ORIGINAL ARTICLE

Intention-to-treat analysis of liver transplantation, resection and thermal ablation for hepatocellular carcinoma in a single centre

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Abstract

Background: potentially curative treatment options for hepatocellular carcinoma (HCC) include liver transplantation (LT), liver resection (LR) and thermal ablation (TA). Long term intent-to-treat (ITT) analysis from a single-centre using all three modalities contemporaneously has not been published.

Methods: An ITT analysis was undertaken of all patients with HCC listed for LT, or have undergone LR or TA.

Results: 444 patients were identified; 145 were listed for LT (121 underwent LT), 190 underwent LR and 109 underwent TA. One and 3-year overall survival (OS) was similar among LT, LR and TA (88/77%, 88/64% and 95/72%) whereas 5-year OS was higher following LT than LR or TA (73% vs. 54% vs. 49%). Disease-free survival at 1- and 5-years was higher for LT (97% and 84%) than LR (66% and 35%) or TA (73%, and 19%).

Conclusion: LT offered the lowest rate of cancer recurrence and highest chance of long-term survival. Differences in outcome likely reflect a combination of cancer-related factors (AFP, micro- and macro-vascular invasion), patient-related factors (performance status, co-morbidities and psychosocial issues) and treatment type. Two thirds of patients treated by LR and three quarters treated by TA had HCC recurrence by 5 years, reinforcing the need for close long-term surveillance.

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Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related mortality worldwide and has the fastest growing cancer mortality rate, attributable to the current hepatitis C and obesity epidemics.[1] Almost 750,000 people die from HCC each year, most within the Asia–Pacific region.[2] Most cases of HCC develop in the presence of underlying chronic liver disease. The routine screening of patients at risk of developing HCC has enabled the detection an early stage when curative interventions may be possible. Surgery, either replacing the whole liver by transplantation, or removing part of the liver by resection, or thermal ablation in a subset of patients with small targetable tumours, are the only treatment modalities with the potential to cure HCC.[3,4]

Liver resection (LR) has traditionally been considered the preferred method of treatment for patients with HCC with preserved liver function and absence of portal hypertension. Unfortunately, only a minority of patients meet these criteria. Liver transplant (LT) is the treatment of choice in patients with limited HCC and poor underlying liver function.[5,6] LT also has the advantage of lowering the risk of metachronous tumours by eradicating the underlying field defect but feasibility of LT as first-line treatment is limited by the availability of donor organs. Furthermore a proportion of patients experience tumour progression on the waiting list despite loco-regional therapies. LT is also associated with long term problems such as surgical complications, graft rejection, recurrence of primary liver disease and complications related to lifelong immunosuppression. Thermal

ablation (TA), including radiofrequency (RFA) and microwave ablation (MWA), are relatively new technologies that offer potential advantages over LT and LR, such as lower procedure-related morbidity, mortality and cost. Also, TA can be performed via a percutaneous approach, laparoscopically, or at open surgery. The chief technical limitations of TA are incomplete ablation leading to lesion recurrence, related to tumour size and proximity to major vessels, and thermal injury to important structures. Another major limitation of both LR and TA is the long-term risk of metachronous tumours arising in the remnant liver.

Many previous reports have compared LT with LR, and LR with TA, but there have not been any published studies that have analysed all three modalities contemporaneously in a single institution. The present study is an intent-to-treat (ITT) analysis of outcome for all patients with HCC treated with curative intent at a single centre, where all three modalities were available.

Patients and methods

Study design

This study was an ITT analysis of all patients, more than 18 years of age, with first presentation of HCC that were treated with curative intent at Auckland City Hospital, Auckland, New Zealand since the inception of the New Zealand Liver Transplant Unit in February 1998, to December 2014.

All patients were discussed in a dedicated HCC multidisciplinary meeting and treatment allocation determined as follows. Patients with anatomically resectable tumours and preserved liver function with no portal hypertension, and no prohibitive co-morbidities, were offered LR as first treatment. Those with HCC within University of California San Francisco (UCSF) criteria[6] who were not resectable either because of tumour distribution or severity of underlying liver disease, and who otherwise had no contraindications to transplantation, were offered LT as first treatment. Those with targetable lesions who were not LR or LT candidates were offered TA as first treatment. The treatment modality for patients with very early HCC (Barcelona Clinic Liver Cancer[4] (BCLC) stage 0) that was both resectable and targetable for TA was determined by surgeon and/or patient preference.

