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Liver Transplantation or Resection for Treatment of Hepatocellular Carcinoma in Patients with Well-Compensated Cirrhosis: A Decision Analysis Model

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Abstract

Background: Hepatocellular carcinoma (HCC) is a lethal tumor, for which liver resection and transplantation are the only potentially curative treatments. No prospective, randomized study has compared survival in patients with compensated cirrhosis after the two operations.

Methods: Decision analysis modeling is an objective method to quantify risks and benefits. This study aimed to use decision analysis with a Markov model to estimate the impact of liver transplant and surgical resection on survival for patients with early stage (i.e., within Milan criteria) HCC and compensated cirrhosis.

Results: The model considered waitlist drop off due to tumor progression, the probability of tumor recurrence, and the impact of hepatitis C on post-transplant survival. Peri-operative mortality was estimated as 4% after resection and 7% after transplantation. The resection

group had a 67% probability of tumor recurrence at 5 years and a median survival time after recurrence of 24 months. The transplant group had a 36% probability of tumor recurrence at 5 years, and a median survival time after recurrence of 8 months. The baseline analysis of this model revealed an overall survival benefit of 2.4 years for the transplant group over the resection group. Sensitivity analyses suggest that this survival benefit remains unless the probability of recurrence in the surgical resection group decreases to less than 50% at 5 years or the transplant waitlist time is longer than 27 months.

Conclusions: In conclusion, considering the advantages and disadvantages of each surgical therapy, liver transplantation for HCC in patients with well compensated cirrhosis due to hepatitis C is associated with better overall survival than resection over a wide range of likely scenarios.

Keywords

Hepatectomy; Milan criteria; hepatitis C; cirrhosis; cancer

1. Introduction

There are two main surgical options for the treatment of hepatocellular carcinoma (HCC), resection and transplantation [1]. Liver resection is typically limited to patients with well-compensated cirrhosis and solitary tumors. Transplantation is often reserved for patients with solitary tumors no larger than 5 cm or up to three tumors no larger than 3 cm, which constitute the Milan criteria.

Retrospective series, of comparable patients, report either equivalent outcomes or superior outcomes for transplantation vs resection [2-11]. However, metadata analysis of these studies do not address the complexity of treating patients with HCC as most of the studies do not account for tumor progression or death while on the transplant waitlist. Moreover, there is great variation in how patients were selected into each treatment paradigm, with respect to tumor burden and underlying liver reserve. Finally, a variety of resection techniques and the diversity among the patient populations in resection and transplant series also limit the ability of meta-analysis to merge patient groups and increase the power of the observation. These limitations identify that prospective randomized trials and metadata analysis struggle to deal with a complex patient population, resulting from heterogeneous patient and tumor characteristics that would make patient accrual for a randomized trial difficult. Despite these limitations the question of how to stratify patients for surgical treatment for HCC is important due to rising concerns over resource utilization in American healthcare as well as the finite availability of donor livers.

In response to this problem decision modeling represents the next best approach for weighing the risks and potential benefits of the two treatment options, while accounting for the complex factors impacting the survival of these patients. Decision analysis is a quantitative method of evaluating surgical decisions by breaking complex decisions down into their component parts [12]. A decision model includes plausible therapeutic options for treating a particular condition and the potential consequences of each option [13]. Values reported in the published literature are used to quantify the probability of a potential outcome occurring and its associated improvement in or

detriment to survival. During the analysis of the model, the expected overall survival benefit of each therapy is calculated to determine which treatment maximizes survival for a hypothetical cohort of patients with the specified medical condition. The strength of the model's conclusion is tested using sensitivity analysis to vary probabilities in the model and determine which probabilities, if any, change the preferred therapy. This allows the reader to put the trade-offs in risks/benefits associated with each treatment strategy into perspective.

This study aimed to use decision analysis to address the long-debated question of whether transplantation or resection maximizes survival for patients with HCC and well-compensated cirrhosis due to hepatitis C. This is particularly relevant in the context of less decompensation of liver disease (improved liver function), but no objective change in de novo tumor emergence or tumor recurrence after successful treatment of hepatitis C.

Hepatitis C patients are particularly vulnerable to multifocal disease and at high risk of tumor recurrence over a 5-year time frame, irrespective of resection or transplant. The emergence of successful antiviral treatment for hepatitis C may potentially impact de-novo tumor emergence in the remnant liver after resection as well as decrease the likelihood of reactivation of hepatitis C after liver transplant. However, an objective impact on cancer specific events after successful treatment of hepatitis C has not yet been realized and de novo tumor emergence rates after resection remain > 50% [14]. Therefore, a better understanding of the complexities involved in the model and inclusion of important variables not previously extracted from the published data would help clarify the appropriate weight of the two approaches on outcome.

