**The chances of hepatic resection curing hepatocellular carcinoma**

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**Running head:** Chance of cure after resection of hepatocellular carcinoma

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#### **ABSTRACT**

#### **Background/Aims:** The popular sense of the word “cure” implies that a patient treated for a specific disease will return to have the same life-expectancy as he/she had never had the disease. In analytic terms, it translates into the concept of statistical cure which defines when a group of patients return to have similar mortality of a reference population. The aim of the study was to assess the probability of being cured from hepatocellular carcinoma (HCC) by hepatic resection.

#### **Methods:** Data from 2523 patients resected for HCC were used to fit simple and multi-variable non-mixture cure models to compare disease-free survival (DFS) after surgery to survival expected for chronic hepatitis – cirrhotic patients and the general population, matched by sex, age, race/ethnicity and year of diagnosis.

#### **Results:** The probability of resection to provide the same life-expectancy of patients with chronic hepatitis – cirrhosis, was 26.3%. The conditional probability to achieve such a result was time-dependent, and the time necessary to accomplish such a goal with 95% of certainty was about 8.9 years. Considering the general population as the reference, the cure fraction decreased to 17.1%. Uncured patients had a median DFS of 18.3 months. In a multi-variable analysis, patient’s age and the risk for early recurrence (<2 years) were independent determinants of chances of cure (p<0.001). Subjects at low risk for early recurrence had about 36.0% chance of being cured, those at medium risk about 13.7%, and those at high risk only about 3.6% of chance.

#### **Conclusion:** Estimates of the chance of being cured of HCC by resection showed that this goal is achievable and its likelihood increases with the passing of recurrence-free time. The present information can be used to inform patients about the probability of success of surgery, as well as permitting clinicians to make informed post-resection clinical decisions.

#### **Abstract word count:** 298 words

**INTRODUCTION**

 Worldwide, hepatocellular carcinoma (HCC) is one of the most common cause of cancer-related death, with a rapidly increase in the western world[1]. Hepatic resection (HR) remains the most widely applied, potentially curative, therapeutic option [1,2] Unfortunately, and in contrast to liver transplantation (LT), although resection can remove the main tumour burden, the risks associated with the underlying chronic liver disease (CLD) and undetectable micro-metastases remain [3]. Thus, many patients undergoing resection will die as the consequence of tumour relapse or because of complications of chronic liver disease [4].

 The two competing causes of death (tumour recurrence and cirrhosis/chronic liver disease) both influence survival and have implications for therapy. On the one hand, resection might not be appropriate in a patient who will likely die from advanced liver dysfunction, and conversely, treatment of viral hepatitis, with expensive antiviral agents, may only be appropriate if the risk of death as a consequence of HCC recurrence is relatively low [4-6]. To quantify these issues it is necessary to evaluate whether a patient undergoing resection would experience a life expectancy similar to that of patients with chronic hepatitis or cirrhosis. An approach able to capture this relies on the concept of *statistical cure* [3,7]. This occurs when the mortality of patients treated for a specific disease returns to the value expected in a reference population [8]. Commonly, the reference population is represented by the ‘general’ population – people matched for age and gender who do not have the disease in question. However, in the present clinical scenario, the reference population is most appropriately represented by those with chronic liver disease/cirrhosis, in order to return an estimation of the probabilities of being cured from HCC, assuming that chronic liver disease remains since it is obviously not cured by resection.

 The present study aimed to apply a *cure model* to the outcome of surgical treatment of HCC. Disease-free survival (DFS) was modelled as the primary outcome measure to estimate the benefit obtainable with HR in terms of probability of returning to the same chance of being alive and without tumor recurrence as the analogous member of the CLD population, uncomplicated by HCC development. Overall survival (OS) was also used in the *cure model* since HCC recurrence would not necessarily be a terminal event because further treatments of relapse can significantly improve survival.

