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ORIGINAL ARTICLE

Hepatocellular Carcinoma in Transplantable Child-Pugh A Cirrhotics: Should Cost Affect Resection vs Transplantation?

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Abstract

Background There is no consensus regarding the optimal surgical treatment for transplantable hepatocellular carcinoma (HCC) patients with well-compensated cirrhosis. Our aim was to compare outcomes between Child-Pugh A (CPA) cirrhotics who underwent liver resection or transplantation for HCC.

Methods Clinicopathologic data were retrospectively collected for all surgically treated HCC patients between 7/1992 and 12/2015. Disease-free survival (DFS) and overall survival (OS) were calculated from the time of operation or diagnosis (intention-to-treat analysis including patients removed from the transplant list). The average overall cost including pre-operative and post-operative procedures was calculated for each group.

Results Of the 513 surgically treated HCC patients, 184 had CPA cirrhosis and fulfilled the Milan criteria (MC). Of those, 95 (52%) were resected and 89 (48%) were transplanted. Twenty-two patients were removed from the transplant list. Transplanted patients were younger ($p < 0.001$), had a higher MELD score ($p < 0.001$) and a higher frequency of hepatitis C ($p < 0.001$). Length of stay and postoperative complication rates were similar between groups. DFS was longer for transplanted patients (3-, 5-, and 10-year DFS rates 48, 44, 31% vs 96, 94, 94%, respectively, $p < 0.001$). OS was similar between groups (3-, 5-, and 10-year OS rates 76, 62, 41% vs 82, 77, 53%, respectively, $p = 0.07$). Only size of greatest lesion and T stage were independent predictors of OS. The cost was much higher for the transplant group, even when accounting for the treatment of recurrences ($37,391 vs $137,996).

Conclusions Since OS is similar between CPA cirrhotics within the MC undergoing resection or transplantation for HCC, but cost is significantly higher for transplantation. Resection should be considered for first-line treatment.

Keywords Hepatocellular carcinoma · Hepatectomy · Transplantation · Cirrhosis · Healthcare cost

Introduction

Globally, primary liver cancers represent 5.4% of all cancers and are the third most common cause of cancer mortality worldwide. The highest incidence is seen in Asia and Africa. In the last three decades, the incidence of hepatocellular carcinoma (HCC) has tripled in the USA.[1–3] In 2017, an estimated 40,710 new cases will be diagnosed and 28,920 deaths will occur due to HCC.[4]

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Advancement in imaging, surgical techniques, patient selection, and perioperative care has led to improvements in the outcomes of patients with HCC. HCC in the early stages is curable by surgical resection or liver transplantation offering 5-year survival rates of up to 55%[5–7] and 70%,[8,9] respectively. Hepatectomy for HCC is being performed more often due to the increased incidence and the shortage of organs available for transplantation. It has become increasingly safe over the past few decades and it is being considered an option for many patients.[10,11] In cirrhotic patients, partial hepatectomy is a more challenging procedure with a high recurrence rate and associated risk of long-term complications due to underlying liver disease.[10] With regard to liver transplantation, the Milan experience has demonstrated that a subset of patients with a solitary HCC < 5 cm in size or ≤ 3 tumors ≤ 3 cm in size have excellent outcomes offering long-term survival and a recurrence rate of less than 15%.[12] Excellent survival following liver transplantation has also been demonstrated for patients fulfilling more extended criteria such as the University of California, San Francisco,[12] or the Barcelona criteria.[13]

For transplantable patients with compensated cirrhosis, however, there is no consensus regarding the optimal clinical and cost-effective therapeutic option.[14] Although in this subgroup, there is a substantial disease-free survival benefit for transplant patients, the few published studies have failed to demonstrate a clear overall survival benefit of transplantation, and most centers prioritize those patients for hepatectomy. The first aim of this study was to compare recurrence rates and overall survival between Child-Pugh A (CPA) cirrhotics within the Milan criteria (MC) who underwent either liver resection or transplantation of their HCC. The second aim was to compare in an intention-to-treat analysis overall survival between CPA-MC resection and transplant patients, including those removed from the transplant list. The third aim was to compare the cost between resection and transplant, taking into account the cost of pre-operative bridging procedures and post-operative procedures for the treatment of recurrences.

