Chapter 7
Surgical Treatment of Hepatocellular Carcinoma: Resection Versus Transplantation

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Abstract Hepatocellular carcinoma is the second most common cause of cancer mortality worldwide and its incidence is rising in North America, with an estimated 35,000 cases in the U.S. in 2014. The best chance for cure is surgical resection in the form of either segmental removal or whole organ transplantation although recent survival data on radiofrequency ablation approximates surgical resection and could be placed under the new moniker of "thermal resection". The debate between surgical resection and transplantation focuses on patients with "within Milan criteria" tumors, single tumors, and well compensated cirrhosis who can safely undergo either procedure. Although transplantation historically has had better survival outcomes, early diagnosis, reversal of liver disease, and innovations in patient selection and neo-adjuvant therapies have led to similar 5-year survival. Transplantation clearly has less risk of tumor recurrence but exposes recipients to long term immunosuppression and its side effects. Liver transplantation is also limited by the severe global limit on the supply of organ donors whereas resection is readily available. The current data does not favor one treatment over the other for patients with minimal or no portal hypertension and normal synthetic function. Instead, the decision to resect or transplant for HCC relies on multiple factors including tumor characteristics, biology, geography, co-morbidities, location, organ availability, social support and practice preference.

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Introduction

Liver transplantation and surgical resection have remained the key first-line therapies for hepatocellular carcinoma (HCC) as they hold the greatest chance for a cure. The Barcelona Clinic Liver Cancer (BCLC) staging and treatment guidelines best incorporate tumor, liver and patient characteristics to assess survival with all HCC-directed interventions [1]. According to this guideline, curative surgical resection and liver transplantation are reserved for patients with early stage disease whereas intermediate and advanced stage tumors are subject to palliative therapies [2] that may prolong life and occasionally be associated with a cure.

Patients with early stage tumors and advanced liver disease (Child-Pugh Class B and C), especially if multiple tumors, clearly benefit from liver transplantation as resection results in poor overall survival [3]. On the other hand, surgical resection is most beneficial for those patients with early stage tumors, single tumors and early cirrhosis or no underlying liver disease [4]. The debate lies within the small group of patients whose tumors are within Milan criteria, especially those with a single tumor, who have Child-Pugh Class A cirrhosis, who have no significant portal hypertension as determined by hepatic vein pressure gradient, and who are without liver dysfunction. Liver transplantation appears to be the obvious choice for cure as the entire tumor along with the field defect of cirrhosis is removed. However, transplantation is not available to everyone as fewer than 30 % of patients are eligible at the time of presentation and it is severely limited by the number of donor organs available [1]. For this reason, hepatic resection continues to play a significant role in the treatment of HCC even though it is applicable to only approximately 15 % of cases. It is readily available without the need for a waitlist and may be less restrictive than Milan criteria in regards to tumor size.

The aim of this discussion is to review the current data detailing outcomes such as overall survival, disease free survival, and recurrence following resection and/or transplantation for Milan criteria HCC. Numerous studies and meta-analyses have been performed addressing this topic but heterogeneous patient populations and retrospective observations have produced moderate to low quality data. Here we analyze current data, provide evidence-based recommendations for clinical practice and discuss future avenues of research.

Search Strategy

A literature search of peer-reviewed English language publications from 1996 to 2014 was used to identify data on liver resection and/or transplantation as the treatment for hepatocellular cancer. Databases searched were Pub Med and Cochrane Evidence Based Medicine. Terms used in the search were “hepatocellular carcinoma surgical treatment,” “HCC resection versus transplantation,” “HCC resection,”

"HCC transplantation," "HCC downstaging," "Milan Criteria expansion." "UCSF criteria," "salvage transplantation AND secondary transplantation." Articles were excluded if they included hepatocholangiocarcinoma, fibrolamellar HCC and non-cirrhosis HCC. Living donor liver transplantation for HCC was also excluded from this analysis. No randomized controlled trials were identified. Articles analyzed here include ten retrospective studies, two prospective cohort studies, three review articles, four meta-analyses and two clinical guidelines. The data was classified using the GRADE system.