Patients were stratified by their primary treatment modality to either LT, LR, or TA (Fig. 1). The LT group included all patients who were placed on the waiting list with the intent to undergo LT. Reasons for removing patients from the LT waitlist included tumour progression beyond transplant criteria, hepatic decompensation (died while on the waiting list), psychosocial issues (substance abuse, psychiatric illness), and co-morbidities

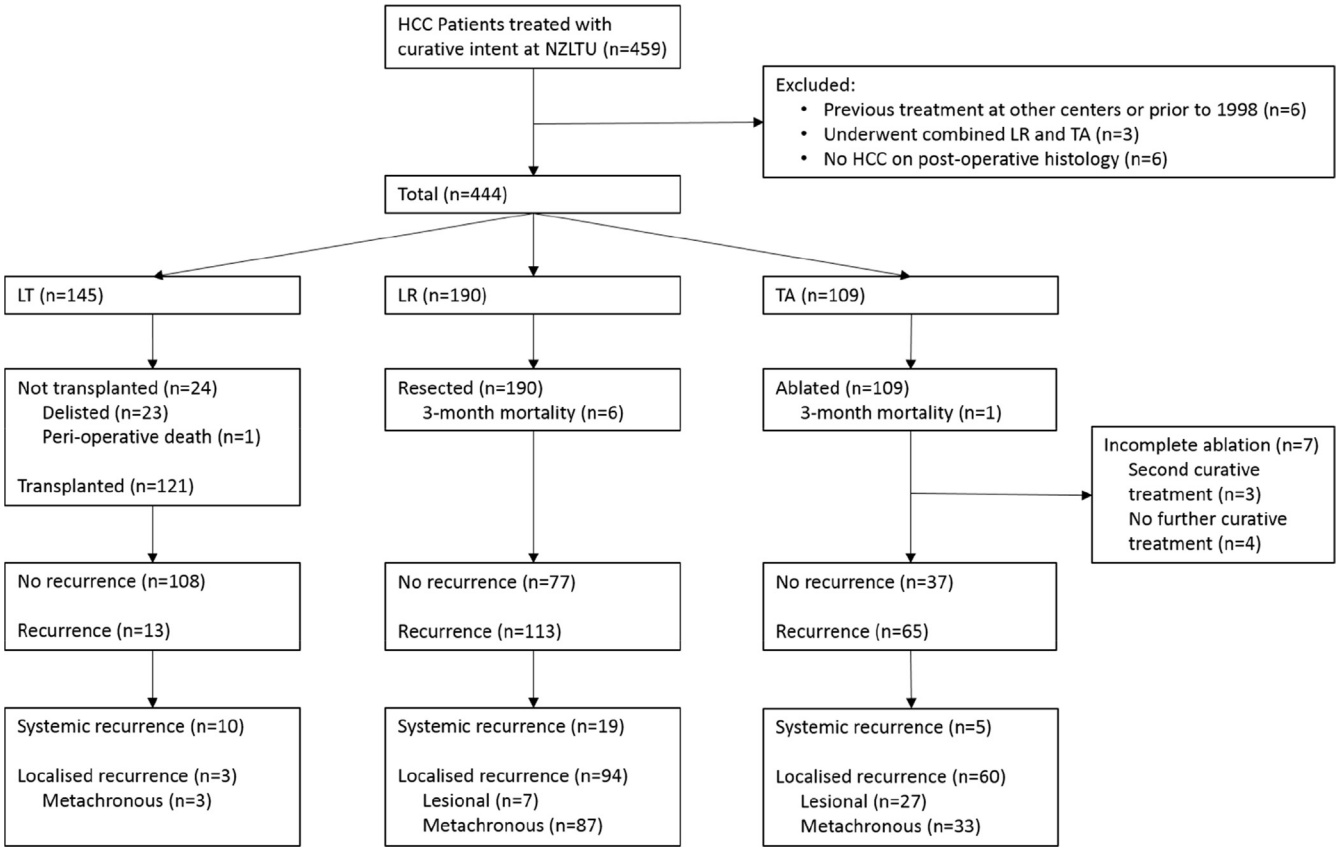

Figure 1 Overview of treatment and recurrence for all patients undergoing LT, LR or TA for HCC included in the study

(development of comorbid diseases that precluded LT). The TA group included patients who underwent RFA or MWA by the percutaneous, laparoscopic or open approach.