Materials and Methods

The institutional internal review board approved this study, and none of the authors has any conflict of interest. Retrospective review of the medical records of HCC patients treated surgically at the Massachusetts General Hospital between July 1992 and December 2015 was performed. The study included patients who were CPA cirrhotics within MC, who underwent either hepatectomy or liver transplantation, or were listed for transplantation, but were removed from the transplant list before receiving surgical treatment. Patients with de novo tumors in the setting of normal livers have not been included.

Patient tumor and treatment-related variables were retrieved and analyzed. Follow-up data were obtained through hospital records and the social security death index. Patient characteristics evaluated included age, gender, underlying disease (history of hepatitis B or hepatitis C virus infection), body mass index (BMI), ethnicity, diabetes, and alcohol as well as tobacco abuse. Treatment factors included the type of operation, estimated blood loss, preoperative treatment, status at last follow-up, and recurrence. Histological confirmation of HCC was determined by hepatobiliary pathologists. Pathologic factors included number and size of lesion(s), nodes, metastases, TNM stage, resection margin (positive or negative), vascular invasion, and grade. Maximal tumor size was defined as the maximum diameter at pathological analysis.

Patients were considered to be within the Milan criteria if radiographic assessment demonstrated a solitary lesion of 5 cm in max diameter, or 3 tumors up to 3 cm in size each, with no portal vein involvement and no extra-hepatic disease. MELD score[15] was calculated using the formula MELD = $3.8\times\log_e$(serum bilirubin [mg/dL]) + $11.2\times\log_e$(INR) + $9.6\times\log_e$(serum creatinine [mg/dL]) + 6.4, with laboratory values < 1 set to 1.0 and maximum serum creatinine level set to 4.0 mg/dL, according to the UNOS modification.

Continuous variables are reported as median (interquartile range [IQR]) and compared using independent sample t tests or the Kruskal-Wallis method. The χ^2 test was used for the comparison of categorical variables.

Disease-free survival (DFS) and overall survival (OS) were calculated from the date of operation to the date of recurrence or death, respectively (event), or last follow-up (censored), and were then compared between resected and transplanted patients. For the intention-to-treat analysis, OS was calculated from the date of diagnosis for the complete cohort and was compared between resection and transplant patients, including those removed from the transplant list. Survival functions were estimated using the Kaplan-Meier method and were compared between groups with the log-rank test. Multivariate backward conditional Cox proportional hazards model was applied to compare DFS and OS between groups. The survival models were determined by a combination of clinical expertise and stepwise variable selection procedures.

Cost data were derived from the Agency for Healthcare Research and Quality (AHRQ)/Healthcare Cost and Utilization Project (HCUP) database.[16,17] The following ICD-9 codes were used to identify procedures and their respective costs: partial hepatectomy 50.22, hepatic lobectomy 50.3, liver transplant 50.59, transarterial chemoembolization (TACE) 99.25, ablation (radiofrequency, microwave, thermal, ethanol, cryoablation) 50.24, and radiotherapy 92.24. Of note, the amounts used represent costs and not charges, and they represent costs from a societal perspective. The number and type of pre-operative procedures used as a bridging therapy as well as of post-operative procedures used for the treatment of recurrences were identified for each patient. Thereafter, the average cost per patient in the transplant and the resection group was calculated taking into account pre- and post-operative procedures. All statistical analyses were performed using SAS Version 9.2. A p value less than 0.05 was considered significant.

Results

Complete CPA-MC Cohort

Between July 1992 and December 2015, 587 patients with HCC were treated surgically with resection or transplantation, or were listed for transplantation with HCC exception MELD points, but were removed from the transplant list before receiving surgical treatment. Of the 587 patients, 313 were CPA cirrhotics, of whom 206 were within the MC (Table 1). Of the 206 CPA cirrhotics within the MC, 95 (46%) underwent a hepatectomy, 89 (43%) received a transplant, and 22 (11%) progressed and were removed from the transplant list. Seventy-five percent of the procedures were performed in 2005 or later and more than half (52%) in 2010 or later.

The majority of patients were Caucasian (81%), male (82%), with a median age of 61 years (IQR 56–66). Hepatitis B infection was present in 18% of patients, while over half of the patient cohort had a history of hepatitis C (57%). Approximately half of the patients had a history of alcohol abuse (46%). Median number of lesions was 1 (IQR 1–2) and median size of the greatest lesion was 3.3 cm (IQR 2.1–4.5). Median laboratory MELD score, platelet count, and α-fetoprotein (AFP) were 9 (IQR 7–10), 140,000/μL (IQR 100,000–188,000), and 12.5 ng/mL (IQR 4.2–54.1), respectively.