Results

Resection of Hepatocellular Carcinoma

When considering patients for surgical resection, various factors such as tumor size, number, tumor biology, vascular invasion, underlying liver dysfunction, presence of portal hypertension, type of resection, and ability to treat the underlying liver disease help determine patient survival [5]. Reported 5-year overall survival and disease-free survival are 50–60 % and 25–35 %, respectively, in patients with HCC and preserved liver function [6, 7]. Preserved liver function refers to those with Child-Pugh Class A cirrhosis with or without portal hypertension (PHTN). According to the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), PHTN is a relative contraindication to resection because of increased morbidity and mortality following surgery [2]. Santambrogio et al. and others have challenged this dogma and have shown that patients undergoing resection who had clinically significant portal hypertension (splenomegaly >12 cm, platelet count <100 k/mm^3) and preserved liver function (INR, bilirubin, and albumin within normal limits) had 5-year survival equivalent to that of patients without PHTN who undergo resection, 65 % vs. 70 % [8]. Multivariate analysis identified albumin as an independent predictive factor for survival. Although not found to be significant in this study, bilirubin has been shown to be an independent predictor of survival in other studies [3, 7]. All patients included in the Santambrogio et al. study had transplantable tumors that were single lesions <5 cm, Child-Pugh Class A, BCLC stage Class A1 to A3. The study's findings helped establish a role for resection for HCC as patients with early tumors and well compensated cirrhosis can safely undergo resection.

Transplantation for Hepatocellular Carcinoma

Soon after liver transplantation was deemed successful, surgeons began using transplantation as a treatment for HCC. The benefits of transplantation over resection for cancer appeared obvious in that the entire organ-containing tumor was removed and in most cases the significant risk factor for malignancy (cirrhosis) was also removed.

Unfortunately, poor understanding of the biology of HCC resulted in high recurrence rates, as evidenced by studies showing recurrence as high as 74 % within 2 years [9, 10]. It was clear that simple removal of the tumor with transplantation was not sufficient to cure patients with HCC.

It was not until 1996 that Mazzaferro and colleagues published the results of a prospective cohort study that investigated 48 cirrhotic patients who underwent liver transplantation for HCC with single tumors ≤5 cm, or up to three tumors, the largest of which is ≤3 cm. Evident radiographical evidence of vessel and lymph node invasion were also excluded. Survival of these patients was comparable to that of patients who underwent transplantation for nonmalignant diagnoses (70 % at 5 years) [11]. In this cohort, 60 of 295 patients (20 %) were deemed candidates for liver transplantation. Forty-eight of these 60 patients were ultimately transplanted secondary to wait list drop off. This landmark article gave birth to the widely adopted Milan criteria which are used to guide decision making in most transplant centers today. Numerous retrospective studies have validated improved survival of patients transplanted within Milan criteria [12–14].

The difficulty in analyzing transplant outcomes is that patients are naturally selected when evaluated for transplant. This is seen in the landmark study by Mazzaferro et al. where 48 of 60 patients eventually underwent transplantation while the remaining 12 suffered from waitlist dropout. Although not specifically detailed in that study, the most common reasons for removal from the waitlist are tumor growth outside of Milan criteria, death and development of contraindications to transplant [15]. It is possible that patients who undergo transplant tend to have less aggressive tumors than those who exceed Milan criteria while on the wait list. To offset this selection bias seen in outcome studies where survival and tumor recurrence are measured at the time of transplant, intention to treat (ITT) analyses were performed where outcome is measured starting at the time of listing. Llovet et al. performed an ITT analysis in patients who underwent transplant (n = 87) or resection (n = 77) from the years 1989 to 1997 [7]. Upon analyzing patients with early HCC (single tumors ≤5 cm), survival between resection and transplant groups were similar at 74 % at 5 years when resection patients with clinically relevant portal hypertension were excluded. Interestingly, the most common causes of death in the transplant arm were wait list drop off (n = 8) and post-transplant infections (n = 8). The most common cause of death post- resection was tumor recurrence (n = 26). This study sparked the debate on resection versus transplant for early stage tumors and several ITT analyses following it showed similar results [16, 17]. These studies included patients from the pre-Model for End Stage Liver Disease (MELD) era where HCC patients were allocated according to time on the waitlist which has been shown to be a poor predictor of death [18]. After MELD criteria were adopted by the United Network for Organ Sharing (UNOS) in 2002, special allocation was given to HCC patients which resulted in decreased wait time, with 87 % of patients being transplanted within 3 months [19]. To this date there have been no publications that compare resection to ITT survival in only MELD-era patients undergoing transplant for Milan criteria HCC.