Patients who underwent LR (n = 8) or TA (n = 3) but were subsequently listed for LT for the treatment of recurrent HCC were analysed according to their initial treatment allocation. Five patients listed for LT who received first curative treatment for HCC at other centres were excluded from the study. Three patients who underwent combined LR and TA were excluded from the analysis. Patients found not to have HCC on post-operative histopathology were excluded from the study (five LT recipients and one LR patient).

Patients were identified from a prospective database maintained by the New Zealand Liver Transplant Unit, and electronic query using ICD-10 codes from the prospective clinical databases in the Departments of Pathology, Surgery and Radiology. The results were cross-referenced to ensure all patients were identified.

The diagnosis of HCC was based on typical imaging characteristics using computed tomography (CT) and/or Magnetic Imaging Resonance dynamic contrast techniques.[3,7–12] A serum alpha fetoprotein (AFP) level of >200 mmol/L was confirmatory. Biopsy of the tumour was performed only in cases which did not fulfil AASLD criteria. Pathological confirmation was obtained from explant or resected specimens for patients who underwent LT or LR, and in those TA patients treated with "biopsy and ablate".

All data were collected from a prospective electronic hospital clinical information system. Model for End-Stage Liver Disease (MELD) scores[13] were prospectively collected in the LT patients and was calculated retrospectively in TA and LR patients. Patients diagnosed with HCC by regular 6 monthly ultrasound scan and/or alpha fetoprotein were classified as "screen detected". Patients were classified as 'non-screen detected' if HCC was diagnosed following investigations for other pre-existing conditions, or following investigations for new onset symptoms or abnormal laboratory or clinical examination findings.

The severity of liver disease was assessed using the Child-Pugh classification,[14] MELD scores and Albumin-Bilirubin (ALBI) grade.[15] Portal hypertension was identified by the presence of varices or splenomegaly on imaging, varices seen at endoscopy, thrombocytopenia (platelet <100 × 109/L), or the presence of a portal-hepatic vein pressure gradient of >10 mmHg. Tumour stage was determined using the Cancer of the Liver Italian Program (CLIP) score,[16] Okuda score,[17] BCLC and Hong Kong Liver Cancer (HKLC) staging systems.[18]

Patients undergoing TA had CT at 6 weeks to check adequacy of ablation. Patients treated by LR or TA had CT at 3 months, 6 months, then 6 monthly for 2 years, then ultrasound 6 monthly thereafter.

Study outcomes

The primary outcome of the study was overall survival (OS) utilizing an ITT model, measured either from the date of listing for LT, or the date of treatment for LR or TA, to the date of last censoring or death. Disease-free survival (DFS) was calculated from the time of treatment by LT, LR or TA to the date of recurrence, last censoring or death.

Prognostic variables

Seventeen variables were included in the univariate analyses for OS, DFS and recurrence: age, gender, ethnicity, aetiology of liver disease, presence of cirrhosis, portal hypertension, MELD score, platelet count, ALBI grade, AFP, Eastern Cooperative Oncology Group Performance Status[19] (ECOG PS), screen detected vs. non-screen detected, UCSF criteria, histological tumour differentiation, the presence of macrovascular or microvascular invasion, and the method of treatment. Prognostic analyses for DFS or recurrence excluded patients who had DFS of zero, including 24 patients who did not undergo LT, and 7 patients who had incomplete ablation.

Statistical analysis

Categorical variables were expressed as valid percentages and compared using the chi-squared test or Fisher's exact test as appropriate. Continuous normally-distributed variables were expressed as the mean ± standard deviation and compared using analysis of variance; non-parametric data were expressed as median with range and compared using the Kruskal–Wallis test. Patients with missing data were excluded from each respective analysis. Survival and recurrence were estimated using the Kaplan–Meier method, as previously described overall survival was analysed with respect to intention-to-treat groups and recurrence as per treatment groups. Univariate analyses were performed using Cox proportional hazards model to determine variables associated with survival and recurrence. Factors deemed clinically significant or those that achieved $p < 0.1$ on univariate analysis were entered into a multivariate analysis model, again using Cox proportional hazards. Those factors with p-values of <0.05 were considered as independently predictive for the outcome. All statistical analyses were performed using STATA (Ver 13.1, Statacorp, TA, US).

Results

A total of 444 consecutive patients underwent first curative treatment for HCC by LT, LR or TA and were included in the final analysis (Table 1). Initial curative treatment was LT in 145 patients, LR in 190 and TA in 109.