**METHODS**

 The present study population was derived from an international retrospective cohort including a total of 3,903 surgically treated patients with HCC from 6 centres in different countries who were accrued (Early Recurrence After Surgery of Liver tumor – ERASL dataset), from Eastern and Western countries [9]. All centres fulfilled ethical requirements according to local practice as previously disclaimed. This database included only patients submitted to potentially curative surgical resection as first treatment of HCC. For the purpose of the present study, only cases with complete chronological, clinical, survival and tumour-related data were retained. Patients with macro-vascular invasion were excluded and only resections performed between January 2000 and December 2016 were considered. After application of these entry criteria, the final dataset comprised 2523 patients from Hong Kong (n:328), mainland China (n:999), Italy (n:742) and Japan (n:454). The criteria for surgical resection were those already published [9].

**The ‘Early Recurrence after Surgery of Liver tumours (ERASL)’ framework**

 Early recurrence of HCC after hepatectomy is commonly defined as recurrence within 2 years of surgery and is the main determinant of ultimate survival. [9-11]. The present evaluation of the *cure fraction* was modelled on the predicted risk of developing a recurrence, aiming to provide information on both the risk of early recurrence and the probability of cure. To accomplish this we adopted the ‘ERASL-post’ model: 0.677 × Gender (0:Female, 1:Male) + 0.458 × Albumin-Bilirubin (ALBI) grade (0:Grade 1; 1:Grade 2/3) + 0.661 × micro-vascular invasion (0:no, 1:yes) + 0.082 × ln(Serum alpha-fetoprotein [AFP in µg/L]) + 0.451 × ln(Tumour size in cm) + 0.379 × Tumour number (0:Single; 1:Two or three; 2:Four or more). Using the published cut-off points for the linear prediction three risk groups (for recurrence) were generated: ≤2.332 (low), >2.332 to ≤3.445 (intermediate), >3.445 (high) and used here to model the predicted *cure fraction*.

**Survival end-points**

 Disease-free survival was defined as the time from surgery to death, recurrence or last follow-up and this was used as the primary survival measure for the cure model. This end-point was preferred over overall survival (OS) since it would be inappropriate to define as “cured”, a patient who, even if alive, has tumour recurrence [12, 13]. Overall survival was defined as the time from surgery to death or last follow-up visit.

**Cure model specifications**

 The essential pre-requisite when applying the *cure model* is its statistical plausibility [3,7], meaning that if a proportion of patients who did not relapse and/or die from the disease exists, the survival curve will tend to flatten on the y-axis, implying that cure occurs within a reasonable time frame [7,8]. Thus, DFS and OS curves were first checked for the correctness of this assumption. As can be seen in ***Figure 1***, the DFS curve tends to a plateau during follow-up confirming that for the DFS end-point the model assumption was not violated. OS curve violated such a pre-requisite and thus was excluded from the analysis. The cure models used here fitted a parametric (Weibull) function. When the excess of mortality equals that of the reference population, matched by age, sex, race and year, the asymptote of the fitting equation on the calculated relative survival curve returns the cure fraction.

**Reference populations**

 Two reference populations were taken into account (***Figure 1a***). The primary reference population was extracted from a population-based cohort study reporting the life-expectancy of health insurance beneficiaries with and without certain comorbid conditions, as described by Cho and Mariotto [14,15]. This latter population involved only non-cancer patients and contained mortality figures for patients with chronic hepatitis – cirrhosis. Subsequently, estimated survival probabilities were compared with the life-expectancy of the general population, returning a *“**health-adjusted age”*. As a brief example, a man aged 75 years without any comorbidity, showed a life-expectancy similar to that of general population aged 67 years, conversely in the presence of high comorbidity, such as chronic hepatitis – cirrhosis, the analogous figure was 80 years (***Figure 1b***). The secondary reference population was represented by the general population. For both reference populations life-tables were obtained from the World Health Organization (WHO) database, matched by sex, age, race/ethnicity and year [16].