Patients removed from the transplant list either deteriorated medically and were deemed unfit candidates for a transplant (86%) or died due to disease progression (14%) while awaiting a transplant.

For the entire cohort ($n = 206$), median OS from the time of diagnosis was 98.6 months (IQR 37.4–142.7) and overall survival rates at 3, 5, and 10 years from diagnosis were 76%, 65%, and 45%, respectively (Table 2(C)). For the combined resected and transplanted cohort, the median OS from the time of operation was 111.5 months (IQR 45.6–156.1), and 3-, 5-, and 10-year OS rates were 79%, 70% and 46%, respectively (Table 2(B)).

CPA-MC Patients Who Underwent an Operation: Resection vs Transplant

When comparing CPA-MC patients who underwent either resection or transplantation for their HCC (Table 1), transplanted patients were younger (63 vs 59 years, $p < 0.001$), had a higher MELD score (8 vs 9, $p < 0.001$), a lower platelet count (172,000 vs 115,000/μL, $p < 0.001$), and more lesions ($p < 0.001$). Furthermore, history of HBV infection was more frequent in the resection cohort (26% vs 11%, $p = 0.010$), while HCV was more frequent in the transplant group (38% vs 73%, $p < 0.001$). Preoperative treatment with ablation or chemo embolization was more common among transplanted patients (12% vs 88%, $p < 0.001$). The estimated blood loss volume was higher in transplanted patients (550 vs 1400 mL, $p = 0.012$), while LOS and postoperative complication rates were similar between the two groups (LOS 6 vs 7 days, $p = 0.130$; postoperative complication rate 32% vs 36%, $p = 0.512$, in the resection and transplant groups, respectively).

DFS calculated from the time of operation was significantly longer for transplanted patients ($p < 0.001$) with 3-, 5-, and 10-year DFS rates being 48%, 44%, and 31% for resected patients, and 96%, 94%, and 94% for transplanted patients, respectively (Table 2(A), Fig. 1).

OS calculated from the date of the operation was similar for resected and transplanted patients ($p = 0.07$); median OS was 96 (IQR 36–140) and 134 months (IQR 77.2-N/A) for resected and transplanted patients, respectively. OS rates at 3, 5, and 10 years were 76%, 62%, 41% for resected patients, and 82%, 77%, 53% for transplanted patients, respectively (Table 2(B), Fig. 2).

In multivariate analyses, transplantation was associated with a better DFS (HR = 0.47, $p = 0.01$). Size of the greatest lesion (HR = 1.3, $p = 0.005$) and T stage (HR = 2.1, $p = 0.02$) were the only independent prognostic factors of OS, while the type of operation did not significantly influence OS ($p = 0.85$) (Table 2(A), (B)).

Intention to Treat Analysis of Resection vs Transplantation

When resected patients were compared with transplant patients, including those who were removed from the transplant list group (TR), the former were older (63 vs 59 years, $p < 0.001$), had a lower MELD score (8 vs 9, $p = 0.001$), a higher platelet count (172,000 vs 116,000/μL, $p < 0.001$), and fewer lesions ($p = 0.001$). Additionally, preoperative treatment (12% vs 89%, $p < 0.001$) and history of HCV infection (38% vs 73%, $p < 0.001$) were more frequent in the TR group, while a history of HBV was more common in the resection group (11% vs 27%, $p = 0.002$).

OS calculated from the time of diagnosis continued to be similar between the resection and TR groups ($p = 0.18$, Fig. 3). Median OS was 99 (IQR 37–142) and 122 months (IQR 39-N/A) for the resection and TR groups, respectively. OS rates at 3, 5, and 10 years are shown in Table 2(C). Size of the greatest lesion (HR = 1.4, $p = 0.005$) was the only independent prognostic factor of OS on multivariate analysis, while the type of surgical treatment did not seem to affect survival ($p = 0.82$). Similar results were yielded when our analysis was restricted to patients who underwent an operation in 2002 or later (87% of patients), after the MELD exception point system was implemented (multivariate $p = 0.23$ for type of surgical treatment).

