**Liver transplantation and hepatic resection can achieve the cure for hepatocellular carcinoma**

Antonio Daniele Pinna1, Tian Yang2, Vincenzo Mazzaferro3, Luciano De Carlis4, Jian Zhou5, Sasan Roayaie6, Feng Shen2, Carlo Sposito2, Matteo Cescon1, Stefano Di Sandro3, He Yi-feng5, Philip Johnson7 and Alessandro Cucchetti1

1 Department of Medical and Surgical Sciences – DIMEC; Alma Mater Studiorum – University of Bologna, Bologna, Italy

2 Eastern Hepatobiliary Surgery Hospital; Second Military Medical University, Shanghai, China.

3 General Surgery and Liver Transplantation Unit, University of Milan and Istituto Nazionale Tumori (National Cancer Institute), IRCCS Foundation, Milan, Italy

4 General Surgery and Abdominal Transplantation Unit**, University of Milano-Bicocca and Niguarda-Cà Granda Hospital, Milan, Italy**

5 Liver Surgery Department, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China

6 Liver Cancer Program; White Plains Hospital - Montefiore Health System, White Plains, New York, USA

7 Department of Molecular and Clinical Cancer Medicine, The Duncan Building, Daulby Street, University of Liverpool, Liverpool, UK

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**Corresponding Author:** Antonio Daniele Pinna, Department of Medical and Surgical Sciences – DIMEC; Alma Mater Studiorum - University of Bologna, S.Orsola – Malpighi Hospital, Via Albertoni 15, 9; 40138 Bologna; ITALY. e-mail: [antoniodaniele.pinna@aosp.bo.it](mailto:antoniodaniele.pinna@aosp.bo.it)

**Running head**: *Statistical cure* after surgery for HCC

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**ABSTRACT**

**INTRODUCTION**

Hepatocellular carcinoma (HCC) represents the sixth most frequent malignancy worldwide and one of the most frequent cause of cancer-related death [1]. Among the various therapeutic options, principally guided by liver function and tumor characteristics, surgery remains the best choice to adopt. The scarcity of donors for liver transplantation (LT) forced surgeons to search for alternative treatments, with the eventual aim to bridge patients until transplant. In addition, Western countries were strongly afflicted by hepatitis C virus (HCV) by untreatable recurrence after LT in the last decades [2]. This disgraceful event represented another motivation to delay the need for an eventual LT as much as possible [3,4], opting for hepatic resection (HR) when feasible also for those patients that would be otherwise transplantable.

Several surgical series suggested similar survival outcomes after LT and HR for HCC [4-8], contravening the fundamental concept that LT cannot only remove the tumor but also the underlying liver disease which caused it. In some series, HR was even superior to LT in terms of 5-year overall survival (OS) [5-7] fetching some authors to suggest the resectability of the tumor as a potential contraindication to LT, especially in HCV patients [8]. Surely, LT and HR can provide similar survivals in the middle-term (3-5 years) for some specific cases, but tumor inevitably recurs and cirrhosis complications frequently lead to patient death. This contrast between the basic rationale for LT in HCC patients and observed outcomes after HR and LT is mainly the consequence of the time-horizon they refer, and what would be the entire expectation of residual life remains unexplored [9].

An approach able to capture this aspect relies on the concept of *statistical cure* [10,11]. In epidemiology, *statistical cure* occurs when the mortality of patients treated for a specific disease returns to the value expected in the general population [11]. Cure models assume that exists a proportion of patients which will never die as a consequence of the specific disease that has been treated, determining a plateau of the survival curve for long-term survivors.

In the present study we sought to apply a cure model to the outcome of surgical treatment of HCC. Disease-free survival (DFS) was modeled as primary outcome measure to estimate the benefit obtainable with LT over HR in terms of probabilities to return to have the same possibilities of being alive and without HCC of the general population. We also used OS in the cure model considering in this way HCC as a chronic health condition suitable for further treatments in the case of relapse. Finally, we adjusted cure probabilities for different drop-out risks while in waiting-list for LT, to return information also from an intention-to-treat point of view.

**METHODS**

**Study population**

The study population included total of 3286 surgically treated HCC patients from 7 international centers located in Italy (3 centres), China (2 centres) and United States (1 centre) between January 2000 and December 2016.