Liver transplantation

One-hundred and forty-five patients were listed for LT, 99% had underlying cirrhosis. Nineteen patients exceeded Milan criteria but were within the UCSF criteria. The median waiting time to transplant was 3.0 (range 0–19.7) months. 86 patients (56%) received one or more pre-transplant loco-regional therapies to prevent tumour progression, including transarterial chemoembolization

Table 1 Characteristics of the 444 HCC patients treated with curative intent by LT, LR and TA

Variable	LT (n = 145)	LR (n = 190)	TA (n = 109)
Age (years)	55.0 ± 6.5	58.7 ± 11.6	62.6 ± 9.6
Sex (m/f)	119/26	152/38	87/22
Ethnicity: Asian/European/MPI/others	13/77/53/2	55/44/87/4	24/53/30/2
Aetiology: HBV/HCV/alcohol/others	55/64/9/17	108/29/8/45	39/43/18/9
Cirrhosis	144	95	99
Portal hypertension	134	40	76
Child-Pugh stage (A/B/C)	81/40/24	189/1	99/10
MELD score	10.7 ± 3.7	7.5 ± 1.5	8.7 ± 2.7
Analytical data			
Platelet count (10^9/L)	109 ± 61	218 ± 100	134 ± 61
Serum albumin (g/L)	34.7 ± 6.4	40.9 ± 4.1	39.5 ± 4.8
Serum bilirubin (μmol/L)	32.5 ± 25	10.3 ± 6.3	15.8 ± 13.4
ALBI grade: 1/2/3	38/76/31	144/42	63/45/1
AFP (μg/L)	30.8 (1.2–24,186)	44.9 (0.9–35,000)	3.5 (1.1–264)
ECOG performance status: 0/1/2	112/28/5	175/14/1	79/30
Screen detected	138	136	103
Number of tumours: 1/2/3/4	98/36/11	168/15/6/1	99/10
Within UCSF criteria	145	129	108
BCLC stage: A/B/C/D	86/15/20/24	151/18/21	76/2/31
HKLC stage: I/IIa/IIb/IIIa/IIIb/Va	72/47/1/1/0/24	104/7/75/0/2/1	70/38/1
Okuda stage (1/2/3)	80/50/15	182/8	99/10
CLIP stage: A/B/C/D	43/54/39/9	112/55/12/1	84/20/4
Pathological data			
Histological differentiation (I/II/III)[a]	20/66/19	19/91/70	–
Macrovascular invasion	2	7	–
Microvascular invasion	35	73	–

Normally distributed variables are presented as mean ± standard deviation and non-normally distributed variables are presented as median (range).
Abbreviations: MPI, Maori and Pacific Island; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-stage Liver Disease; ALBI, Albumin-Bilirubin; AFP, Alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group; UCSF, University of California, San Francisco; BCLC, Barcelona Clinic Liver Cancer; HKLC, Hong Kong Liver Cancer; CLIP, Cancer of the Liver Italian Program.
[a] I, Well; II, moderately; and III, poorly differentiated HCC.

(TACE) in 76, TA in 5 and combination TACE and TA in 5 patients. Of the 145 patients listed for LT, 24 patients did not undergo LT due to tumour progression (n = 19), psychosocial issues (n = 2), hepatic decompensation (n = 1) and cerebral infarction (n = 1). One patient died from an anaesthesia-related complication during liver transplantation. Therefore, the intention-to-treat analysis for overall survival included 145 patients listed for transplantation but the analysis for recurrence post-transplant included 121 patients.

Survival. After a median follow-up of 49.8 (range 4.3–198.1) months, 42 patients (29%) had died. The most frequent causes of death are summarized in Table 2. The OS from an intention-to-treat perspective at 1, 3, and 5 years was 88.3%, 76.9%, and 72.9%, respectively (Fig. 2a). After excluding the 24 patients who were listed but never received LT, the OS at 1, 3, and 5 years was 96.7%, 90.5%, and 86.8%, respectively.

Recurrence. Thirteen recurrences were observed at a median time of 15.7 months post-transplant (range 0.9–66.3). The 1-, 3- and 5-year probability of HCC recurrence after transplantation was 3.3%, 7.1% and 10.9%, respectively, with the DFS at 1, 3, and 5 years being 96.7%, 89.6%, and 84.6%, respectively (Fig. 2b).

Liver resection

One-hundred and ninety patients underwent LR, of whom 15 (7.9%) had no underlying chronic liver disease. There were no 'drop-outs' while waiting for resection. Sixteen patients (8.4%) underwent pre-operative portal vein embolization to induce hypertrophy of future liver remnant.[20] Ten patients (5.3%) underwent pre-operative down-staging with TACE. Of the patients that underwent LR, 181 (95%), 3 (2%) and 6 (3%) had an R0, R1 and R2 resection, respectively.