**Statistical analysis**

Categorical variables are reported as number of cases and percentages and compared using Fisher’s exact test if necessary. Continuous variables are reported as medians and interquartile ranges (IQR: 25th and 75th percentiles), and differences between the subgroups were compared with the Mann-Whitney test. The cure model was computed using the *strsmix* and *strsnmix* package for STATA software (StataCorp. 2011. College Station, TX: StataCorp LP). Variables having a non-negligible effect (p<0.05) on the cure fraction were entered into a backward multivariate cure model. A p-value of <0.05 was considered statistically significant in all the analyses.

**RESULTS**

 Clinical and tumour characteristics of the 2,523 resected patients are detailed in **Table 1**. The median follow-up after resection was 3.4 years during which period 1,221 patients had a recurrence (48.4%) and 755 died (29.9%). The median DFS was 23.8 months (95%C.I: 21.4 – 25.2) and the median OS was 7.8 years (95%C.I.: 6.9 – 8.3). The risk of early recurrence was low in 76.5% patients, medium in 21.7% and high in 1.9% of them, according to the ERASL model. The median DFS was 30 months in patients at low-risk of early HCC recurrence (95%C.I.: 26.9 – 33.7), 12.2 months in medium-risk patients (95%C.I.: 10.9 – 14.2) and 4.4 months in high-risk patients (95%C.I.: 3.6 – 6.0).

**Cure model results**

 The cure model showed that the probability that resection would offer the same life expectancy as patients with chronic hepatitis – cirrhosis (without HCC) was 26.3% (95%C.I.: 21.7 – 30.8). The conditional probability of achieving such a goal was time-dependent, as depicted in the ***Figure 2***. If a patient was alive without recurrence 2 years after surgery, his/her likelihood of being ‘cured’ was about 50%. Over time, the likelihood rises, reaching 95% at about 8.9 years (95%C.I.: 6.8 – 11.6).

 This cure fraction was lower with respect to the general population, being only 17.1% (95% C.I.: 13.2% – 21.0%). This latter figure represents the probability of achieving the same life expectancy, and tumour-free, as the matched general population. The remaining ‘uncured’ patients had a median DFS of 18.3 months.

**Probabilities to achieve the same life-expectancy of chronic hepatitis – cirrhotic patients.**

 Results from the multi-variable cure model are reported in ***Table 2***. Patient’s age and the ERASL risk class were independent determinants of chances of cure. As depicted in ***Figure 3***, when patients were stratified by their risk of early recurrence, subjects at low risk showed a median of a 36.0% chance (minimum:10.1%, maximum:61.4%. IQR: 28.5% - 44.3%) to return to have the same life-expectancy to that of patients with chronic hepatitis – cirrhosis (without HCC). Patients at medium risk had a median of 13.7% (minimum: 3.3%, maximum: 28.5% IQR:9.7% - 18.3%) and those at high risk showed a median of only 3.6% (minimum:0.8%, maximum:9.1% IQR:2.4% - 5.1%). In the three risk classes the median time-to-cure was of 8.1, 9.7 and 10.9 years respectively. That is, if after these time-points a resected patient was alive without tumour recurrence, he/she can be considered as never having had HCC with the 95% of certainty.

**Probabilities to achieve the same life expectancy of general population.**

 Applying the ERASL risk classes with this outcome, subjects at low risk showed a median of a 23.2% chance (minimum: 9.1%, maximum: 46.6%. IQR:19.0% - 30.1%) to return to have the same life-expectancy to that of patients with chronic hepatitis – cirrhosis (without HCC). Patients at medium risk had a median of 6.7% (minimum: 2.4%, maximum: 15.9% IQR: 5.3% - 9.3%) and those at high risk showed a median of only 1.6% (minimum: 0.6%, maximum: 3.9% IQR: 1.2% - 2.2%). In the three risk classes the median time-to-cure was of 10, 12 and 13.6 years, respectively.