2. Materials and Methods

2.1 Decision Model

The decision model was built and analyzed using TreeAge Pro (Williamstown, MA). It considered a hypothetical cohort of 55-year old patients, healthy enough to tolerate major surgery, with hepatitis C, Child's A cirrhosis, and tumors meeting Milan Criteria. The age was chosen based on a published median age range of 45-65 for patients with HCC undergoing resection or transplantation [15-43]. At the initial decision node in the model, hypothetical patients had an equal chance of either: 1) undergoing immediate resection or 2) being placed on the liver transplant waitlist. The model considered waitlist dropout after tumor progression, peri-operative mortality, probability of tumor recurrence, likelihood of hepatitis C recurring after transplant and survival after both transplantation and resection for patients with hepatitis C (Figure 1). Patients assigned to the waitlist entered a Markov simulation whereby, during each cycle, they either: 1) remained on the waitlist, 2) experienced tumor progression and waitlist dropout, or 3) underwent a liver transplant (Figure 2). The Markov simulation was run with one-month cycle lengths over a 5-year period. This timeframe was chosen because 5-year survival and recurrence data is well-documented for both operations. For patients who did not experience a peri-procedural death or tumor recurrence, tail utilities were assigned using the declining exponential approximation of life expectancy (DEALE) [44]. Uncertainty surrounding the probability of each outcome was addressed by using sensitivity analysis to examine the impact of varying each probability over a range of values.

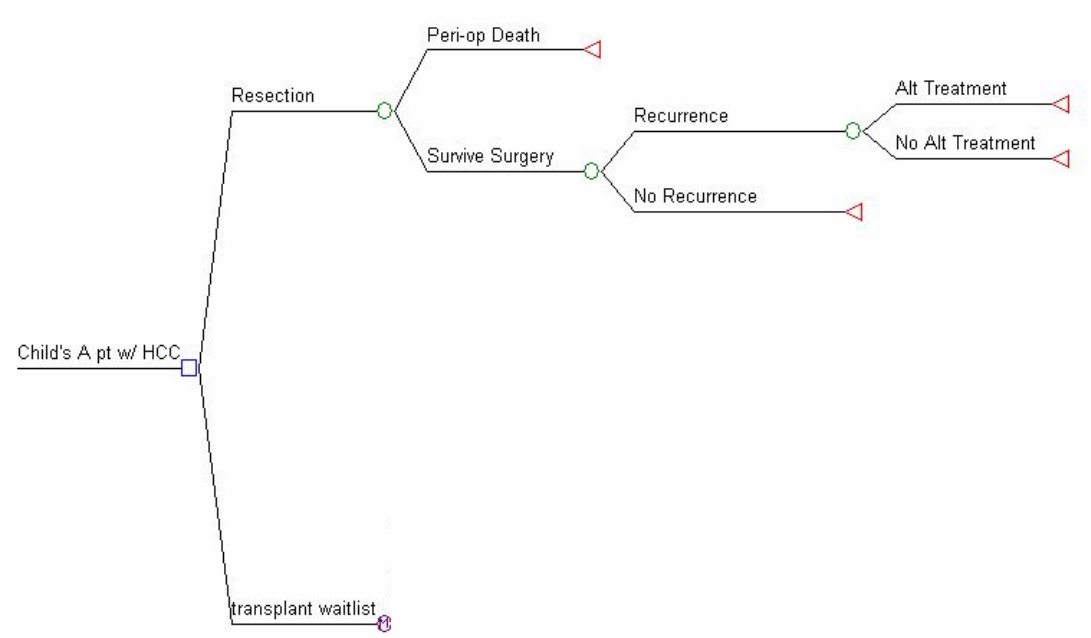

Figure 1 Basic decision tree outline. Branches subsequent to transplant waitlist are represented in figure 2. Decision nodes are represented by boxes, chance nodes are represented by circles and terminal nodes are represented by triangles. Pt=patient, HCC=hepatocellular carcinoma, peri-op=peri-operative, alt=alternative.

