ORIGINAL RESEARCH

International Journal of Surgery 11 (2013) 1078–1082

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Original research

Tumour size and differentiation predict survival after liver resection for hepatocellular carcinoma arising from non-cirrhotic and non-fibrotic liver: A case-controlled study☆

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ARTICLE INFO

Article history:
Received 22 July 2013
Received in revised form
22 September 2013
Accepted 2 October 2013
Available online 12 October 2013

Keywords:
Hepatectomy
Hepatic resection
Hepatocellular carcinoma
Non-cirrhosis
Non-fibrosis

ABSTRACT

Aims: The aims of this study were to assess the outcomes of patients who underwent potentially curative hepatic resection for hepatocellular carcinoma (HCC) in a background of non-cirrhotic/non-fibrotic livers, and to determine prognostic factors that influenced survival.
Methods: Over a 15-year period, all patients undergoing hepatectomy for HCC were identified. Collated data included demographics, laboratory analysis, operative findings and histo-pathological data. Survival differences between these factors following liver resection were determined.
Results: 57 patients were included with a median age of 70 years. The majority of patients underwent a hemi-hepatectomy or more radical resection ($n = 37$). Overall R0 resection rate was 90.4% ($n = 51$). The overall morbidity and mortality rates were 26.3% and 3.5%, respectively. The median follow-up period was 28 months. The 1-, 3- and 5- year disease-free survival was 65.4%, 41.8% and 39.1%, and the overall survival was 73.5%, 49.6% and 39.5%, respectively. AFP ($p = 0.039$) was the only predictor of poorer disease-free survival on univariate analysis. On multi-variable analysis, poorly differentiated tumour and large tumour size were independent predictors of overall survival.
Conclusions: Liver resection is a feasible treatment option for HCC in non-cirrhotic/non-fibrotic livers with good survival outcome. Tumour size and differentiation are adverse predictors of outcome in these patients.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth commonest malignancy worldwide,[1] and recent evidence suggests that its incidence is on the rise in the Western World. Irrespective of aetiology, over 80% of HCC occur in patients with a background of liver cirrhosis.[2] The therapies which are capable of providing potential long term cure are hepatic resection and liver transplantation. Liver transplantation is regarded as the optimal treatment for selected cirrhotic patients, as it treats both the malignancy and underlying parenchymal disease. The Milan criteria and the University of California, San Francisco (UCSF) criteria are widely used for the selection of patients for liver transplantation,[3] as these criteria have been shown to be associated with better overall survival.[4–6] However, HCC arising from non-cirrhotic livers tend to have better outcomes following liver resection as it is associated with a lower recurrence rate compared to liver transplantation.[7]

The majority of published studies on the surgical management of HCC are from the Far East and Africa due to the higher prevalence of viral hepatitis B and C, which is associated with liver cirrhosis in these geographical regions.[8] These studies tend to analyse the clinical outcome of both non-cirrhotic and cirrhotic livers as the same entity.[2,9–11] In comparison, there are currently fewer published reports on HCC arising from non-cirrhotic livers in Western

☆ **Presentation**: 32nd Congress of the European Society of Surgical Oncology, Valencia, Spain (September 2012).

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http://dx.doi.org/10.1016/j.ijsu.2013.10.001

cohorts,[12–15] and it has been suggested that the aetiology and disease process of HCC arising within non-cirrhotic livers may be different from that of the cirrhotic livers.[16]

The aim of this study was to assess the outcomes of patients who underwent potentially curative hepatic resection for HCC in a background of non-cirrhotic and non-fibrotic livers. The secondary aim included determining prognostic factors that influenced survival.

2. Patients and methods

All patients with HCC undergoing hepatic resection with curative intent at our Hepatobiliary Unit during the 15-year period from January 1996 to August 2011 were identified from a prospectively maintained hepatobiliary database. Patients with final histological diagnosis of HCC and without liver fibrosis and cirrhosis were included in this study; whereas histo-pathological diagnosis of fibrolamellar HCC was excluded.

Preoperative evaluation

Collated data included patient demographics, laboratory analyses (<1 week prior liver resection), type of surgery, histopathology analysis and clinical outcome. Pre-operative radiological assessment included a computer tomography (CT) scan of the thorax, abdomen and pelvis, and magnetic resonance imaging (MRI) of the liver (from 2008). All patients were discussed in our specialist multidisciplinary meeting that consisted of hepatobiliary surgeons, hepatologist, oncologist, radiologist and pathologist prior to surgery.