Cost Analysis

Based on publicly available information,[16] the average costs for liver resection and liver transplantation were estimated to be $28,492 and $122,286, respectively. In this study, we observed that patients in the resection and transplant group underwent a total of 10 and 92 pre-operative procedures, respectively (Table 3). These included either ablative techniques or TACE. For patients who developed a recurrence, we noticed that patients in the resection and transplant group underwent a total of 41 and 1 post-operative procedures for

Table 1 Patient and tumor characteristics of 206 HCC Child-Pugh class A transplantable patients who underwent either resection or transplantation, or were listed for transplant with HCC exception MELD points but were removed from the list, between 1992 and 2015

		Resection *n* = 95 *n* (%)	Transplant *n* = 89 *n* (%)	Removal *n* = 22 *n* (%)	Total *n* = 206 *n* (%)
Age, years [median (IQR)]*		63 (56–73)	59 (55–63)	59.5 (57–65)	61 (56–66)
Gender Race	Male	74 (77.9)	76 (85.4)	18 (81.8)	168 (81.6)
	Female	21 (22.1)	13 (14.6)	4 (18.2)	38 (18.4)
	Caucasian	73 (76.7)	71 (79.8)	22 (100)	166 (80.6)
	African American	3 (3.2)	7 (7.9)	0 (0.0)	10 (4.9)
	Hispanic	3 (3.2)	5 (5.6)	0 (0.0)	8 (3.9)
	Asian	13 (13.7)	6 (6.7)	0 (0.0)	19 (9.2)
	Other	3 (3.2)	0 (0.0)	0 (0.0)	3 (1.5)
BMI, kg/cm^2 [median (IQR)]		26.4 (24.2–31.2)	26.7 (24.7–32)	28.8 (26.6–33.05)	26.7 (24.7–31.5)
HBV infection*		25 (26.3)	10 (11.2)	1 (4.5)	36 (17.5)
HCV infection*		36 (37.9)	65 (73.0)	17 (77.3)	118 (57.3)
Alcohol abuse		41 (43.2)	44 (49.4)	10 (45.5)	95 (46.1)
Removal Reason	Died	N/A	N/A	3 (13.6)	3 (13.6)
	Deteriorated			19 (86.4)	19 (86.4)
Number of lesions [median (IQR)]*^		1 (1–1)	1 (1–2)	1 (1–1)	1 (1–2)
Size of greatest lesion, cm [median (IQR)]		3.4 (2.4–4.5)	3.4 (1.8–4.5)	2.8 (2.1–3.9)	3.3 (2.1–4.5)
Stage T	T0#	0 (0)	10 (11.2)		10 (5.4)
	T1	54 (56.8)	36 (40.4)		90 (48.9)
	T2	34 (35.8)	34 (38.2)		68 (37)
	T3	7 (7.4)	9 (10.1)		16 (8.7)
Stage N	NX#	89 (93.7)	65 (73)	N/A	154 (83.7)
	N0	5 (5.3)	22 (24.7)		27 (14.7)
	N1	1 (1.1)	2 (2.2)		3 (1.6)
Grade	GX#	0 (0.0)	17 (19.1)	N/A	17 (9.2)
	G1	28 (29.5)	26 (29.2)		54 (29.3)
	G2	56 (58.9)	38 (42.7)		94 (51.2)
	G3	11 (11.6)	8 (9.0)		19 (10.3)
MELD score [median (IQR)]*		8 (7–9)	9 (8–11)	9 (7–10)	9 (7–10)
Platelets, 1000/μL [median (IQR)]*		172 (123–237)	115 (79–161)	118 (80–178)	140 (100–188)
AFP, ng/mL [median (IQR)]		8.3 (3.8–66)	13.3 (4.7–47.5)	16.1 (8.6–50.6)	12.5 (4.2–54.1)
Preoperative Treatment*		11 (11.6)	78 (87.6)	20 (90.9)	109 (52.9)
EBL, mL [median (IQR)] *		550 (300–1200)	1400 (800–2000)	N/A	1000 (500–1600)
LOS, day [median (IQR)]		6 (4–10)	7 (6–9)	N/A	7 (5–9)
Postoperative complications		30 (31.6)	32 (36.0)	N/A	62 (33.7)
Early (90 days) post-operative mortality		6 (6.3)	4 (4.5)	N/A	10 (5.4)

*Statistically significant difference between the resection and transplant groups; ^Statistically significant difference between the transplant and removal groups; # Group does not enter the χ^2 analysis but is presented for reporting purposes; MELD score was calculated from laboratory values; *IQR*, interquartile range; *EBL*, estimated blood loss; *LOS*, length of hospital stay

the treatment of recurrences. These included radiation therapy, TACE, ablation, or re-resection. Overall, taking into account the cost of pre-operative bridging therapies and the cost of treatment of recurrences, the average overall cost of care was estimated to be $37,391 for resected patients vs $137,996 for patients in the transplantation group.