Expanding the Milan Criteria

Since its induction in 1996, the Milan criteria have been the cornerstone for HCC transplant evaluation. Expansion of these criteria is underway so as to offer transplantation to a wider group of patients at initial presentation. Yao et al. have proposed the UCSF criteria which include solitary tumors ≤6.5 cm or no more than three tumors with the largest ≤4.5 cm not totaling more than 8 cm [20]. This finding was retrospectively determined by explant tumor characteristics and excluded tumors with gross vascular invasion. Survival at 5 years for 70 patients total was 75 % for those within UCSF criteria (n = 18) but only 50 % at 1 year for patients beyond their newly defined criteria. This 5-year survival was not significantly different from those transplanted within Milan criteria but not UCSF criteria. In a subsequent retrospective study by Duffy et al. encompassing 467 patients, 5-year survival again was not significantly different between those of UCSF criteria and Milan criteria [14]. More recently, a UNOS analysis by Patel et al. analyzed post-transplant survival of HCC patients who were within Milan criteria and those who were outside Milan but within UCSF [21]. Of the 3434 patients identified between 2002 and 2007 only 59 were within UCSF criteria and 1913 were within Milan criteria. Four year survival was 72 % for Milan and 51 % for UCSF with no statistical difference ($p = 0.21$). Opponents of criteria expansion suggest that the UCSF criterion applies to a small and clinically insignificant subset of patients and that they used explant pathology to stage the disease. This small number of patients that are within these criteria may contribute to the inability to detect significance in survival between UCSF and Milan criteria patients. Further evaluation with long term prospective studies are needed to elucidate this matter.

Salvage Transplantation

Salvage transplantation refers to transplantation after primary resection secondary to tumor recurrence or deterioration of liver function. The proposed benefit from this approach is that patients with resectable Milan tumors will be spared the morbidity and cost of organ transplantation and thus make more donor organs available for those who will clearly benefit from them (advanced liver disease, unresectable but transplantable tumors). One major drawback is that transplantation is only available to those who have recurrence within Milan criteria. Thus, patients who were transplantable at the time of presentation who undergo resection may then not be transplantable at the time of recurrence. Adam et al. retrospectively compared 17 patients undergoing salvage transplantation to that of 195 patients undergoing primary transplantation for HCC [22]. They found that secondary liver transplantation was associated with a significantly higher operative mortality, tumor recurrence and lower overall 5-year survival (41 % vs 61 % $p = 0.03$); 98 transplant eligible patients

underwent resection and 69 (70 %) had recurrence. Only 17 (25 %) of the 69 patients had recurrence within Milan criteria. In an ITT analysis by Del Gaudio et al. comparing 10 patients undergoing salvage transplantation to 293 patients listed for transplantation, overall 5-year survival was 66 % following secondary transplant and 58 % following primary transplant with no significant difference observed [17]. One of the limiting factors in these retrospective ITT analyses is that patients listed for transplantation who forego resection have more advanced liver disease while those who undergo resection tend to have early liver disease but more advanced tumors (outside Milan criteria). This in part may explain the high recurrence rate seen after resection and the relatively few patients who have transplantable recurrence. It remains unclear whether the benefit of saving allografts by resecting first outweighs the number of patients who potentially would have been cured with primary transplantation but now have non-transplantable disease following resection.

