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A pre-operative clinical model to predict microvascular invasion and long-term outcome after resection of hepatocellular cancer: The Australian experience

S.M. Schlichtemeier [a], T.C. Pang [b,d], N.E. Williams [a], A.J. Gill [c,d], R.C. Smith [d], J.S. Samra [a,d], V.W.T. Lam [b,d], M. Hollands [b,d], A.J. Richardson [b,d], H.C. Pleass [b,d], S. Nozawa [a], M. Albania [a], T.J. Hugh [a,d,*]

[a] *Upper Gastrointestinal Surgical Unit, Royal North Shore Hospital and North Shore Private Hospital, Australia*
[b] *Department of Upper Gastrointestinal Surgery, Westmead Hospital, Australia*
[c] *Department of Anatomical Pathology, Royal North Shore Hospital and Cancer Diagnosis and Pathology Research Group, Kolling Institute of Medical Research, Royal North Shore Hospital, Australia*
[d] *Discipline of Surgery, University of Sydney, Australia*

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Abstract

Background: Hepatocellular cancer (HCC) is a leading cause of mortality worldwide. Liver resection or transplantation offer the best chance of long-term survival.

The aim of this study was to perform a survival and prognostic factor analysis on patients who underwent resection of HCC at two major tertiary referral hospitals, and to investigate a pre-operative prediction model for microvascular invasion (MVI).

Methods: Clinico-pathological and survival data were collected from all patients who underwent liver resection for HCC at two tertiary referral centres (Royal North Shore/North Shore Private Hospitals and Westmead Hospital) from 1998 to 2012. An overall and disease-free survival analysis was performed and a predictive model for MVI identified.

Results: The total number of patients in this series was 125 and the 5-year overall and disease-free survival rates were 56% and 37%, respectively. MVI was the only factor to be independently associated with a poor prognosis on both overall and disease-free survival. Age ≥64 years, a serum alpha-fetoprotein (AFP) ≥400 ng/ml (×40 above normal) and tumor size ≥50 mm were independently associated with MVI. An MVI prediction model using these three pre-operative factors provides a good assessment of the risk of MVI.

Conclusion: MVI in the resected specimen of patients with HCC is associated with a poor prognosis. A preoperative MVI prediction model offers a useful way to identify patients at risk of relapse. However, more precise predictive models using molecular and genetic variables are needed to improve selection of patients most suitable for radical surgical treatment.

Keywords: Microvascular invasion; Hepatocellular cancer; Liver resection

Introduction

Hepatocellular cancer (HCC) is the second most common cause of cancer-related death worldwide.[1] High-incidence regions include many Asian countries (i.e. Japan, Korea, Taiwan, Singapore and China), whereas Australia, North America and most of Europe are low incidence areas with rates <10 per 100,000.[2] However, these incidence rates have been changing over the past 30 years partly as a result

* Corresponding author. Upper Gastrointestinal Surgical Unit, Level 8, Clinical Administration 8A, Acute Services Building, Royal North Shore Hospital, St Leonards, NSW 2065, Australia. Tel.: + 61 2 9463 2899; fax: + 61 2 9463 2080.
E-mail address: tom.hugh@sydney.edu.au (T.J. Hugh).

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of population dynamics.[1] In Asia, and in New South Wales Hepatitis B is the most frequent risk factor associated with HCC while Hepatitis C and excessive alcohol usage are more commonly associated in Europe and North America.[3,4]

The management of patients with HCC is multidisciplinary and depends on tumor extent, underlying liver reserve, co-morbidity, local expertise and availability of resources. For small tumors (<5 cm), liver transplantation offers the best chance of long-term cure but is not widely used because of donor shortages.[5,6] Instead, hepatic resection with reported 5-year overall survival rates ranging from 37% to 53%[7–10] is the most frequent treatment option especially for patients with good functional liver reserve. Percutaneous ablation for small HCCs (<4 cm) may offer similar survival as resection but this is associated with high local recurrence rates and the technique is not suitable for all tumors.[11,12]