**DISCUSSION**

 The term ‘potentially curative’, widely applied to hepatic resection for HCC, needs careful consideration. For most cancers, survival plateaus several years after surgery, at a point when the mortality rate of the diseased individuals is the same as that of the general population, i.e. the excess mortality rate is equal to zero and there is population cure [17]. However, in the case of HCC where most patients will have underlying chronic liver disease, with its own attendant mortality, survival will plateau at a time at which mortality is similar to that of a population with chronic liver disease/cirrhosis. We therefore first considered life-expectancy deriving from population-based studies which identified expected survival figures for subjects suffering from chronic hepatitis / cirrhosis without cancer.

 Our results show that the probability of achieving the same life expectancy as a similar patient who did not develop HCC is in the order of 26.3% after resection, and that this is a conditional probability which becomes more likely with the passing of recurrence-free time (**Figure 2**). A patient alive without HCC recurrence at 2 years from surgery, the period during which most recurrences will occur, has a 50% chance of being alive and free of tumour. After 3 years of recurrence-free survival, the chance of remaining alive and tumour-free, increases to 60%. Since the cure models base their estimation on the asymptote of the relative survival curve, the 100% of certainty tends to infinity but to have a 95% of long term cure, we need to wait approximately 9 years. This surely represents a long time-span but further clinical considerations are needed.

 The first clinical consideration relies on the plausibility of being cured from HCC. The prognosis of resected HCC patients inevitably depends not only on tumour recurrence but also the progression of the underlying liver disease. Any impact on the first of these requires that adjuvant therapies would be available for reducing the early HCC recurrence. Unfortunately, results from the STORM trial indicated that Sorafenib is not an effective intervention in the adjuvant setting for HCC following resection [18]. Current hopes in this respect rest on Nivolumab and Pembrolizumab as adjuvant therapies [19,20]. In the case of positive results i.e. that early recurrence can be eliminated, the chances of being cured from HCC will ameliorate from the baseline of 17.1%, relative to the chronic liver disease population, and from 26.3% relative to the general population. Both relative survivals will increase as well as conditional probability by year with a magnitude that will need to be completely redefined.

 The second issue relating to probability of cure, the impact of the underlying liver disease, is less insurmountable and future scenarios will still be adequately depicted by present results. Curative therapy is now a reality also for HCV patients with chronic liver disease and the achievement of sustained virological response can provide a life-expectancy similar to that of the general population [21,22]. In the HCC population, the reduction of decompensation events will primarily translate into a benefit relative to the general population (i.e. it will increase from 17.1%), because the reference life-expectancy of chronic hepatitis / cirrhotic subject will also be ameliorated by effective antivirals. However, any improvement in liver function will increase the chances of cure in relation to the chronic hepatitis / cirrhotic population.

 These aspects informed the choice made in the present study of considering two different reference populations that is the subject with chronic hepatitis / cirrhosis without HCC, and the general population. In summary, the chances of cure from HCC will primarily increase in respect to both those of the chronic hepatitis / cirrhotic population and the general population by effective adjuvant therapies and primarily in respect to that of general population by effective antivirals or other effective therapies for chronic liver disease.

 In the present study, we chose to model cure fractions within the framework of the Early Recurrence After Surgery of Liver tumour (ERASL) prognostic model. [9] This model has shown good discrimination and calibration in both Eastern and Western series being capable of stratifying patients into three distinct groups with discrete risk profiles. The analysis we present here permits the addition of a further prognostic parameter namely the probability of cure, rather than formulating another complex and distinct model.

 Early recurrence is the main determinant of prognosis after resection but identification of patients who are at intermediate or high risk of such an event can allow clinicians to schedule appropriate surveillance to detect recurrent HCC at its earliest stage, when curative therapy may still be feasible as well as identifying potential candidates for clinical trials of adjuvant therapy [9-11]. Thus, within a single analytical framework the present work takes account of both probabilities of early recurrence as well as its counterpart, the probability being cured of the tumour.