Discussion

HCC continues to be a major cause of cancer death around the world. It is one of few cancers for which both surgical resection and transplantation are treatment options. Despite these two management modalities, overall prognosis remains poor. Indications for liver resection have evolved due to reductions

Table 2 Survival estimates and survival rates at 3, 5, and 10 years for 206 Child-Pugh class A HCC transplantable patients who underwent either resection or transplantation, or were listed for transplant with HCC exception MELD points but were removed from the list, between 1992 and 2015

A. DFS from time of operation							
	DFS (m)		DFS rate (%)				
	Median	IQR	3 years	5 years	10 years	*p*, univariate	*p*, multivariate
Resection	33.0	15.6-N/A	48	44	31	< 0.001	0.01
Transplant	N/A	N/A	96	94	94		
Overall	N/A	26.5-N/A	71	68	60		
B. OS from time of operation							
	OS (m)		OS rate (%)				
	Median	IQR	3 years	5 years	10 years	*p*, univariate	*p*, multivariate
Resection	96.4	36.1–140.4	76	62	41	0.07	0.85
Transplant	133.5	77.2-N/A	82	77	53		
Overall	111.5	45.6–156.1	79	70	46		
C. OS from time of diagnosis							
	OS (m)		OS rate (%)				
	Median	IQR	3 years	5 years	10 years	*p*, univariate	*p*, multivariate
Resection	98.5	37.4–141.8	77	62	42	0.18	0.82
Transplant and removal	122.2	38.8-N/A	76	68	52		
Overall	98.6	37.4–142.7	76	65	45		

Disease-free survival (DFS) is calculated from the time of operation (A). Overall survival (OS) is calculated from the time of operation (B), or the time of diagnosis (C). *IQR*, interquartile range. *p* values for the comparison between groups was yielded by the log-rank test (univariate) or the backwards Cox model (multivariate)

in morbidity and mortality. Better surgical technique, anesthesia management, perioperative care, establishment of high-volume referral centers specializing in hepatobiliary surgery, and patient selection have resulted in a decrease in perioperative mortality rates to $\leq 5\%$.[18–20] Despite different treatment modalities, disease-free and overall survival are paramount to cancer patients.

During the last decades, survival after hepatic resection has improved. The 5-year overall survival rate following curative resection of an HCC in our series was 62%,

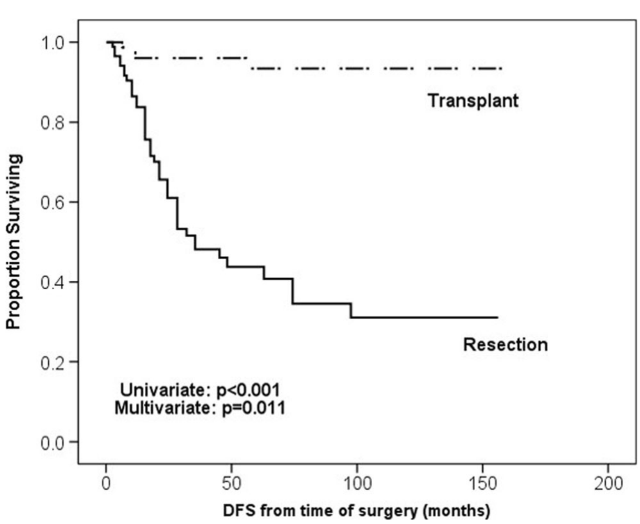

Fig. 1 Kaplan-Meier disease-free survival curves: Resection ($n = 95$) vs transplantation ($n = 89$) for hepatocellular carcinoma among patients with Child-Pugh A cirrhosis and within the Milan criteria. Disease-free survival (DFS) is calculated from the time of operation to recurrence. *p* values were derived from log-rank test (univariate) or Cox proportional hazards model (multivariate)