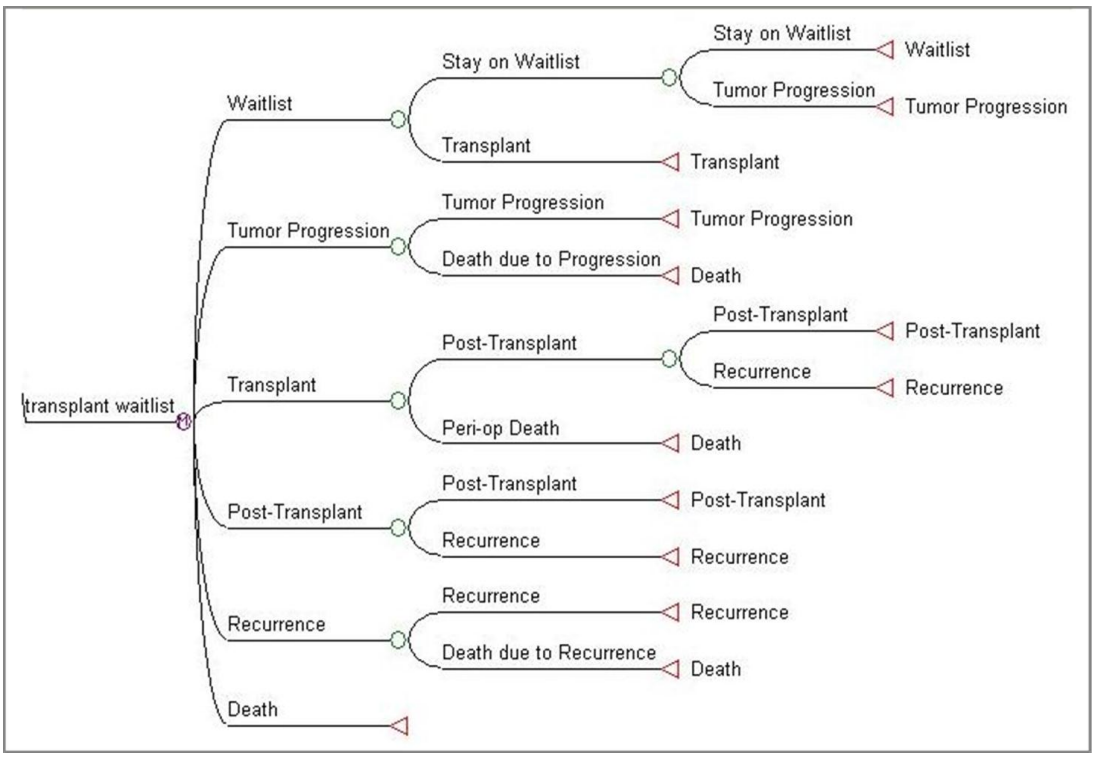

Figure 2 Markov node representing potential outcomes after placement on the transplant waitlist. Chance nodes are represented by circles and the Markov node is represented by the M inscribed in a circle. Triangles represent nodes that refer back to one of the initial branches of the Markov node. Death represents a terminal node. Peri-op=peri-operative.

2.2 Data Sources

The probabilities input into the decision model were abstracted from published data, including national transplant data from the Organ Procurement and Transplantation Network [45]. Medline and PubMed searches were performed to locate articles reporting results after hepatectomy or transplantation for HCC. Additional studies were identified from the bibliographies of the articles obtained during the literature search (Table 1). Articles published prior to 1996 were excluded from calculation of peri-operative mortality and tumor recurrence as significant advances in operative technique and modifications in post-transplant immunosuppression have occurred since then. Over the past decade, better patient selection, preoperative portal vein embolization [46, 47], and enhanced surgical techniques have minimized intra-operative bleeding, decreased peri-operative mortality, and helped improve short-term outcomes after surgical resection of hepatocellular carcinoma (HCC). When studies from the same institution reported overlapping dates of patient accrual, the study with patients most closely matching our hypothetical patients was selected. When multiple sources reported data for a particular probability, the probability entered into the model was a weighted average of the data from all sources.

2.3 Assumptions

The model assumes the following:

1. Patients with a tumor recurrence after transplantation are ineligible for alternative liver-based therapies (e.g., chemoembolization or radiofrequency ablation) or for an additional transplant. This assumption is based on the low incidence of isolated intrahepatic tumor recurrences after transplantation for HCC [36, 48].
2. Patients awaiting a transplant may undergo liver-directed therapies, such as chemoembolization, radiofrequency ablation, or yttrium-90 radioembolotherapy.
3. Patients with a tumor recurrence after resection are ineligible for transplantation.
4. Patients with a tumor recurrence after transplantation are ineligible for resection.

2.4 Waitlist Outcomes

The monthly probability of transplantation while on the waitlist was based on the national averages for waitlist time as reported by the Organ Procurement and Transplantation Network [45]. Regional variations in waitlist time were taken into account with sensitivity analysis. The risk of tumor progression and subsequent waitlist dropout was based on studies reporting liver transplant waitlist dropout rates for patients with HCC [30, 49-51]. Based on data in the literature, the probability of tumor progression was varied over time, with the monthly probability of progression increasing as waitlist time increased (Table 2).

2.5 Treatment Efficacy

Postoperative mortality, incidence of tumor recurrence, and survival after post-operative tumor recurrence were based on data from series of patients with HCC undergoing transplantation or resection. Based on data reported in the literature, tumor recurrence risk after

transplantation was also varied over time, with the risk of recurrence declining in each postoperative year (Table 3) [30, 50-52].

Table 1 Probabilities used in the base case analysis and sensitivity analyses.