 The present study shares the limitations of the previous ERASL model, which were mainly represented by the fact that antiviral treatment was not included because it was available for a small proportion of our cohorts [9]. It could be argued that, especially when analysing long-term outcome, this data would be necessary. However, there are two aspects deserving consideration. First, the effect of antivirals would be seen both in the HCC resected population as well as the primary reference population used here, so that any impact would likely be relatively small. The second limitation is the retrospective nature of the present analysis. Nonetheless, we have made realistic estimates of the current probabilities of being cured of HCC by resection but we acknowledge that these figures will probably change in the future and, like all prognostic models, will require ‘updating’. However, it could be argued that a prospective study would be rather unrealistic to be realized considering the continuous evolution of modern therapies.

 Finally, the reference population of chronic hepatitis / cirrhotic population characteristics probably may not fully fit those of the present study population since it was derived from the Surveillance Epidemiology and End Results–Medicare database [14-15]. In addition, this reference population was provided without distinguish life expectancy of subjects with chronic hepatitis from that of cirrhotic patients, now allowing for an useful strtification of prognosis and statistical cure estimate. However, this represents an insurmountable limitation since at present and, to the best of our knowledge, no population-based statistics stratified by chronic liver disease are available to support the present requirement. Additionally, the sex, age, year of onset and ethnicity match could have mitigated this discrepancy, but we acknowledge that a fully matched reference population stratified by aetiology as well as fibrosis stage will probably provide a more accurate picture of cure probabilities.

 In conclusion, in the present analysis we provide estimates of the chance of being cured of HCC by hepatic resection. This includes both the chance that an individual will experience the same life expectancy as that of an individual who has chronic hepatitis/cirrhosis but has never developed HCC as well as the analogous measure in comparison to that of the general population. The likelihood of being cured increases with the passing of recurrence-free time. The clinical utility of cure models is predicated on the possibility of correctly informing patients about the probabilities of success (‘cure’ in the popular sense of the word) of the proposed treatment as well as permitting clinicians to make informed post-resection clinical decisions.

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**Table 1. Clinical characteristics of the study population of resected HCC patients.**

| **Characteristics** |  **(n: 2,523)** |
| --- | --- |
| Age [years, median (IQR)] | 60 (50 - 68) |
| Male gender  | 2063 (81.8%) |
| Caucasian  | 742 (29.4%) |
| Etiology |  |
| HCV | 739 (29.3%) |
| HBV | 1394 (55.3%) |
| Alcohol / Other | 428 (17.0%) |
| Bilirubin [µmol/L, median (IQR)]  | 12.7 (9.0 – 17.1) |
| Albumin [g/L, median (IQR)]  | 41 (38 – 44)  |
| ALBI grade |  |
| 1 | 1659 (65.8%) |
| 2 | 853 (33.8%) |
| 3 | 11 (0.4%) |
| Child – Pugh class A | 2414 (95.7%) |
| Number of tumours |  |
| Single nodule | 1948 (77.4%) |
| 2-3 nodules | 451 (17.9%) |
| More than 3 nodules | 119 (4.7%) |
| Largest tumor [cm, median (IQR)] | 4.0 (2.5 – 6.2) |
| Last AFP prior to surgery [ng/mL, median (IQR)]  | 21.5 (5.6 – 300)  |
| Microscopic vascular invasion  | 547 (21.8%) |
| ERASL-post risk class \* |  |
| Low risk | 1929 (76.5%) |
| Medium risk | 547 (21.7%) |
| High risk | 47 (1.9%) |
| Disease-free survival \*\* |  |
| 1-year | 65.7% |
| 3-year | 39.3% |
| 5-year | 27.7% |
| 10-year | 13.9% |
| Overall Survival  |  |
| 1-year | 90.3% |
| 3-year | 74.9% |
| 5-year | 61.6% |
| 10-year | 39.9% |

\* The ERASL-post risk class derived from the following formula: 0.677 × Gender (0:Female, 1:Male) + 0.458 × Albumin-Bilirubin (ALBI) grade (0:Grade 1; 1:Grade 2/3) + 0.661 × micro-vascular invasion (0:no, :yes) + 0.082 × ln(Serum alpha-fetoprotein [AFP in µg/L]) + 0.451 × ln(Tumour size in cm) + 0.379 × Tumour number (0:Single; 1:Two or three; 2:Four or more).