Several prognostic scoring systems help predict survival in patients undergoing resection. Variables most frequently involved and found to be predictive of long-term outcome post-resection include tumor size,[13–16] tumor number[16] and severity of the underlying liver disease.[16–18] Other prognostic factors outside these scoring systems include Hepatitis B or C infection,[19,20] serum AFP,[13,15,16] albumin level,[10,21] peri-operative blood transfusion,[10,22] and histopathological findings (macro- or microvascular invasion (MVI),[13,16,21,22] tumor grade/differentiation[18,23] and resection margin[23]). Of these, MVI has emerged as one of the most important predictors of poor survival and, as a consequence is now included in the latest TNM staging system.[16]

Liver resection is a major undertaking and it would be valuable to predict pre-operatively patients with a high risk of recurrence who will either not benefit from an operation or who might be enrolled in neoadjuvant trials. Ideally, this should be done without the need for a pre-operative needle biopsy.[24]

The primary aim of this study was to analyze the variables associated with MVI in patients who underwent resection of HCC in two Australian non-transplant tertiary referral units with relatively low rates of chronic liver disease. These variables were then used to develop a pre-operative prediction model with a secondary aim to confirm the importance of MVI on long-term outcomes.

Materials and methods

A retrospective review was undertaken of all patients who underwent resection for hepatocellular cancer (HCC) at the Northern (Royal North Shore Hospital and North Shore Private Hospital) and Westmead Hospitals from June 1998 to July 2012. Ethics approval was obtained from the ethics committees at all institutions. Patients <18 years of age, those with fibrolamellar HCC, mixed HCC or cholangiocarcinoma, as well as those with evidence of macroscopic vascular invasion on imaging were excluded from this study.

Preoperative assessment

Selection criteria for liver resection included: (1) surgically fit patients with Child-Pugh Class A or select Class B (score of 7 only) and (2) tumors deemed resectable with a microscopically clear margin and an adequate remnant liver volume. Preoperative investigations included routine blood tests, viral hepatitis status, serum alpha-fetoprotein (AFP) level, computed tomography (CT) scan and selective use of magnetic resonance imaging (MRI). Diagnostic biopsy was not done prior to resection. Tumor size was defined as the largest diameter of the tumor in the resected specimen. Correlation between the histopathological and pre-operative imaging measurements was undertaken in a sample of 29 patients in this series to ensure concordance. MVI was defined as histological identification of tumor emboli within vessels of any size including veins, capillaries and lymphatic spaces.

Surgical technique

Anatomical resections were favoured and parenchymal transection was performed using the Cavitron Ultrasonic Surgical Aspirator (CUSA) dissector (Integra LifeSciences Corp, NJ, USA) under low central venous pressure conditions, and with intermittent inflow occlusion. The Brisbane nomenclature was used with further sub-classification as either minor resections (≤two Couinaud liver segments) or major resections (≥three Couinaud liver segments).[25]

Liver resection margins were defined as: R0, negative microscopic margin; R1, a margin with microscopic involvement; and R2, a margin with macroscopic involvement.

Post-operative follow-up

Morbidity was classified according to the Clavien-Dindo system.[26] Complications such as bile leak, haemorrhage, and liver failure were further sub-classified based on grading proposed by the International Study Group of Liver Surgery.[27–29] Perioperative mortality was defined as death within 90 days of operation. Patients who died in the perioperative period were excluded from the survival analyses as otherwise death would represent both a predictor and an outcome measure in this group.

Follow-up involved 6-monthly clinical evaluations, serum AFP and annual CT scans for the first five post-operative years. Patients were reviewed annually and indefinitely thereafter. After diagnosis of recurrent disease, further treatment was decided based on multidisciplinary team meetings. Overall survival (OS) was defined as the time (in months) from hepatic surgery to date of death (all-cause mortality) or date of last review. Disease-free survival (DFS) was defined as the time (also in months) from hepatic surgery to date of either death or first evidence of recurrence (local, regional or metastatic).

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