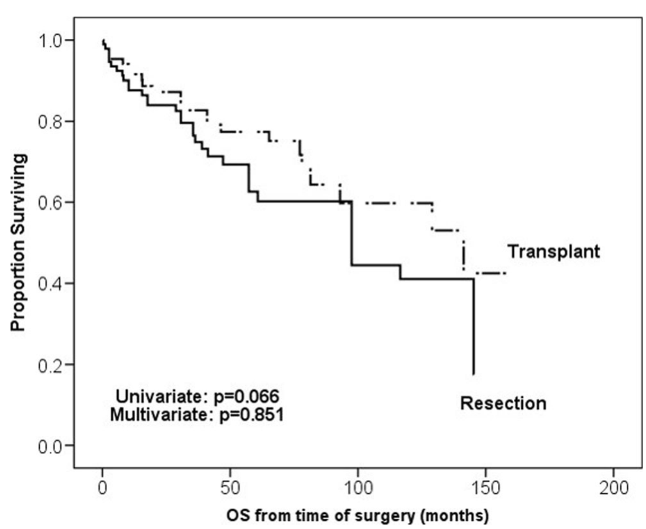

Fig. 2 Kaplan-Meier overall survival curves: Resection ($n = 95$) vs transplantation ($n = 89$) for hepatocellular carcinoma among patients with Child-Pugh A cirrhosis and within the Milan criteria. Overall survival (OS) is calculated from the time of operation to death. *p* values were derived from log-rank test (univariate) or Cox proportional hazards model (multivariate)

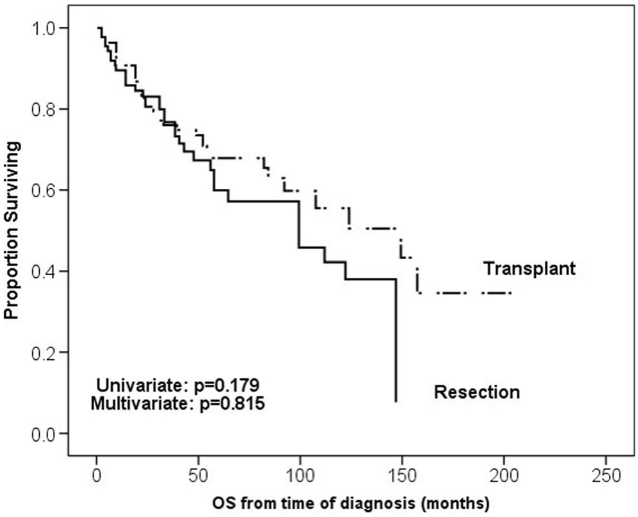

Fig. 3 Kaplan-Meier overall survival curves. Resection ($n = 95$) vs transplantation including removed patients ($n = 111$) for hepatocellular carcinoma among patients with Child-Pugh A cirrhosis and within the Milan criteria. Overall survival (OS) is calculated from the time of diagnosis to death. p values were derived from log-rank test (univariate) or Cox proportional hazards model (multivariate)

Table 3 A. Cost and frequency of pre-operative, operative, and post-operative procedures among 206 HCC Child-Pugh class A transplantable patients who underwent either resection or transplantation. B. Average overall cost of care, including the cost of pre-operative, operative, and post-operative procedures for patients who underwent either resection or transplantation

A.			
Procedures per group (*n*)			
Procedure	Cost	Resection	Transplant
Pre-operatively			
Ablation	$14,445.00	5	69
TACE	$16,729.00	5	23
Operatively			
Resection	$28,492.00	95	n/a
Transplantation	$122,286.00	n/a	89
Post-operatively			
Ablation	$14,445.00	19	0
TACE	$16,729.00	14	1
Radiotherapy	$19,082.00	5	0
Re-resection	$28,492.00	3	0
B.			
		Resection	Transplant
Average overall cost		$37,391	$137,996