Variable	Baseline	Range Tested	References	Threshold Value	Threshold in Range
Resection					
Peri-operative Mortality	4%	1-21%	[16, 22, 24, 31, 34, 41-43, 49, 53-58]	None	no
5-yr Tumor Recurrence	67%	55-93%	[35, 41, 42, 52, 54, 55, 59]	<50%	no
Median Time to Recurrence*	18	13-24	[23, 24, 31, 53, 60]	>63	no
Recurrences Amenable to Alternative Therapies	61%	25-72%	[52-54, 60]	None	no
5-yr Survival for Compensated Hepatitis C cirrhosis	93%	85-96.5%	[61-69]	None	no
Median Survival After Alternative Therapies*	46		[70]	>120	no
Median Survival After HCC Recurrence*	24	11-40	[21, 43, 53, 54]	>137	no
Transplant Waitlist					
Median Waitlist Time*	10.5	0-36	[45]	>27	yes
1-yr Dropout from Transplant Waitlist	28%	25-38%	[30, 50-52]	(see results)	
Median Survival after Tumor Progression*	19.5	17-24	[52, 71-73]	None	no
Peri-operative Mortality	7%	0-13%	[16, 18, 30, 34, 43, 49, 55, 58, 74-79]	>30%	no
5-yr Tumor Recurrence	36%	8-63%	[15, 19, 22, 27, 29, 31-35, 39, 40, 43, 55, 75, 78, 79]	(see results)	
Median Survival After HCC Recurrence*	8	1-9	[19, 20, 29, 36, 43, 79, 80]	None	no
5-yr survival after Transplant for Hepatitis C	69%	61-80%	[38, 81-88]	<58%	no

- unless otherwise indicated values expressed as percent
- All median times are expressed in months

Table 2 Tumor progression while on waitlist.

Waitlist Time (months)	Monthly Probability of Tumor Progression
1-6	0.017
7-12	0.029
13+	0.045

Table 3 Tumor recurrence after transplant.

Postoperative Month	Monthly Probability of Tumor Recurrence
1-12	0.0165
13-36	0.0043
36-60	0.0023

2.6 Life Expectancy

The life expectancy of patients surviving the first five post-operative years was estimated using the DEALE. The DEALE estimates life expectancy based on 5-year survival rates for patients with a particular medical condition using the following formulas:

$\mu = - 1/5 \ln (S)$

in which, μ = average annual mortality rate for patients with the condition,

S = 5-year survival probability,

and

life expectancy = $1/ \mu$.

2.7 Sensitivity analysis

The impact of changing each probability in the model was examined with sensitivity analyses. One-way sensitivity analysis varies a single probability over a range. For each parameter in both treatment groups, a one-way sensitivity analysis was performed and a threshold value (if any) was determined, beyond which the preferred choice of operation changed. Two-way sensitivity analysis varies two probabilities simultaneously. Selected two-way sensitivity analyses were also performed.

3. Results

3.1 Baseline Analysis

In the baseline analysis of our model, the following probabilities were used for the resection arm: 4% peri-operative mortality, 67% risk of tumor recurrence at five years, and 61% of

recurrences amenable to alternative therapies. After resection, patients with hepatitis C and compensated cirrhosis, but no recurrence, had a 93% survival at five years. This survival probability takes into account both age-specific and hepatitis C cirrhosis-related mortality. The resection arm also included a median time to tumor recurrence of 18 months, a median survival of 46 months after a recurrence treated with alternative therapies, and a median survival of 24 months after an untreated recurrence (Table 1).

The following probabilities were used for the transplant waitlist arm: 28% risk of waitlist dropout at 1 year, 7% peri-operative mortality, and 36% risk of tumor recurrence at five years. Hepatitis C patients without a post-transplant cancer recurrence had a 69% survival at five years. This post-transplant survival probability is specific to patients with hepatitis C and accounts for patients who develop recurrent hepatitis C in their graft and thus, are at risk of recurrent liver failure. The transplantation arm also included a median waitlist time of 10.5 months, a median survival of 19.5 months after tumor progression for patients on the waitlist, and a median survival of 8 months after tumor recurrence (Table 1).

Baseline analysis revealed a survival benefit of 8.7 years with resection and 11.1 years with placement on the transplant waitlist (net survival gain of 2.4 years with assignment to the transplant waitlist).

