Research Article

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Is resectable hepatocellular carcinoma a contraindication to liver transplantation? A novel decision model based on "number of patients needed to transplant" as measure of transplant benefit

A. Vitale[1,*,†], A. Cucchetti[2,†], G.L. Qiao[3], M. Cescon[2], J. Li[3], R. Ramirez Morales[1], A.C. Frigo[4], Y. Xia[3], F. Tuci[1], F. Shen[3], U. Cillo[1,‡], A.D. Pinna[2,‡]

[1]*Department of General Surgery and Organ Transplantation, Hepatobiliary Surgery and Liver Transplantation Unit, University Hospital of Padua, Padua, Italy;* [2]*Liver and Multi-Or gan Transplantation Unit, St. Orsola Hospital, Alma Mater Studiorum – University of Bologna, Bologna, Italy;* [3]*Eastern Hepatobiliary Surgery Hospital, Shanghai, China;* [4]*Biostatistics Unit, University of Padua, Padua, Italy*

Background & Aims: Number-needed-to-treat is used in assessing the effectiveness of a health-care intervention, and reports the number of patients who need to be treated to prevent one additional bad outcome. Although largely used in medical literature, there are no studies measuring the benefit of liver transplantation (LT) over hepatic resection (HR) for hepatocellular carcinoma (HCC) in terms of "Number of patients needed to transplant (NTT)."

Methods: Exclusion criteria: Child-Turcotte-Pugh (CTP) Classes B–C, very large (>10 cm) and multi-nodular (>2 nodules) tumours, macroscopic vascular invasion and extra-hepatic metastases. Study population: 1028 HCC cirrhotic patients from one Eastern (n = 441) and two Western (n = 587) surgical units. Patient survival observed after HR by proportional hazard regression model was compared to that predicted after LT by the Metroticket calculator. The benefit obtainable from LT compared to resection was analysed in relationship with number of nodules (modelled as ordinal variable: single *vs.* oligonodular), size of largest nodule (modelled as a continuous variable), presence of microscopic vascular invasion (MVI), and time horizon from surgery (5-year *vs.* 10-year).

Results: 330 patients were beyond the Milan criteria (32%) and 597 (58%) had MVI. The prevalence of MVI was 52% in patients within Milan criteria and 71% in those beyond (p <0.0001). In the 5-year transplant benefit analysis, nodule size and HCC number were positive predictors of transplant benefit, while MVI had a strong negative impact on NTT. Transplantation performed as an effective therapy (NTT <5) only in oligonodular HCC with largest diameter >3 cm (beyond conventional LT criteria) when MVI was absent.

The 10-year scenario increased drastically the transplant benefit in all subgroups of resectable patients, and LT became an effective therapy (NTT <5) for all patients without MVI whenever tumor extension and for oligonodular HCC with MVI within conventional LT criteria.

Conclusions: Based on NTT analysis, the adopted time horizon (5-year *vs.* 10-year scenario) is the main factor influencing the benefit of LT in patients with resectable HCC and Child A cirrhosis.

Introduction

Liver transplantation (LT) is theoretically the best treatment for patients with hepatocellular carcinoma (HCC) and cirrhosis, since it cures both the tumour and the underlying liver disease [1]. Its main limit is the scarcity of donor resources, leading to a high risk of patient drop-out from the waiting list, and thus of death before the LT [2]. When intention-to-treat survival is used as outcome endpoint, hepatic resection (HR) potentially competes with LT as main curative first line treatment for HCC patients [3]. The term cure for HCC patients is quite relative and usually, in this complex field, defines therapies reaching a 5-year survival higher or equal to 50% [1,3,4]. The main limit of HR is that positive survival perspectives are limited to patients with compensated cirrhosis.

There are several studies comparing HR and LT in this particular clinical setting [4]. Most of the studies support a strategy based on HR as first line therapy and salvage LT in case of transplantable tumour recurrence or severe liver decompensation. There are several problems in these studies worth noting. First, they generally compare therapies from a transplantation perspective only, since the main inclusion criterion is the fulfilment

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* Corresponding author. Address: Unità di Chirurgia Epatobiliare e Trapianto Epatico, Azienda Ospedaliera-Università di Padova, Via Giustiniani, 2, 35128 Padova, Italy. Tel.: +39 0498218624; fax: +39 0498211816.

E-mail address: alessandro.vitale@unipd.it (A. Vitale).

† These authors contributed equally to this work.

‡ These authors share senior authorship.

of the Milan criteria [4]. From this standpoint, many studies present a selection bias in terms of liver function or tumour characteristics and aggressiveness. Conversely, none of the studies in this comparison were done from a HR perspective: i.e., analysing transplantation performance in resectable HCC patients with compensated cirrhosis independently from fulfilment of the Milan criteria. In exploring this particular subgroup of patients, conversely, it may be scientifically interesting not to propose an expansion of current selection criteria for LT but to better substantiate biologically (i.e., increasing prevalence of MVI) why LT is contraindicated in this population. Second, comparison between LT and HR is usually limited to a 5-year survival perspective, while it is well known that the survival advantage of LT is probably higher after this time-point. Last but not least, intention-to-treat survival is the ideal outcome endpoint to be used in well-designed prospective studies, but it cannot be used as a good treatment decision tool since it is strictly dependent on local waiting list characteristics [5,6]: i.e., patients with same tumour characteristics but with longer waiting times have intrinsically lower intention-to-treat survival perspectives than patients with a lower number of competitors or lower priority points. An innovative priority-allocation endpoint has been recently introduced in LT, the transplant survival benefit [7]. This endpoint is based on the ratio and/or difference between post-LT outcome and outcome before/without LT. Recent studies [8–10] evaluating transplant benefit in HCC patients have studied patients both within and beyond the Milan criteria. Moreover, transplant benefit may be evaluated also using a non-waiting list population, avoiding all the biases intrinsic to this kind of control group.