The cut-offs of the linear prediction for generating three risk groups were as follows: ≤2.332 (low), >2.332 to ≤3.445 (intermediate), >3.445 (high).

\*\* Disease-free survival was defined as the time elapsed from surgery to recurrence, death or last follow-up visit.

**Table 2.** Results from backward multi-variable cure fraction models having chronic hepatitis / cirrhotic patients and general population as references

|  | **Chronic hepatitis / cirrhosis** |  | **General population** |
| --- | --- | --- | --- |
| **Characteristics** | **Coefficient (95% C.I.)]** | **p** |  | **Coefficient (95% C.I.)** | **p** |
| Age  | 0.038 (0.028 / 0.048) | **0.001** |  | 0.031 (0.020 / 0.042) | **0.001** |
| Caucasian | 0.022 (-0.216 / 0.259) | 0.858 |  | -0.088 (-0.339 / 0.163) | 0.492 |
| Year of diagnosis | -0.026 (-0.061 / 0.007) | 0.123 |  | -0.023 (-0.058 / 0.012) | 0.196 |
| HCV | 0.158 (-0.081 / 0.397) | 0.195 |  | 0.039 (-0.212 / 0.291) | 0.758 |
| HBV | 0.132 (-0.164 / 0.428) | 0.383 |  | 0.236 (-0.077 / 0.550) | 0.140 |
| ERASL-post risk class | -1.345 (-1.602 / -1.089) | **0.001** |  | -1.454 (-1.746 / -1.162) | **0.001** |
| Constant | -2.841 (-3.527 / -2.157) | **0.001** |  | -2.992 (-3.732 / -2.252) | **0.001** |
| ln\_lambda | -1.247 (-1.424 / -1.069) | **0.001** |  | -1.526 (-1.692 / -1.361) | **0.001** |
| ln\_gamma | 0.112 (0.053 / 0.171) | **0.001** |  | 0.078 (0.026 / 0.129) | **0.001** |

ERASL score already includes Gender, Albumin, Bilirubin, micro-vascular invasion, AFP as well as tumor size and number, thus, these variables were not included in the analysis to avoid co-linearity.

Beta-coefficients were directly related with the probability of being cured from HCC in respect to the reference population. Consequently, negative beta-coefficients indicate a reduction in the cure fraction achievable and positive values indicate increased possibilities.

To obtain individual cure predictions the following formulas are needed: exp(xb) = exp [constant + coefficient\_age \* age + coefficient\_erasl \* ERASL risk class (0: low, 1: intermediate, 2: high risk)] and cure = exp(xb) / [1 + exp(xb)].

Coefficients of constant, lambda and gamma referred to the last step of multi-variable analyses.

**LEGENDS TO FIGURES**

**Figure 1.** **Panel A.** Disease-free survival (DFS) of HCC resected patients and survivals of the reference populations used matched by sex, age, year and race. **Panel B.** Health-adjusted age derived from chronic hepatitis — cirrhotic population provided by Cho and Mariotto [14,15]. The health-adjusted age represents the hypothetical age of a chronic hepatitis — cirrhotic patient in respect to the life-expectancy of the general population. A man aged 75 years with comorbidity, such as chronic hepatitis or cirrhosis provided a health-adjusted age of 80 years, that is such patient will have the life-expectancy of an octogenarian.

**Figure 2.** Degree of certainty of the achievement of cure from HCC in respect to the reference population of chronic hepatitis — cirrhotic patients.

**Figure 3.** Distribution of cure probabilities in respect to the reference population of chronic hepatitis / cirrhotic patients stratified by the risk of early HCC recurrence.