3.2 Sensitivity Analyses

3.2.1 One-Way

Each probability was tested with one-way sensitivity analysis. Transplantation maximized survival relative to resection at all values of (i.e., the model outcome was insensitive to) the following variables: perioperative mortality after resection, percent of recurrences amenable to alternative therapies after resection, five-year post-resection survival for patients with compensated hepatitis C, median survival after waitlist drop off due to tumor progression, and median survival after post-transplant tumor recurrence. In the resection arm, each of these variables had a threshold value beyond which resection resulted in a longer overall survival than transplantation: five-year risk of tumor recurrence (threshold <50%), median time to tumor recurrence (threshold >5.2 years), median survival with alternative therapies for tumor recurrence (threshold >10 years), and median survival with untreated tumor recurrence (threshold >11.4 years). In the transplantation waitlist arm, each of these variables had a threshold value beyond which survival after resection exceeded survival after transplantation: median waitlist time (threshold >27 months), perioperative mortality (threshold >30%), and five-year post-operative survival for patients with hepatitis C (threshold <58%). Of all these variables, only the 27-month waitlist time was within the range reported in the literature (Table 1). If the monthly probability of waitlist dropout exceeded a constant rate of 6% or the monthly probability of tumor recurrence after transplantation exceeded a constant rate of 1%, resection had a greater survival benefit.

3.2.2 Two-Way

Peri-operative Deaths. In the literature, the risk of peri-operative death after resection for HCC ranges from 1 to 21%. The reported risk of peri-operative death after transplantation for HCC ranges from 0 to 13% (Table 1). Simultaneously varying of these both risks in a two-way sensitivity

analysis demonstrated that over the entire range of reported values, overall survival for patients with HCC was longer after transplantation (Figure 3).

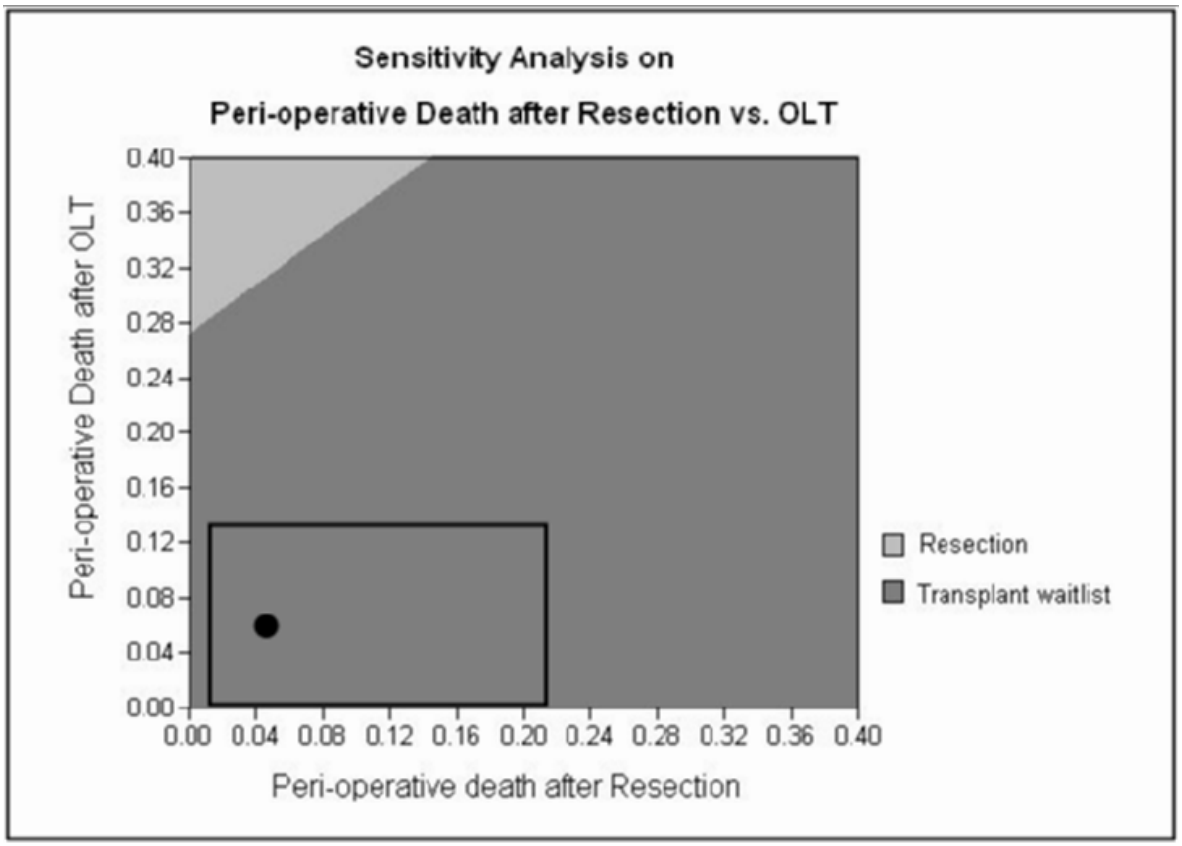

Figure 3 Two-way sensitivity analysis: Risk of peri-operative death after resection vs. transplant. Light gray represents combinations of probabilities where resection maximizes survival. Dark gray represents combinations of probabilities where listing for transplantation maximizes survival. Black box represents the published range of probabilities. Black dot represents the baseline values in the model. OLT=orthotopic liver transplant.