Cost data were derived from the Agency for Healthcare Research and Quality (AHRQ)/Healthcare Cost and Utilization Project (HCUP) database. Ablation includes radio frequency, thermal, ethanol, microwave, and cryoablation

slightly higher than the 30–55% reported in multiple large series.[7,21–23] Despite oncologically sound operations, tumor recurrence is the main cause of treatment failure. The main risk factor for recurrence in resected patients is the remaining cirrhotic liver. The 5-year recurrence rate in our series was 56%, slightly better than other cohorts, which documented a 70–100% 5-year recurrence rate.[23,24] Thankfully, the options for treating recurrences are numerous including chemoembolization, yttrium 90, re-resection, radiation, and transplantation. A salvage transplant is the most attractive option for patients who have recurred in the liver, but is not always an option. Series by Poon et al. and Cherqui et al. documented that 80% of the HCC patients with recurrence after partial hepatectomy are transplant candidates,[25,26] and based on the large series by Cherqui et al.[26,] 5-year OS after salvage transplant for recurrent HCC was 87%, similar to patients with upfront transplantation. In 2005, Itamoto et al.[10] demonstrated that although patients with transplantable recurrences had a better prognosis than patients with advanced recurrences, the 5-year survival rate after diagnosis of the recurrence was only 31%.

Liver transplantation has the clear advantage of treating the underlying liver dysfunction, but is challenged by organ shortage. By removing the diseased liver and restoring the hepatic function, the literature and our series demonstrate an improved disease-free survival when compared to resection, thus suggesting that transplantation might be a better oncologic procedure. However, even with the increased use of living donor transplantation, the need for organs is unmet. Although the organ shortage affects HCC patients to a lesser degree given the HCC exception points system, the saved organs could be allocated to patients with other diseases who are in need of a liver.

Our series, as well as other series in the literature, despite the difference in DFS, were unable to document a survival benefit for patients who were resected or transplanted.[14,27] This could be explained in part by the efficacy of post-resection procedures for the treatment of recurrences in controlling the disease. While our cost analysis is crude and does not include actual real-time costs corrected for inflation, we are able to demonstrate that transplantation is significantly more expensive than resection as an initial intervention in Child-Pugh Class A patients radiographically within Milan criteria. The recurrence rates were higher for patients who were initially resected, but even when the cost of treating the recurrences was taken into account, the average total cost for patients receiving a transplant was significantly higher. We elected to use the most recent HCUP data instead of real-time MGH cost data, in order to generate more widely applicable contemporary results. Health care spending in the USA accounted for 17.8% of the gross domestic product in 2015 and is projected to rise to 19.9% by 2025.[28] Considering there is no improvement in overall survival, it is unclear whether such a significant increase in cost can be justified.

Conclusion

In conclusion, our series demonstrates that there was no difference in overall survival for Child-Pugh A patients within the Milan criteria undergoing resection vs transplantation. The overall cost per patient among those who received upfront transplant was significantly higher. In this era of organ shortage and cost containment, we should advocate for resection as the first line of treatment for patients with Child's A cirrhosis and HCC within the Milan criteria.