Treatment Prior to Transplantation

The dropout rate while awaiting transplant has increased because of greater demand without significant increase in the supply of donor organs [7, 23]. Dropout rates are estimated to be between 12 and 20 % [15]. This has led most transplant centers to adopt the use of ablative therapies prior to transplant to halt tumor progression and thus prevent dropout although conclusive data showing decreased waitlist removal or improved post-liver-transplant survival has not been published. This bridge therapy includes radiofrequency ablation (RFA), transarterial chemoembolization (TACE), transarterial bead embolization (TABE), transarterial radioembolization (TARE) and percutaneous ethanol injection (PEI). Because PEI for the most part has been replaced by RFA, TACE, TABE, TARE, microwave and RFA are now the most common treatments used for pre-transplant ablative therapy [24]. Several studies have suggested that RFA, TACE and TABE are safe and efficacious treatments to prevent tumor progression and waitlist dropout [25, 26]. There are few studies that directly compare dropout rates in treated and untreated pre-transplant patients. Interpretation of these studies is difficult given their heterogeneous patient populations without clear criteria for treatment [27]. In one study that used a decision model based on a review of the current literature to simulate a randomized trial of treatment with TACE vs. no TACE in 600 virtual patients with HCC and cirrhosis, it was found that the benefit of neoadjuvant TACE may be limited to those patients transplanted from 4 to 9 months from first TACE [28]. In another study that used a Markov model to assess a hypothetical cohort of cirrhotic patients with early HCC, it was found that adjuvant therapies for HCC while waiting for liver transplantation provide moderate life expectancy gains and are cost effective for waiting lists of 1 year or more, but that only percutaneous treatment confers a relevant survival advantage for shorter waiting times [29].

Living Donor Liver Transplantation for HCC

Although living donor liver transplant (LDLT) for HCC has waned in frequency in the United States, it has gained popularity in Asian countries such as Japan, South Korea and China [30, 31]. This is because the paucity of deceased donors available in those countries makes LDLT a desirable option. LDLT has the potential advantage of decreased time to transplant as compared to those waiting for deceased donor livers. The major drawback is the risk to the donor who undergoes a major operation with a morbidity rate of 16 % and mortality estimated at one in 500 persons [32]. Studies comparing outcomes between LDLT and deceased donor liver transplant have shown that living donor recipients experience shorter wait times, are more likely to have tumors that exceed Milan criteria, have higher alpha fetoprotein levels and are less likely to have undergone pre-operative therapies such as embolic or thermal ablation [33]. This and other studies show little to no survival benefit of LDLT over deceased donor transplant [34, 35]. Although LDLT offers transplantation for those outside of Milan criteria who would not qualify for deceased donor transplant, the potential harm to the donor for similar outcomes results in its remaining controversial. This likely has contributed to the trend of performing less LDLT for HCC in the United States.

Comparative Outcomes Between Resection and Transplantation for HCC

The debate between resection and transplantation revolves around patients who have well compensated cirrhosis with Milan criteria resectable tumors. Patients within these criteria represent a very small proportion of those who initially present with HCC. This is especially true in western countries where hepatitis C is the most common cause of liver failure and HCC is a result of the progressive and in most cases advanced cirrhosis [15]. Given the need for a large number of patients to show statistical significance, it would be difficult to perform a high-quality prospective randomized controlled trial comparing resection and transplantation. In fact, our search of the literature revealed that no randomized controlled trials addressing this issue exist. Instead, outcomes of surgical treatment for HCC stem from retrospective analyses that have inherent detection, selection and attrition biases. Given the numerous articles available on this subject, several meta-analyses have been published to delineate the role of transplantation and resection for treatment of HCC [36–39]. However, there is reason to be wary of these meta-analyses because they pool data from heterogeneous populations with variable selection criteria and treatment protocols. One such meta-analysis by Dhir et al. focused their choice of articles to strict criteria which excluded studies with non-cirrhotic patients, fibrolamellar HCC and hepatocholangiocarcinomas but included those with HCC within Milan criteria

and computation of 5-year survival; between 1990 and 2011 they identified ten articles that fit within these criteria, of which six were ITT analyses, six included only well-compensated cirrhotics (Child-Pugh Class A without liver dysfunction) and three were ITT analyses of well-compensated cirrhotics [37]. Analysis of the six ITT studies that included all cirrhotics (n = 1118) (Child-Pugh Class A through C) showed no significant difference in survival at 5 years (OR = 0.600, 95 % CI 0.291–1.237 l; p = 0.166) but ITT analysis of only well-compensated cirrhotics (Child-Pugh Class A) revealed that patients undergoing transplant had a significantly higher 5-year survival as compared to those with resection (OR = 0.521, 95 % CI 0.298–0.911; p = 0.022). A more recent ITT retrospective analysis from Spain assessed long-term survival and tumor recurrence following resection or transplant for tumors <5 cm in 217 cir rhotics (Child-Pugh Class A, B and C) over the span of 16 years [40]. Recurrence at 5 years was significantly higher in the resection group (71.6 % vs. 16 % p < 0.001) but survival at 4 years was similar (60 % vs. 62 %) which is likely explained by the evolving role of adjuvant therapies to treat post -resection recurrence.