3.3 Tumor Recurrence

The literature reports five-year risks of tumor recurrence after resection ranging from 55 to 93%. Five-year tumor recurrence risks after transplantation range from 8 to 63% (Table 1). Simultaneously varying both risks in a two-way sensitivity analysis showed that over the majority of these ranges, transplantation resulted in longer survival. With a 60% five-year tumor recurrence risk after resection (the lower end of the reported range), post-transplant tumor recurrence would have to exceed 54% (near the upper end of the reported range) for resection to be the preferred strategy (Figure 4).

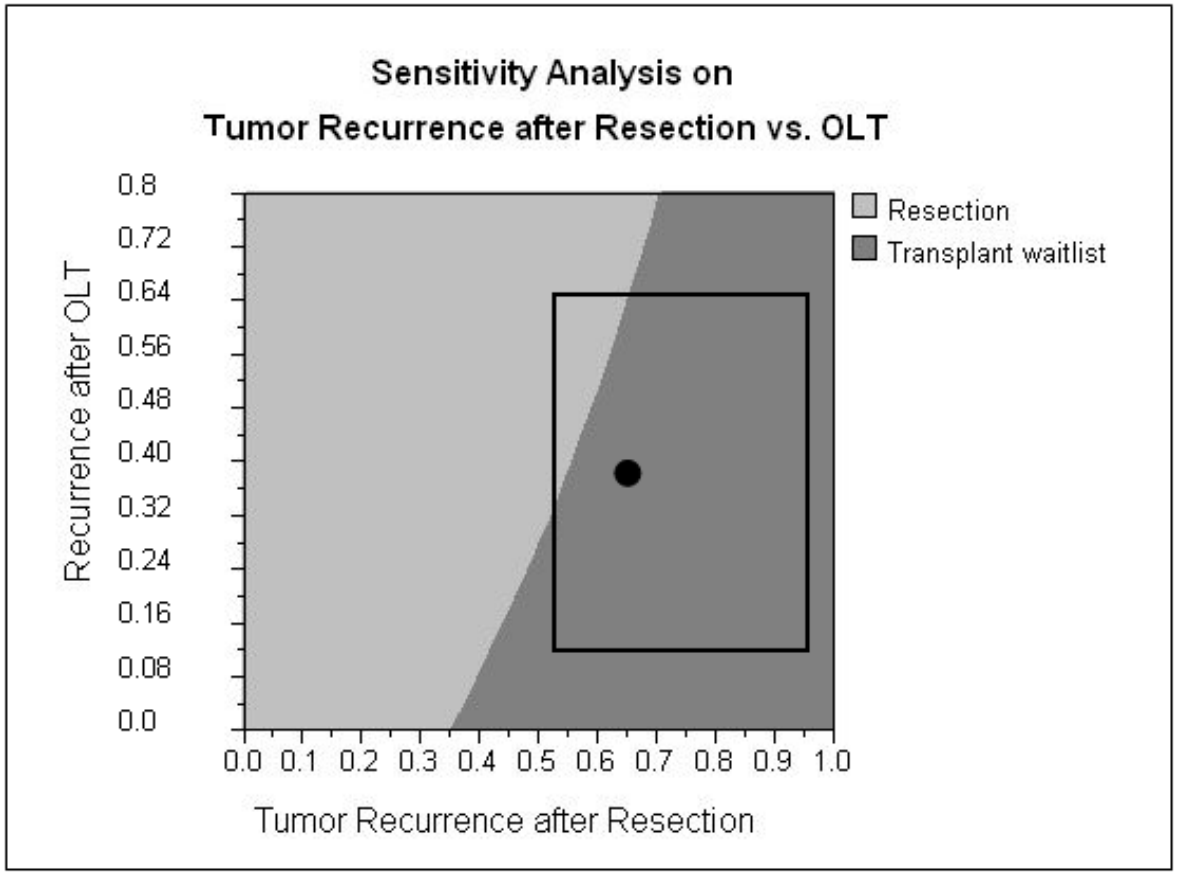

Figure 4 Two-way sensitivity analysis: 5-year risk of tumor recurrence after resection vs. transplantation. Light gray represents combinations of probabilities where resection maximizes survival. Dark gray represents combinations of probabilities where transplant listing maximizes survival. Black box represents the published range of probabilities. Black dot represents the baseline probabilities. OLT=orthotopic liver transplant.

4. Discussion

The optimal treatment for patients with well-compensated cirrhosis and early stage HCC is often debated. Hepatitis C is particularly daunting since these patients are more vulnerable than other liver patients to post-operative morbidity and mortality even in the face of what appears to be well -compensated liver disease. This is in contrast to patients with Hepatitis B who are more likely to have better underlying liver reserve since cancer can occur prior to the development of significant fibrosis. For this reason, we cannot extrapolate survival data from Asian series of patients undergoing resection for HCC. This analysis was restricted to patients with Hepatitis C alone, as these patients account for the majority of HCC cases within the United States.

