Research Article

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Validation of the "Metroticket" predictor in a cohort of patients transplanted for predominantly HBV-related hepatocellular carcinoma

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Background & Aims: The "Metroticket" prognostic model for survival post liver transplant for hepatocellular carcinoma (HCC) was developed from a European cohort of patients with predominantly alcoholic liver disease and hepatitis C-related HCC. The aim of this study was to evaluate the prognostic value of the Metroticket in an independent cohort of patients with predominantly HBV-related HCC, in an Asia–Pacific transplant programme.

Methods: All patients listed for HCC at the New Zealand Liver Transplant Unit (NZLTU) between January 1998 and November 2009 were included. For each patient, the predicted 3 and 5 year post-transplant survival score was calculated using the Metroticket model (http://www.hcc-oltmetroticket.org/calculator/ind ex.php). The observed and predicted survivals were compared.

Results: Ninety-five patients with HCC were listed, 82 were transplanted (40 with HBV) and 13 delisted for progression. Predicted survival calculated by the Metroticket model based on pre-transplant radiological data (n = 82) was 76.3% and 69.7% at 3 and 5 years, respectively, while the observed survival was 83% (49/59) and 74% (35/47), respectively. Of the 40 patients with HBV, observed survivals were 84% (26/31) and 80% (20/25) at 3 and 5 years, compared with 80% (23/28) and 69.6% (16/23), respectively, for the 42 patients without HBV. On intent to treat analysis, survival after listing was 73.8% (95% CI 62.7–82.1) at 3 years and 69.1% (53.7–78.2%) at 5 years. AFP level was associated with vascular invasion.

Conclusions: The Metroticket calculator incorporating pre-transplant radiological Staging was an accurate predictor of post-transplant survival in a cohort of predominantly HBV-related HCC.

Keywords: Liver transplantation; Hepatocellular carcinoma; Prognosis.
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Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplant; NZLTU, New Zealand Liver Transplant Unit; AFP, alpha-fetoprotein; TACE, transarterial chemoembolisation.

Introduction

Hepatocellular carcinoma (HCC) is the 5th most common cancer globally [1] and has the fastest growing cancer mortality, related to the current epidemic of Hepatitis C [2]. It is the leading cause of mortality in patients with cirrhosis [3]. Liver transplant (LT) addresses the cancer, its potential multifocal nature, as well as the underlying liver cirrhosis [4]. The role of LT has been firmly established since the "Milan Criteria" were generated in 1996 and demonstrated good long term survival and low recurrence rates in patients with either one tumour under 5 cm or up to three tumours under 3 cm (actuarial survival 75% and recurrence-free survival 83% after 4 years) [5].

Selection criteria for LT have been gradually expanded over subsequent years in an effort to include more patients who could potentially benefit, yet still preserve an acceptable survival. Yao *et al.* modestly expanded these parameters with the "UCSF expanded criteria" [4], which were subsequently validated in a prospective cohort based on pre-operative imaging [6]. Mazzaferro *et al.* have recently developed the "Up to seven" criteria based on a large multicentre cohort of 1112 patients who exceeded the Milan criteria – 238 met the up to seven criteria and had an acceptable 5 year survival of 71.2% [7].

In the same study, the authors developed a novel prognostic model called the "Metroticket", based on a continuum of size and number, whereby each patient is assigned an individual prognosis for 3 and 5 year survival. This provides a paradigm shift from a dichotomous to continuous prognostic stratification for patients with HCC being assessed for LT.

The Metroticket model has not been externally validated on an independent series of patients undergoing LT for HCC. The aim of this study is to test the prognostic accuracy of the Metroticket in an independent cohort of patients. In addition, whilst the original European study cohort included predominately HCC cases secondary to alcoholic liver disease and hepatitis C-related, this current Asia–Pacific study includes predominately hepatitis B-related HCC.

Patients and methods

Patients

This was a retrospective cohort study of all patients listed for liver transplantation with known HCC (including those not transplanted) at the New Zealand Liver Transplant Unit (NZLTU) between January 1998 and November 2009. A

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prospectively maintained database of all patients listed and transplanted was supplemented by medical records, laboratory, radiological, and pathological data.

Baseline demographic data (age, gender, and ethnicity), aetiology of underlying liver disease, and HCC-related characteristics at the time of listing (size and number of tumours, alpha feto-protein [AFP]) were recorded. Post-transplant HCC-related characteristics were derived from the explant pathology (size and number of tumours, macroscopic or microscopic vascular invasion, and lymph node involvement). Recurrence and survival data, including cause of death, were obtained for all patients up until December 2009.

For each patient, a "Metroticket" predicted survival score was calculated using the online calculator (available at: http://www.hcc-olt-metroticket.org/calculator/index.php). The 3 and 5 year survival predictions were based on pre-transplant radiological measurements obtained at the time of listing (primary analysis), and another 5 year survival prediction was based on tumour measurements and the presence or absence of vascular invasion in the explant (secondary analysis).

Outcomes

The primary analysis was the comparison between observed and predicted survival following LT when the Metroticket model incorporated the tumour size and number derived from the pre-transplant radiological assessment. A subgroup analysis of observed and predicted survival following LT in HBV *vs.* non HBV-related HCC was also performed. The secondary analyses were: (I) the comparison between observed and predicted survival following LT, when the Metroticket model incorporated explant pathological data (tumour measurements and vascular invasion); (II) an intent-to-treat survival analysis from the time of listing; (III) outcome stratified according to 3 HCC selection criteria – within Milan, beyond Milan, and within Up-to-seven, and beyond Up-to-seven.