The LT cohort consisted of 1218 adult cirrhotic patients transplanted at four hepato-biliary and transplant centres located Italy (3 centres) and China (one centre: Zhongshan Hospital, Fudan University, Shanghai). This sample included only patients with complete clinical and tumoral data used for the present analysis. All patients had documented pre-operative diagnosis of HCC without evidence of macro-vascular invasion, according to guidelines criteria at the date of release. No particular restriction was adopted on whether LT was performed after any kind of neo-adjuvant therapies, if any, according to different transplant policies [12]. Transplant policies and waiting-list priorities varied among the transplant centres involved but HCC beyond Milan criteria was not considered an absolute contraindication to LT, especially in the Chinese center. Only active nodules ≥1 cm were considered as HCC if meeting the guidelines criteria. In presence of complete radiological response to neo-adjuvant therapies nodules and diameter were considered as having zero values [12].

The HR cohort was consisted of 2068 adult cirrhotic patients resected at five hepato-biliary surgical centres located in Italy (3 centres), China (one centre: Eastern Hepatobiliary Surgery Hospital; Second Military Medical University, Shangai) and United States (1 center). All patients underwent curative (R0) surgical resection for primary HCC. The criteria for surgical resection were not strictly based on the Barcelona Clinic Liver Cancer (BCLC) algorithm but based on a personalized approach based on multidisciplinary discussions [13-15]. In particular, the presence of clinical signs of portal hypertension or a hepatic venous pressure gradient (HVPG) ≥10mmHg were not considered absolute exclusion criteria for surgery. The present sample included only patients with complete clinical and tumoral data used for the analysis and did not comprehend patients with macro-vascular invasion and/or with spontaneous rupture of HCC.

**Survival end-points**

Disease-free survival (DFS) was used as the primary survival measure for the cure model. We decided to use DFS (from surgery to tumor recurrence or death of the patient) instead of disease-specific survival (which is calculated from the time of surgery until cancer-related death) since this latter measure did not take into account, as events, patients who are alive with recurrence [10]. However, it can be argued that in presence of increased efficacy of therapeutic strategies for HCC recurrence, patients can experience long-term survivals even after recurrence [17]. Thus, we modelled *statistical cure* also on overall survival (OS), considering HCC as a chronic illness requiring continuation of specific cares.

Cure probability was also to be considered from an intention-to-treat point of view, considering probabilities of being cured since enlistment for LT. The risk of drop-out represents a condition which reduces the probability of being cured since listing, by reducing the proportion of patients that will be consequently transplanted. Thus, cure estimates were also adjusted at varying of drop-out risk. Drop-out from waiting-list strongly depends on the transplant criteria adopted and consequently on its different definitions, being highly variable among different transplant centres [12, 17-21]. For this reason, we tested a plausible range of drop-out risk between 5% and 20% in a sensitivity analysis. The adjustment required simple maths, by multiply the inverse of drop-out risk by the estimated cure probability, thus, reflecting the reduction of the proportion of patients that will be transplanted, and accomplishing to the present task.

**Cure fraction model**

The chief requirement for the application of the cure model regards the statistical plausibility of cure [11,22,23].This means that if a proportion of patients who are not expected to succumb to the disease exists, the survival curve will tend to a plateau on the y-axis meaning that cure occurs within a reasonable time frame within the patient’s lifetime [10,22]. Thus, DFS and OS curves were first checked for the correctness of this assumption. As can be noted from ***Figure 1***, the DFS and OS curves tends to flatten with the passing of time confirming that the cure hypothesis can be accepted.

By using DFS as survival measure a non-mixture model was preferred, since this model has a background in modelling tumour recurrence [11,23]. When using OS a mixture model was applied as suggested by developers of this technique [23]. Statistical details of the cure model were already previously published [22,23]. Briefly, the survival measure (DFS or OS) of the study population was fitted through a parametric model. When the excess of hazard equals that of the general population used as reference, matched by age, sex and race, the asymptote of the fitting equation on the calculated relative survival curve returns the estimated cure fraction. The parametric survival function was fitted using a Weibull function and covariate effects were expressed as log odds. This approach was preferred to avoid boundary problems for low or high cure fractions. The estimation of expected hazard of the general population, at the time of patient event (death/recurrence) was derived from population survival tables obtained from the World Health Organization (WHO) database [24].