Surgical and post-operative details

Parenchymal transection was performed using the Cavi–Pulse Ultrasonic Surgical Aspirator (CUSA) or Kellyclasia. Intra-operative ultrasound was performed to confirm the findings of pre-operative imaging and to assist in surgical planning. The number of hepatic (Couinaud's) segments[17] resected was determined by the procedure performed as stated in the Brisbane nomenclature.[18] Type of surgical procedure was dependent on the resection of all macroscopic disease and achieving a clear resection margin, while preserving sufficient remnant liver. The length of hospital stay, post-operative complications and 30-day mortality were recorded. Clavien–Dindo classification (Grade I–V) was used to quantify post-operative complications.[19]

Histo-pathological analysis

The non-fibrotic and non-cirrhotic status of the liver was confirmed by an independent pathologist (MT). The tumour differentiation was graded as well, moderately and poorly differentiated HCC. Largest diameter of the tumour (mm), capsular involvement, micro- and/or macro vascular involvement, and resection margin (mm) were also recorded. R0 resection was defined as no microscopic evidence of tumour at or within 1 mm of the margin.

Follow-up protocol

Patients were followed up in specialist hepatobiliary clinics. Following initial post-operative review at one month, all patients were examined in the outpatient clinic at 3, 6, 12, 18 and 24 months and annually thereafter. At each clinic review, blood tests were performed for liver function tests and α-fetoprotein (AFP) levels. All patients had a minimum follow-up of 1 year following surgery. Patients underwent 6-monthly surveillance CT scan of the thorax, abdomen and pelvis during the first two post-operative years, followed by annual CT scans thereafter. Liver MRI was used to characterize suspicious hepatic lesions demonstrated on CT.

Over the past 6 years or so, with the increasing availability of using Sorafenib for advanced HCC, patients with disease recurrence after HCC resections were referred to oncologist for the consideration of adjuvant chemotherapy.

Overall and disease-free survival data was recorded, with disease-free survival defined as the time from primary hepatic resection to the first documented disease recurrence on imaging or death. Overall survival was defined as the time interval between the date of primary hepatic resection and the date of death or most recent date of follow-up if the patient was still alive.

Statistical analysis

Categorical data was presented as frequency and proportions (%) and was analyzed using the Pearson's chi-squared test or Fisher's exact test. Median and range were used to describe continuous data. The Kaplan–Meier method was used to assess the actuarial survival and disease-free survival. Univariate analysis was performed to assess for a significant difference in clinico-pathological characteristics that influenced disease recurrence and survival following curative resection. A multivariate analysis was performed by Cox regression (Step-wise forward model) for variables significant on univariate analysis. All statistical analyses were performed using the SigmaPlot v.12 for Windows (Systat, US) and statistical significance was taken at the 5% level.

3. Results

During the study period, 57 consecutive hepatectomies for non-cirrhotic and non-fibrotic HCC were identified. All patients were Caucasian, and the majority of patients were male ($n = 33$, 57.9%). The median age was 70 years (range: 24–88 years). Demographics and clinical factors are summarised in Table 1. None of the patients underwent pre-operative liver biopsies.

The frequency of distribution of hepatectomies were segmental resections ($n = 18$), left hemi-hepatectomy ($n = 14$), right hemi-hepatectomy ($n = 12$), extended right hemi-hepatectomy ($n = 8$) and extended left hemi-hepatectomy ($n = 3$).

The overall R0 resection rate was 90.4% ($n = 51$). Fifty (87.7%) patients had a solitary tumour and evidence of micro-vascular invasion was observed in 21 (36.8%) patients. Capsular involvement was reported in 20 (35.1%) cases and mild to moderate steatosis was observed in 20 (35.1%) cases. Tumour differentiation were well, moderate and poor in 15 (26.3%), 29 (50.9%) and 13 (22.8%) cases, respectively.

The overall morbidity rate was 26.3% ($n = 15$), with Grade II complications observed in 12 patients, followed by Grade V ($n = 2$) and Grade IVa ($n = 1$). Twenty one post-operative complications occurred in 15 patients. The 30-day mortality rate was 3.5% ($n = 2$), as a result of pseudomembranous colitis ($n = 1$) and acute liver failure ($n = 1$).

Prognostic factors influencing survival outcome

During the study period, 31 (54.4%) patients died, of whom 24 (42.1%) patients had recurrent disease. Recurrent disease were observed in the remnant liver ($n = 13$), lung ($n = 1$), para-aortic lymphadenopathy ($n = 1$) and widespread metastases ($n = 9$). The median follow-up period was 28 months (range: 12–178 months).