Selection criteria for transplantation

The NZLTU criteria for listing patients with HCC were modified Milan criteria – initially 1–3 lesions up to 5 cm with no macrovascular invasion or extra-hepatic disease [8]. In 2006, these criteria were expanded to the UCSF criteria – single lesion up to 6.5 cm, up to 3 lesions <4.5 cm, and total tumour diameter <8.0 cm, without vascular invasion or extra-hepatic disease [4]. In all patients, the diagnosis of HCC was confirmed by helical triple-phase computerised tomography scans (arterial, portal venous, and delayed venous phases). If there was diagnostic uncertainty or contrast allergy, magnetic resonance imaging was used. Pre-transplant tissue diagnosis was only sought if the AFP was non-diagnostic and the imaging characteristics were atypical for HCC in patients who did not otherwise meet listing criteria. In this case a fine needle aspiration was first obtained and if the direct smear and cell block were unhelpful, a 19 gauge core biopsy was taken. Prior to listing for transplantation, extra-hepatic disease was excluded with CT chest and skeletal MR STIR (Short T1 Inversion Recovery). Serum AFP measurement above 5000 μg/L was considered a contraindication to listing. Patients listed with tumours >3 cm underwent trans-arterial chemoembolisation (TACE) in an attempt to prevent tumour progression on the waiting list.

Radiology and pathology analysis

Tumour size, number, and associated macrovascular invasion were determined by triple-phase CT or MRI scans performed during transplant assessment prior to listing. All scans were reported by experienced consultant radiologists.

The explanted liver was fixed immediately after removal by formalin perfusion via a portal vein cannula and prepared for histopathological examination. The fixed liver was then sectioned in 1 cm slices and all suspicious nodules examined histologically. The size and number of tumours, cellular differentiation, macroscopic and microscopic vascular invasion, and lymph node status were recorded.

Statistical methods

Individual Metroticket predictions were calculated for each patient at 3 and 5 years based on the pre-transplant data, and at 5 years using the post-transplant data (based on explant pathology). The mean of the sum of the individual scores was calculated and compared to the observed survival of our cohort at 3 and 5 years.

Survival analysis was performed using the Kaplan Meier method and compared using the Log-rank Test (GraphPad Prism version 5.0b, January 6 2009, GraphPad Software, San Diego California USA, www.graphpad.com). Logarithmic transformation of AFP levels was undertaken to normalise the data and logistic regression used to determine the relationship with vascular invasion and HCC recurrence (SAS v.9.1, SAS Institute, Cary, NC).

Application of the Metroticket

The Metroticket calculator provides a percentage probability of survival at 3 years and 5 years post-transplant, depending on both the number of tumours and the size of the largest tumour nodule. This was calculated using the best radiological information available at the time of listing for transplant. The Metroticket calculator only incorporates tumours greater than 10 mm diameter, and no more than 10 nodules. Two patients with tumour characteristics outside these parameters were rounded to these maximum and minimum limits.

The Metroticket calculator also gives another 5 year survival prediction based on tumour size and number and the presence or absence of microvascular invasion. As this calculation requires explant pathology it can only be performed on patients who underwent LT.

Results

Between 1st January, 1998 and 30th November, 2009, 95 patients were listed for LT for HCC, of whom 82 were transplanted. There was no peri-operative mortality in patients transplanted with HCC. Thirteen patients were delisted prior to transplantation; 10 for tumour progression, 1 for sepsis and 2 who received alternative treatments (resection and radio-frequency ablation). Twenty-nine patients received 40 TACE treatments whilst on the waiting list.

Baseline demographics for all patients are listed in Table 1 and the explant tumour characteristics are listed in Table 2. There were an additional 9 patients transplanted for decompensated liver disease who had incidental HCC diagnosed following pathological examination of the explanted liver and these patients were not included in the analysis (median diameter of the incidental tumours was 1.1 cm, range 0.5–3.5). Twenty-four patients had evidence of vascular invasion on explant pathology.

Survival analysis was performed on 1st December 2009. There have been 11 deaths prior to transplant (HCC progression in 10, sepsis in 1) and 18 deaths post-transplant (HCC recurrence in 13). The causes of death are listed in Table 3. There were significant discrepancies between pre-operative (radiological) and post-operative (pathological) disease stage. Using pathological stage as the gold standard, the disease was both under-staged (42.7%) and over-staged (14.6%) by radiology. Median follow up for the overall cohort (n = 82) was 67.6 months.

Primary outcome

Predicted post-transplant survival calculated by using the Metroticket model incorporating pre-transplant radiological data (n = 82) was 76.3% at 3 years and 69.7% at 5 years, respectively. Observed post-transplant survival was 83.1% (49/59) at 3 years and 74.5% (35/47) at 5 years. Actuarial 3 and 5 year survivals were 84.2% (95%CI 73.1–91) and 78.2% (66.2–86.9), respectively (Fig. 1). The 3 and 5 year Metroticket predictions both fell within the 95% confidence interval of the actuarial survival.

Of the 82 patients listed and transplanted for HCC, 40 had HBV-related HCC and 42 did not. For the subgroup with HBV, predicted post-transplant survival (using the Metroticket model