Within the US, patients with well compensated Hepatitis C are frequently considered “too healthy” for liver transplantation yet are challenging surgical candidates with underlying liver parenchyma that is at high-risk for developing additional tumors. This dilemma highlights the main challenges of resection: 1) inadequate liver reserve and 2) frequent recurrences within the remnant liver. The former has been addressed with pre-operative portal vein embolization to stimulate remnant liver hypertrophy and pre-operative “functional” evaluation to determine if the remnant liver will be adequate [89]. These practices have lowered post-resection morbidity and

mortality, but unfortunately, efforts to improve five-year recurrence rates have been less successful. By comparison, the main disadvantages of transplanting patients with HCC are: 1) higher peri-operative mortality, 2) risk of hepatitis C recurrence with subsequent graft failure, and 3) predominately extra-hepatic tumor recurrences, for which treatments are limited. Transplant surgeons have lowered postoperative mortality to 5-7% and tumor recurrence is relatively low for patients meeting Milan criteria (Table 1). Prior to the emergence of effective treatment of hepatitis C, viral five-year graft-failure rate from recurrent hepatitis C was approximately 20% [90]. With eradication of the viral component of the disease prior to transplant this variable would be far less likely to handicap the transplant arm of the model and widen the difference between survival benefit between the two groups.

This decision analysis accounts for key issues surrounding both resection and transplantation for the treatment of HCC. The inability to account for all of these issues in retrospective comparisons limits the conclusions that can be reached from review of the existing literature on this topic. Over the vast majority of the ranges of variables in the model, transplantation is preferred for patients with early HCC and well-compensated cirrhosis due to hepatitis C. As expected, the factors most heavily influencing the outcome of the model were recurrence and waitlist time (including dropout after tumor progression). Even with early stage HCC, recurrence rates after resection remain high. Alternative therapies are available to most patients with a recurrence after resection [60], but these treatments are rarely curative. In contrast, recurrence rates are low after transplantation for tumors within Milan criteria. The larger number of cures with transplantation outweighs the negative impact of inadequate systemic therapies for extra-hepatic recurrences, which represent a larger proportion of the recurrences after transplantation.

Transplantation as a treatment alternative invariably introduces issues regarding organ availability and allocation. The primary goal of this study was to use novel methods to evaluate the two treatment options independent of organ allocation practices. However, that should not distract from the applicability of the model. Organ availability and organ allocation practices will contribute to our ability to apply these principles and should continue to motivate us toward improvements in these areas since the model would suggest that to not do so would be accepting a compromise in outcome for patients with cancer as a complication of their liver disease. Variables that do not have an established value within the literature cannot be easily accounted for in any decision analysis model. Organ allocation practices and organ availability within different regions of the US would fall into this category as would surgical resection as a bridge to transplant in patients with hepatitis C. In areas of the world with predominantly hepatitis B related liver disease, resection as a bridge to transplant has been an established strategy. However, the likelihood of successful salvage when a patient recurs after resection in this setting is less than 50% and the cancer specific outcomes are inferior compared to primary liver transplant [91]. In the arena of hepatitis C, the high likelihood of de novo tumor emergence despite successful treatment of the virus would weigh heavily against this strategy in patients otherwise appropriate candidates for transplant upfront.

Sensitivity analyses allow readers to evaluate each strategy in a decision model relative to their own patients and practice. For example, longer waitlist times and/or organ shortages limit transplantation in some regions. To address this problem, many centers have liberalized donor criteria and/or developed living-related donor programs. These changes have successfully shortened waitlist times without negatively impacting patient or graft survival [92, 93]. The results

of this study suggest the potential benefits of these strategies. Other centers, however, continue to offer resection as first line therapy for patients with early HCC. In this regard, this study highlights the need for improvements in neo-adjuvant or adjuvant treatments to decrease five-year recurrence rates after resection to below 50%. As novel anti-angiogenic therapies are introduced [94], a 10-15% decrease may be attainable.