Author Contributions All authors approved the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. T.M. was involved in the conception and design of the study; the acquisition, analysis, and interpretation of data; and drafted the manuscript. D.X. participated in the design of the study; acquisition, analysis, and interpretation of the data; and drafted and revised the manuscript. M.Q. was involved in the conception and design of the study; the acquisition, analysis, and interpretation of data; and revised the manuscript critically for important intellectual content. R.P.-V. was involved in the conception and design of the study; the acquisition, analysis, and interpretation of data; and revised the manuscript critically for important intellectual content. L.C. was involved in the conception and design of the study; the acquisition, analysis, and interpretation of data; and drafted the manuscript. M.S.P. participated in the design of the study, analysis and interpretation of the data, and revised the manuscript critically for important intellectual content. J.T.A. participated in the design of the study, analysis and interpretation of the data, and revised the manuscript critically for important intellectual content. F.F. participated in the design of the study, analysis and interpretation of the data, and revised the manuscript critically for important intellectual content. U.B. participated in the design of the study, analysis and interpretation of the data, and revised the manuscript critically for important intellectual content. P.A.V. was involved in the design of the study, the acquisition and interpretation of data, and revised the manuscript critically for important intellectual content. N.E. was involved in the conception and design of the study, the acquisition and interpretation of data, and drafted and revised the manuscript. K.K.T. participated in the design of the study, analysis and interpretation of the data, and revised the manuscript critically for important intellectual content. D.B. was involved in the design of the study, the acquisition and interpretation of data, and revised the manuscript critically for important intellectual content. H.Y. was involved in the conception and design of the study; the acquisition, analysis, and interpretation of data; and drafted the manuscript. J.F.M. was involved in the conception and design of the study; the acquisition, analysis, and interpretation of data; and revised the manuscript critically for important intellectual content. D.C.C. was involved in the conception and design of the study; the acquisition, analysis, and interpretation of data; and drafted the manuscript. C.R.F. was involved in the conception and design of the study; the acquisition, analysis, and interpretation of data; and drafted and revised the manuscript critically for important intellectual content.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 2009;27:1485–1491.
2. El-Serag HB. Hepatocellular carcinoma: an epidemiologic view. J Clin Gastroenterol 2002;35:S72–78.
3. Monto A, Wright TL. The epidemiology and prevention of hepatocellular carcinoma. Semin Oncol 2001;28:441–449.
4. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7–30.
5. Shuto T, Hirohashi K, Kubo S, et al. Changes and results of surgical strategies for hepatocellular carcinoma: results of a 15-year study on 452 consecutive patients. Surg Today 1998;28:1124–1129.
6. Zhou XD, Tang ZY, Yang BH, et al. Experience of 1000 patients who underwent hepatectomy for small hepatocellular carcinoma. Cancer 2001;91:1479–1486.
7. Fan ST, Mau Lo C, Poon RT, et al. Continuous improvement of survival outcomes of resection of hepatocellular carcinoma: a 20-year experience. Ann Surg 2011;253:745–758.
8. Llovet JM, Bruix J, Fuster J, et al. Liver transplantation for small hepatocellular carcinoma: the tumor-node-metastasis classification does not have prognostic power. Hepatology 1998;27:1572–1577.
9. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–699.
10. Itamoto T, Nakahara H, Tashiro H, et al. Indications of partial hepatectomy for transplantable hepatocellular carcinoma with compensated cirrhosis. Am J Surg 2005;189:167–172.
11. Tanabe KK. New techniques of liver surgery. Semin Oncol 2006;33:S39–41.
12. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001;33:1394–1403.
13. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301–1314.
14. Proneth A, Zeman F, Schlitt HJ, et al. Is resection or transplantation the ideal treatment in patients with hepatocellular carcinoma in cirrhosis if both are possible? A systematic review and metaanalysis. Ann Surg Oncol 2014;21:3096–3107.
15. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–470.
16. HCUP National Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP) [database online]. *Insert City of Publication Here see notes*; 2012.
17. Price RA, Stranges E, Elixhauser A. Cancer Hospitalizations for Adults, 2009: Statistical Brief #125. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville (MD); 2006.
18. Makuuchi M, Kosuge T, Takayama T, et al. Surgery for small liver cancers. Semin Surg Oncol 1993;9:298–304.
19. Torzilli G, Makuuchi M, Inoue K, et al. No-mortality liver resection for hepatocellular carcinoma in cirrhotic and noncirrhotic patients: is there a way? A prospective analysis of our approach. Arch Surg 1999;134:984–992.
20. Jaeck D, Bachellier P, Oussoultzoglou E, et al. Surgical resection of hepatocellular carcinoma. Post-operative outcome and long-term results in Europe: an overview. Liver Transpl 2004;10:S58–63.
21. Bismuth H, Majno P, Adam R. Hepatocellular carcinoma: from ethanol injection to liver transplantation. Acta Gastroenterol Belg 1999;62:330–341.
22. Katz SC, Shia J, Liau KH, et al. Operative blood loss independently predicts recurrence and survival after resection of hepatocellular carcinoma. Ann Surg 2009;249:617–623.

23. Belghiti J, Panis Y, Farges O, et al. Intrahepatic recurrence after resection of hepatocellular carcinoma complicating cirrhosis. Ann Surg 1991;214:114–117.
24. Nagasue N, Kohno H, Chang YC, et al. Liver resection for hepatocellular carcinoma. Results of 229 consecutive patients during 11 years. Ann Surg 1993;217:375–384.
25. Poon RT, Fan ST, Lo CM, et al. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg 2002;235:373–382.
26. Cherqui D, Laurent A, Mocellin N, et al. Liver resection for transplantable hepatocellular carcinoma: long-term survival and role of secondary liver transplantation. Ann Surg 2009;250:738–746.
27. Dhir M, Melin AA, Douaiher J, et al. A Review and Update of Treatment Options and Controversies in the Management of Hepatocellular Carcinoma. Ann Surg 2016;263:1112–1125.
28. Centers for Medicare & Medicaid Services OotA. National Health Expenditure Projections 2016–2025 2017. Available at: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NationalHealthAccountsProjected.html. Accessed October 15, 2017, 2017.