**Statistical analysis**

Categorical variables are reported as number of cases and percentages and compared with the Fisher’s exact test if necessary. Continuous variables were reported as medians and interquartile ranges (25th and 75th percentiles), and differences between the subgroups were compared with the Mann-Whitney test. Length of follow-up in the LT and in the HR populations was estimated through reverse Kaplan – Meier method. The cure model was computed using the *strsmix* and *strsnmix* package for STATA software (StataCorp. 2011. College Station, TX: StataCorp LP). In the present analysis, variables having a non-negligible effect (p<0.05) on the cure fraction were entered into the multivariate cure model. A p-value <0.05 was considered statistically significant in all the analyses. Differences between predicted cure probabilities, in various clinical scenarios between LT and HR, were compared through standardized differences (d) calculation, a measure of the effect size. In particular, d values around |0.2| indicated small differences; d values around |0.5| indicated moderate differences and d values around |0.8| or higher indicated considerable differences.

**RESULTS**

Demographical, clinical and tumor characteristics of LT and of HR cohorts are detailed in the **Table 1.** Before LT, 911 patients (74.8%) underwent pre-LT treatments (HR and/or ablation: 36.6%, TACE 50.5%, Other therapies 2.4%). These neo-adjuvant therapies resulted in 329 patients with non-vital HCC (27.0%) at the last assessment before LT (median time from radiology to LT: 2.3 months). Details of extension of hepatectomy were available for 2014 of the 2068 resected patients and, of them, 378 underwent the removal of ≥3 hepatic segments. The median follow-up after LT was of 6 years during which 172 patients had HCC recurrence (14.1%) and 298 died (24.5%). The median follow-up after HR was of 5.6 years during which 1125 patients had HCC recurrence (54.4%) and 878 had died (42.5%).

**Probabilities of being cured by LT**

Disease-free and overall survivals for the LT cohort are reported in **Figure 1**. These two curves tend to be very near each other in the long-term, and a proportion of patients experienced a plateauing of their survival, confirming the plausibility of *statistical cure*. Using DFS as survival measure in the cure model, the probability of being cured was estimated to be of 74.1% (IQR: 62.6-83.1) requiring 4.9 years (IQR: 3.5-7.5) from LT to be achieved with a 95% of certainty. Using OS, the cure fraction only mildly increased and was of 75.8% (IQR:63.2-85.8) requiring 7.2 years (IQR:4.6-9.7) for being achieved. Results from multivariable cure model regressions are reported in ***Table 2***. As expectable, hepatitis C status, Model for End-Stage Liver Disease, serum alpha-fetoprotein and number and diameter of the largest active tumor were significantly related to the probability of being cured (p<0.05 in all cases). No other variables significantly affected the cure fraction.

**Probabilities of being cured by HR**

Disease-free and overall survivals for the HR cohort are also reported in the **Figure 1**. Again, the trend of these curves confirmed the plausibility of *statistical cure*. However, different from what observed after LT, a large gap between the two curves persisted in the long-term. Using DFS, the probability of being cured was estimated to be of 24.1% (IQR: 15.9-36.4) requiring 10.7 years (IQR:9.8-11.5) from resection to be achieved with a 95% of certainty. Using OS, the cure fraction increased up to 40.5% (IQR: 20.8-57.4) requiring 14.4 years (IQR:11.8-17.9) for being achieved. Predictors of cure after HR were those identified for LT (***Table 2***). No other variables significantly affected the cure fraction.

**Comparison of cure probabilities**

Models reported in **Table 2** were used for prediction of cure fractions reported in the **Table 3** and **Table 4**. The analysis was limited to patients with MELD <11, since this threshold is frequently suggested as the limit for performing a hepatectomy with low morbidity and mortality.

