local, regional or metastatic). Follow-up time was taken as the time from hepatic surgery to the date of last follow-up. Follow-up and survival times were recorded in months.

Histopathological findings in the primary CRC and the liver metastases were obtained from hospital pathology reports. For the primary cancer, these data included the location and differentiation of the tumour, and lymph node status. For liver metastases, these data included the size of the largest tumour, the number of metastases and the tumour differentiation. Patients were stratified according to liver resection margins for the purpose of analysis: R2 represented a margin with macroscopic involvement; R1 represented a margin with microscopic involvement, and R0 represented a negative margin. Margins were measured as <1 mm, 1–10 mm and >10 mm.

Preoperative workup and operative technique

All patients underwent a baseline preoperative assessment that included liver function tests, coagulation studies, serum CEA levels and a fine-cut, multi-phase computed tomography (CT) scan of the abdomen and thorax. From January 2004, a positron emission tomography (PET) scan was also performed to exclude extrahepatic disease. All patients were discussed at a multidisciplinary group meeting prior to liver resection. Operative criteria included the likelihood of achieving an R0 resection (microscopically clear margin) along with the preservation of vascular inflow and outflow and an adequate post-resection liver remnant volume. Patients with limited extrahepatic intra-abdominal disease (e.g. portahepatis lymph node involvement or isolated upper quadrant peritoneal disease) were not excluded from resection. Liver transection was performed using the Cavitron Ultrasonic Surgical Aspirator (CUSA) dissection device (Integra LifeSciences Corp., Plainsboro, NJ, USA) under low central venous pressure conditions with intermittent inflow occlusion.

The follow-up regime included 6-monthly clinical evaluations, assessment of serum tumour markers and annual CT scans of the thorax and abdomen. Triple-phase contrast-enhanced magnetic resonance imaging was performed if clinically indicated. Patients were followed up annually indefinitely after the initial 5-year follow-up.

Statistical analysis

Demographic descriptive statistics were reported using the mean ± standard deviation (SD) and median [interquartile range (IQR)] depending on the distribution. Kaplan–Meier curves with 95% Greenwood bands were constructed for overall and disease-free survival. Patients with Grade V complications (perioperative patient death) were excluded from survival analyses.

Inferential univariate survival analysis was performed using the log-rank test after the conversion of variables into categorical variables. The cut-off value selected for these categorical variables either represented a clinically relevant quantity or was used to divide the groups into equal binary groups. Multivariate analysis was performed by constructing Cox proportional hazards models from potentially significant covariates identified in the univariate analysis (P <0.2). The purposeful selection of covariates method was used to select variables for the final model (i.e. stepwise removal whereby covariates thought to be clinically significant were retained if necessary). The final model was then assessed for the validity of the proportional hazards assumption