All decision analyses have certain limitations. The strength of the model depends on the quality of the data entered and the range of probabilities used for each variable. Decision models often analyze questions that are difficult to address with randomized trials. Therefore, retrospective studies, which are less powerful, often provide the data entered into the model. To overcome this, sensitivity analyses are used to test a range of values for each variable to determine if different values alter the optimal strategy. The outcome of this model did not change over a wide range of probabilities tested, indicating that its conclusion is robust, despite the retrospective studies used in its construction. That said, the studies used in this model introduce other issues that might affect interpretability. For example, few studies report outcomes solely from patients with early HCC and well-compensated cirrhosis, since transplantation has historically been offered to patients with moderate to severe liver dysfunction. This likely handicaps the transplant arm to a greater degree than the resection arm, since resection is limited to patients with better preserved liver parenchyma. Again, this is dealt with in the one- and two-way sensitivity analyses. Even with the data biased against transplant, liver transplantation emerged with a two-year survival benefit over resection in well compensated patients. The strength of the current model is the breadth of variables used in its construction that are noticeably absent from previously published models on this topic [95, 96]. No other model considers the impact of recurrent hepatitis C and graft failure after transplant, nor do the other models include the impact of salvage therapies on post resection survival, both important variables that impact overall survival.

The recent emergence of successful treatment of hepatitis C would introduce another variable that would potentially impact both arms of the model. However, the impact of successful antiviral treatment on post resection recurrence has not been documented and is therefore unavailable for inclusion in the model. The impact of successful antiviral treatment on overall survival in patients otherwise eligible for liver transplant has also not been validated. However, the AJCC staging system for hepatocellular carcinoma and the oncologic principles linked to treatment done with curative intent would support any treatment associated with the best disease specific and overall survival for the patient. For this reason, leveraging for any patient with hepatitis C related liver disease and HCC who meet all other transplant criteria remains our institutional practice.

The depth of this current decision analysis helps practitioners put early stage liver cancer in perspective, highlighting the unique variables that may contribute to outcome in any particular patient. El Serag, et al. published a decision analysis model comparing resection to transplantation for patients with cancer, not limited to patients with well-compensated cirrhosis. For patients who meet transplantation criteria for liver-related variables, there is less debate that transplantation is the preferred strategy. For Child's A patients who are considered "too healthy," the debate continues, and many centers advocate surgical resection initially, with transplantation as salvage for patients who recur. Unfortunately, a minority of patients who recur go on to receive "salvage" transplantation, especially in patients with Hepatitis C [75]. In addition, peri-operative mortality after "salvage" transplantation is significantly higher than after primary transplantation for HCC [75]. These considerations suggest that transplantation up front is the preferred method, thereby

optimizing outcomes, by offering the most efficacious treatment initially and focusing future efforts on the minority of patients who will require other therapies for recurrence. The baseline analyses of El Serag's model [96] did agree with this model's conclusion that transplantation is preferred to resection for treating HCC. The results of their sensitivity analyses, however, differ from those in this model. For example, the baseline analysis of El-Serag's model assumed no waitlist time, which is unrealistic. His sensitivity analysis showed that when waitlist time exceeded 4.3 months, resection was preferable to transplantation [96]. The only other publication on this topic (59) predicted that a waitlist time shorter than 10 months was required before listing for transplantation had a survival benefit over immediate resection [95]. This second study also did not consider waitlist drop off or the impact of salvage therapies on surgical outcome. Our current study found a persistent survival benefit after transplantation with waitlist times up to 27 months. Our lower waitlist dropout rate (28% at 1 year vs. 30% at 6 months) and longer survival with incurable HCC (50% survival at 19.5 months vs. 20% survival at 12 months) [95] are based on contemporary figures from a national database and likely account for this difference. These improvements likely reflect earlier detection of tumors due to improved surveillance of patients with cirrhosis and/or advancements in nonsurgical therapies for hepatocellular carcinoma, which may lower the risk of tumor progression while on the waitlist and extend the life expectancy of patients with advanced disease.

This study suggests that liver transplantation is the preferred surgical option for patients with hepatitis C, well-compensated cirrhosis, and HCC meeting Milan criteria. The survival benefit after transplantation persists over the likely range of probabilities tested with sensitivity analysis. Resection only outperforms transplantation once waitlist times exceed 27 months or the five-year risk of tumor recurrence after resection drops below 50%. In the 2007 report of the Scientific Registry of Transplant Recipients, which includes data from 2001-2006, only 17% of reporting transplant centers had median waitlist times longer than 27 months for livers [97]. Patients at these centers are at risk for tumor progression while on the waitlist and should be evaluated for resection. Centers with limited transplant availability that rely on surgical resection should explore clinical trials focused on decreasing postoperative recurrence rates.

Abbreviations

HCC-hepatocellular carcinoma; DEALE-declining exponential approximation of life expectancy; Peri-op-peri-operative; Alt-alternative; Pt-patient; OLT-orthotopic liver transplant.

Author Contributions

Amanda B. Cooper: Literature search, data modeling, and manuscript drafting; Stephen M. Downs: Data modeling and manuscript drafting; Nicholas J Skill: Literature search, and manuscript drafting; Richard S. Mangus: Manuscript drafting; Chandrashekhar A Kubal: Manuscript drafting; Mary A Maluccio: Project conception and manuscript drafting.

Competing Interests

The authors have declared that no competing interests exist.

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