Clinical scenarios reported in **Table 3** represented the most common transplant criteria adopted worldwide. Using DFS as survival measure for cure probabilities, LT outmatched HR for each of the transplant criteria tested in the analysis, with an effect size above 0.8, suggesting considerable differences between the achievable cure fractions with the two treatments. This superiority decreased, but was still present, even for drop-out risk up to 20% (effect size ~ 0.5). Using OS as survival measure for cure estimation, the superiority of LT over HR decreased consistently, being practically negligible for drop-out risk up to 20% (effect size ~ 0.1).

Cure estimates were also stratified according to different morphological characteristics and results reported in **Table 4**. Using DFS as survival measure for cure probabilities (**Table 3**), LT was always superior to HR for each of combination of number and diameter of the HCC, and this superiority was very large for multiple nodules (effect size ~ 1.0). Using instead OS as survival measure for cure estimation became small or even negligible for tumor <5cm and for the presence of 2-3 nodules (effect size ~ 0.1).

**DISCUSSION**

The decision to resect or to transplant (or both) a patient suffering from HCC is fraught of uncertainty. HR represents a rapidly executable surgical procedure, for which patients are often looking for when they have had the diagnosis of cancer. LT is mostly proposed in patients deemed unresectable because of some clinical necessities and the need for an available donor in presence of a chronic shortage. Nevertheless, HR can be considered as a neo-adjuvant therapy in the perspective of a future LT. The complementary role of the two treatments is familiar among physicians and surgeons having access to liver transplant programs. However, HCC patients managed outside liver transplant centers can have difficult referral to LT programs, and even in tertiary referral hospitals the decision to resect or to enlist for LT is often debated. Consequently, physicians, as well as patients, must be aware of different possibilities of cure deriving from HR and LT and the present results can provide such an accurate picture. The clinical utility of the cure fraction relies in the possibility to correctly inform patients about the probability of success of the proposed treatment, providing a single and comprehensible measure, rather than survival rates as endorsed by the US National Cancer Institute recommendations and press releases [25]. We here suggest that two different scenarios are conceivable, depending on the definition of cure itself.

First, it was already observed that it is incorrect to define patients who are alive with recurrence as *“cured”* from the disease [10,26-27]. Thus, we used DFS as primary outcome measure for modeling cure probabilities. With this survival endpoint, LT outperformed HR in terms of chances of achieving the statistical cure, even in presence of a waiting-list drop-out risk up to 20% (**Table 3**). This superiority was found stable across all transplant criteria considered. This perspective changed when cure was defined as the solely chance of being alive, regardless of tumor recurrence, equal to that of the general population. The cure fraction estimated after LT using OS only slightly increased in comparison to that estimated using DFS, whereas that of HR increased considerably. This phenomenon is easily explainable by looking at survival curves (**Figure 1**) and results. After LT, only 14.1% of patients had HCC recurrence, most of them within the first years of follow-up. Afterwards, the DFS curve remained only slightly lower than the OS curve. On the contrary, a large gap was observed between DFS and OS curves after HR. This is because the HCC recurrence was observed in 54.4% of resected patients which means that the HCC recurrence does not correspond to an immediate death of the patients, suggesting high efficacy of treatments for recurrence [16]. This end-result returned smaller differences between cure fractions after HR and LT for all transplant criteria considered (**Table 3**). In addition, and of most importance, in presence of a drop-out risk around 20% the two treatments were comparable in terms of cure, being the effect size <0.2. This standpoint argues that if HCC is considered as a chronic health condition, requiring continuation of cares, and even salvage LT, the statistical cure can be achieved with HR.

When stratifying patients on the basis of “resectability” criteria (**Table 4**) results showed some interesting arguments for discussion. Using DFS, the magnitude of the benefit in terms of statistical cure remained considerably large, but became particularly large for oligo-nodular (2-3 tumors) and multi-nodular (>3) HCCs with an effect size ~ 1.0, on average. Using OS, these data were confirmed for multi-nodular HCC (effect size ~ 1.0) whereas for oligo-nodular HCCs HR can still confers a reasonable cure probability. Of particular note, the benefit of LT over HR for single tumors <5cm and in presence of a drop-out risk above 5%, was small (effect size ~ 0.1). These results suggest that single HCCs can be reasonably treated with HR in first instance, and that oligo-nodular and especially multi-nodular HCCs need to be treated with LT as primary therapy, with the obvious limitation of fulfilling transplant criteria (**Table 3**)