Recommendations

When evaluating patients for surgical treatment of hepatocellular carcinoma several factors should be considered including age, size and location of tumor(s), presence of extrahepatic disease, presence of cirrhosis, comorbidities, organ waitlist time, blood type and degree of liver dysfunction. Patients with anatomically resectable single tumors and no cirrhosis or Child-Pugh Class A cirrhosis with normal bilirubin, HVPG (<10 mmHg), albumin and INR can be offered resection (evidence quality moderate; strong recommendation). Patients with Milan criteria tumors in the setting of Child- Pugh Class A with low platelets and either low albumin or high bilirubin or Child-Pugh Class B and C cirrhosis, especially those with more than one tumor, should be offered liver transplantation over resection (evidence quality moderate; strong recommendation). Those with Milan criteria tumors and Child-Pugh Class A cirrhosis without liver dysfunction should be considered for transplantation over resection (evidence quality low; weak recommendation). No recommendation can be made in regard to transplanting tumors beyond Milan criteria (evidence quality low) except to follow regional review board criteria. Pre-transplant therapies such as embolic or thermal ablation are safe and by expert opinion considered to be effective in decreasing transplant waitlist dropout and bridging patients to transplant (evidence quality low, weak recommendation). These interventions should be considered for those waiting longer than 6 months (evidence quality low, moderate recommendation). Living donor liver transplantation is a safe and effective option for treatment of HCC that are within and exceed Milan criteria (evidence quality moderate, weak recommendation).

A Personal View of the Data

The debate between resection and transplant for early stage tumors in patients with single tumors and well-compensated cirrhosis has persisted for decades without a clear winning strategy in sight. Fortunately, this accounts for only a small portion of the patients that present with HCC. A prospective randomized trial would require a large number of patients to find significance, something that would be further complicated by variable practice patterns between transplant centers. In addition, it would probably not pass IRB scrutiny due to the fact that thermal or embolic ablation is the standard of care at most institutions. As transplant experts at a high-volume center we prefer transplantation for patients with Milan criteria tumors and early cirrhosis because of superior disease-free survival as compared to resection. The significance of disease-free survival in the setting of chronic immunosuppression has yet to be determined. Survival after resection is steadily improving because of improvement in therapies such as TACE, RFA and possibly radioembolization to treat post-resection recurrence. In addition, the recent availability of highly effective therapy for hepatitis C (HCV) will lead to the elimination of chronic infection in many patients, reversing liver disease and improving liver function as well as decreasing portal hypertension [41] and will ultimately lead to reduced HCV-related HCC. Patients should have their underlying liver disease treated aggressively, including antiviral treatment for those with HBV or HCV infection, weight loss for patients with NASH and abstinence from alcohol for those with alcoholic liver disease. The treatment algorithm for HCC is ever changing with improvement not only in adjuvant therapies but with innovations in organ allocation, selection criteria and minimally invasive techniques which we have already observed in the past two decades. Prospective long term studies assessing outcomes of patients treated within the most recent era will help resolve this debate.

- Patients with single anatomically resectable tumors and no cirrhosis or Child-Pugh Class A cirrhosis with platelet counts over 100,000 and normal bilirubin, albumin and INR can be offered resection (evidence quality moderate, strong recommendation); patients with lower platelets need to have normal synthetic function to be considered for surgical resection
- Patients with Milan criteria tumors in the setting of Child-Pugh Class B and C cirrhosis should be offered liver transplantation over resection (evidence quality moderate, strong recommendation)
- Patients with Milan criteria tumors and Child-Pugh Class A cirrhosis without liver dysfunction should be considered for transplantation over resection (evidence quality low, weak recommendation).
- No recommendation can be made in regards to transplanting tumors beyond Milan criteria (evidence quality low).
- Pre-transplant therapy such as RFA and TACE are safe and effective and should be considered for those waiting longer than 6 months (evidence quality moderate, weak recommendation).

- Living donor liver transplantation is a safe and effective option for treatment of HCC that is within and exceeds Milan criteria (evidence quality moderate, weak recommendation).

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