One very popular measure to express benefits in clinical terms is to calculate the "number needed to treat", which denotes the number of patients who need to be treated with an experimental therapy in order to have one additional favourable outcome in comparison with the control therapy [11]. Number needed to treat is the inverse of the absolute risk increase that is the difference between survivals at specific time points of survival curves. This measure of benefit seems particularly appropriate for the transplantation context in terms of number of patients/organs needed to obtain an additional benefit over alternative therapies.

In this work we introduce the concept of number of patients/organs needed to transplant (NTT) as indicator of the benefit of LT over HR, and we generated a decision model derived from large multi-centre cohorts and evaluating both a 5-year and a 10-year post surgical scenario.

Methods

Study population and assumptions on model covariates

Data prospectively collected of 1137 cirrhotic patients in Child-Turcotte-Pugh (CTP) Class A, without macroscopic vascular invasion and extra-hepatic metastases, consecutively seen and undergoing radical hepatectomy for HCC from January 2000 to December 2011 in one Eastern (n = 507) and two Western (Padua, n = 256; Bologna, n = 374) surgical units, were reviewed. The diagnosis of cirrhosis was confirmed by the surgical specimens for all enrolled patients. The following variables were recorded for each patient: age, sex, aetiology of underlying liver disease, main serological parameters (total bilirubin, creatinine, prothrombin time and/or INR, albumin, platelets count, α-fetoprotein levels), model for end stage liver disease (MELD) score, and main tumour pathological characteristics (number and size of lesions, tumour grade, microscopic vascular invasion). Because data were scarce when tumour size was greater than 10 cm and had more than 2 nodules, higher values were truncated at these thresholds. In total 113 HCC patients were excluded from the final analysis. Thus, the study group used for survival analysis was based on 1024 patients, 441 from Shanghai, 358 from Bologna, and 229 from Padua. Size of largest nodule (SLN) was modelled as a continuous variable, whereas number of nodules (single *vs.* oligonodular, where oligonodular indicates the presence of two nodules), and microscopic vascular invasion (MVI, presence or absence) were modelled as ordinal variables.

Post-HR and post-LT survival models

Overall survival was calculated from the baseline visit until death from any cause or latest follow-up. Survival curves were estimated using the Kaplan-Meier method, whereas the statistical significance between survival curves was tested by the Log-Rank test. We performed several Cox's multivariate analyses based on the size of largest nodule (in cm), tumour number (single or oligonodular), and MVI, and incrementally including each of the following covariates: age, sex, hepatitis C cirrhosis, hepatitis B cirrhosis, MELD score, surgical centre, and tumour grade. None of these covariates maintained statistical significance at multivariate Cox analysis. Thus, 5-year survival predictions on post-HR were performed either based solely on the size of the largest tumour and number of tumours, or also including MVI, as originally done for the Metroticket model [12]. Cox model results were reported as hazard ratios (95% confidence interval) estimates together with corresponding p values. Finally, we used the Metroticket website (http://89.96.76.14/metroticket/calculator/) to calculate the predicted 5-year survival rates (95% confidence interval) after LT according to nodule size, number (1 or 2 nodules) and presence of MVI of each patient in the study group. Statistical significance was set at $p < 0.05$. The calculations were done with the JMP package (1989–2003 SAS Institute Inc.).

Number needed to "transplant"

The number needed to transplant (NTT) was defined as the reciprocal of the absolute risk difference between post-LT and post-HR 5-year survival estimations [11]. We calculated a NTT value for each enrolled patient using the predicted 5-year survival after HR (using the Cox model) and the hypothetical 5-year survival after LT (using the Metroticket model). We then obtained a distribution of 1024 NTT values, one for each resected patient. As a final step, we explored how this distribution was influenced by the main variables considered in this study: diameter of the largest nodule, number of nodules (one or two), and presence of MVI. This NTT variation was measured both graphically and by quantitative determinations including 95% confidence intervals.

We represented the variation of NTT (dependent variable) as a function of tumour diameter (independent variable) in patients with single or oligonodular tumour. We explored this relationship either in a "morphological" model that was based only on tumour size and number (without including MVI) or in a "biological" model that included also MVI. As in other experimental settings [13], we defined three thresholds of NTT to give a clinical evaluation of transplant benefit in resectable patients: a NTT value <5 was used to define an effective treatment, a value between 5 and 15 identified a satisfactory therapy, and, finally, a value >15 described a treatment with low cure rate. A negative NTT indicates that the treatment has an harmful effect. Finally, we calculated also 95% NTT confidence interval (CI) from 95% CI 5-year survival predictions of the resection Cox models, and from 95% CIs available in the Metroticket website.

Simulation of 10-year transplant benefit

To perform a descriptive analysis of the potential transplant benefit at 10-year in resectable patients we performed a simulation analysis. Since most HCC recurrences after LT occur within the first 2 years [14] and based on recent evidences on long term survival after LT [15,16], we assumed a low mortality rate between years 5 and 10 post-transplantation of 2% per year. Thus, we estimated the 10-year individual survival after LT as the 5-year individual post-LT survival (based on Metroticket model) minus 10%.

Since the study population was very recent (study period 2000–2011), the number of patients at risk to estimate 10-year survival after HR in different tumor characteristics subgroups was too low. Based on a recent paper [17], we calculated, therefore, the hypothetical 5-year conditional survival of our patients survived 5-year after HR in the whole study group. In the Cucchetti's study [17], the 5-year conditional survival calculation showed that patients resected for more advanced (T3) tumors or with adverse histologic features will experience the same survival probabilities as patients with less advanced tumors or favourable histology from the third year after surgery onward, as they had probably escaped