In addition to the query whether a patient can be cured, the following is when a patient can be considered cured. In cure models, statistical cure occurs when time tends to infinity, that is the asymptote of the relative survival curve. Consequently, it is only possible to obtain a time to cure at a certain level of confidence. At the 95% level, patients can be considered statistically cured from the HCC (alive and without recurrence) after 4.9 years since LT and after 10.7 years since HR . When tumor recurrence was not considered, the time to cure increased to 7.2 years after LT and 14.4 years after HR. These figures represents the time needed to wait before claim that the patient regains the life-expectancy of the general population. Regarding this latter temporal aspect, it should be featured that a proportion of present resected patients would be censored before reaching this temporal end point. However, specific modeling studies on the cure fraction estimation, suggested that for liver cancers about 4 years are needed to fulfill the cure assumption [28], quite lower than the median follow-up of our study population, supporting the fact that the present assumptions at the basis of the cure model application are justified.

A final discussion should be regarded to comparison of cure from HCC to those of other liver malignancies. Among patients with intra-hepatic cholangio-carcinoma (ICC), the probability of cure after liver resection (DFS used as outcome measure) was found to be dramatically low, and of about 10% [26]. Surgical resection for colorectal liver metastases (CRLM) returns a *statistical cure* (DFS used as outcome measure) in about 20% of cases [27]. In the present study, HR provided the cure in 24% of cases, thus, higher than ICC but very near to that of CRLM. On the contrary, LT provided a cure up to about 74%. Through this comparison, we here provided, for the very first time in literature, a hierarchy of possibilities of cure for the most frequent liver malignancies. Considering these notable differences with LT, it can be of interest to verify whether LT can provide the same survival benefit over HR also for CRLM [29,30] and for ICC [31,32].

Some limitations of the present study need to be discussed. In the present study we were forced to simulate drop-out risk from the WL to provide the intention-to-treat scenario. The ideal approach would be to perform an analysis considering all HCC candidates since listing for LT. However, as stated in the method section, drop-out events strongly depend on the transplant criteria adopted and consequently on its different definitions [12]. Patients dropped because beyond Milan criteria can be still within UCSF or other transplantability criteria. The same clinical scenario can have a certain drop-out risk outside Milan criteria but a lower risk considering criteria adopted. However, with the present approach, which deemed drop-out a proportional reduction in the possibility to reach LT and consequently a cure, we obtained a general model able to cover all possible WL scenarios. It should be noted that a limitation of the present study can be represented by the fact that the tumor burden on the basis of which the cure fraction is estimated can change during waiting list due to progression or response to neo-adjuvant therapies. These possible modifications are captured by the present approach by grouping patients within different transplant criteria, with an eventual growth toward these criteria considered as the drop-out that was here simulated. We acknowledge that this limit persists in the last results reported in the ***Table 4*** but we feel that it is a good estimate of an unavoidable imprecision.

A conceptual aspect regarding the definition of statistical cure after HR and LT must be highlighted. Statistical cure has not to be considered as the possibility of being healed from all diseases. Resection does not remove cirrhosis, thus, resected patients will experience tumor recurrence and potentially deadly complications of cirrhosis. On the other hand, LT removes both the tumor and the cirrhosis but transplanted patients frequently develop metabolic, cardiovascular, renal, and even other oncological diseases. Consequently, statistical cure did not represent an absolute measure of the healing ability of HR and LT. It is a measure of relative survival in respect to the general population, which, in turn, can suffer from other chronic diseases.

In conclusion, we here provided for the very first time an estimation of the chances of cure from HCC achievable with HR and LT. Based on the possibility of being alive and tumor-free (DFS), LT outperform HR. However, considering HCC a chronic health condition and in presence of long waiting-times, HR can reach LT cure probabilities independently from the transplant criteria adopted. This is especially true for single tumors <5cm, whereas LT maintain higher efficacy in presence of multiple HCCs.

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**LEGEND TO FIGURE**

**Figure 1.** Disease-free survival (DFS) and overall survival (OS) after liver transplantation (LT) and after hepatic resection (HR). As can be noted, with the passing of time survival curves tends to reach a plateau supporting the applicability of the cure model.