Table 2 Causes of death

	LT (n = 145)	LR (n = 190)	TA (n = 109)
Mortality before treatment	21[a]	–	–
3-month treatment-related mortality	1	6	1
Mortality during follow-up			
Tumour recurrence	10	74	31
Hepatic failure	4	–	4
Other	6[b]	7[c]	2[d]
Total deaths	42 (29%)	87 (46%)	38 (35%)

[a] Tumour progression (20), hepatic failure (1).
[b] Cancer of the skin (2), cancer of the breast (1), sarcoma (1), myocardial infarction (2).
[c] Cancer of the skin (1), cancer of the colon (1), cancer of the stomach (1), pneumonia (1), cancer of the lung (3).
[d] Cancer of the oesophagus (1), cancer of the lung (1).

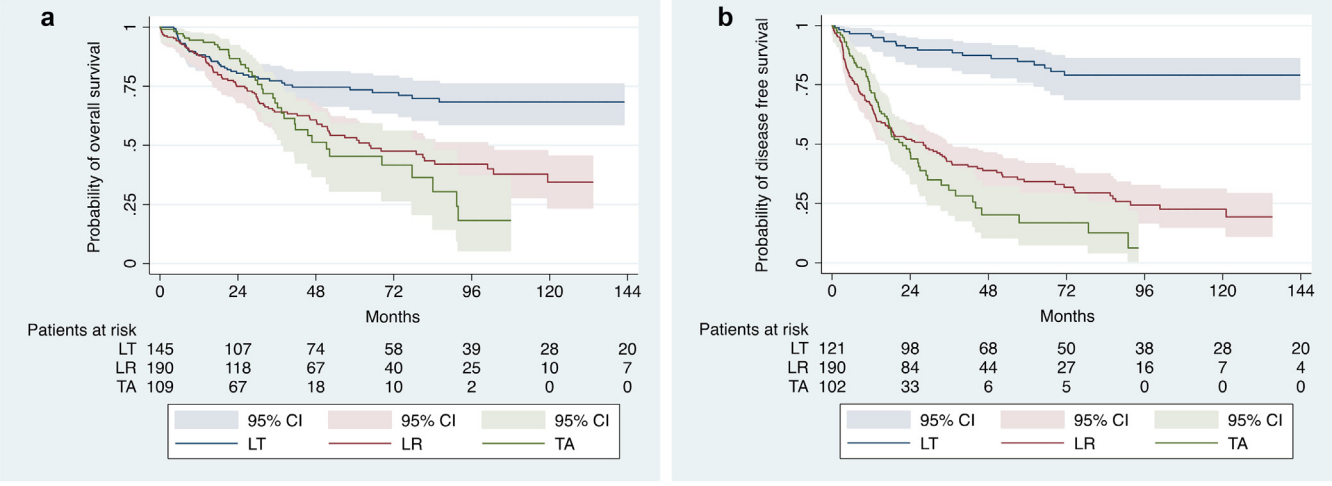

Figure 2 (a) Intention-to-treat overall survival among the 444 HCC patients treated with curative intent. (b) Per treatment disease-free survival of 413 HCC patients who underwent LT, LR or TA. Twenty-three LT delisted patients, 1 peri-operative LT death and 7 incomplete TA patients excluded

Survival. The median follow-up time was 32.2 (range 0.1–189.5) months. The OS probability at 1, 3, and 5 years were 87.9%, 64.3% and 53.8%, respectively. 87 patients (45.8%) died during follow -up. The main cause of death was tumour recurrence in 72 patients, 3-month operative mortality accounted for 6 deaths (3.2%).

Recurrence. One hundred and thirteen recurrences were observed at a median time of 11.6 months post-resection (range 1.4–99.3). The 1-, 3- and 5-year probability of HCC recurrence after resection was 30.6%, 54.6% and 61.7%, respectively, with the DFS at 1, 3, and 5 years being 66.3%, 42.8%, and 34.7%, respectively.

Eight patients (4.2%) underwent salvage transplantation following LR. Median time to recurrence post-LR was 2.2 (1.0–2.9) years. Five of the 8 patients that underwent salvage LT remained recurrence free at the end of the follow-up period, with a median overall follow-up of 5.6 (3.0–10.2) years. One patient died from an anaesthesia-related complication during liver transplantation. Two patients died due to tumour recurrence at 4 years and 4.4 years post-LT.

Thermal ablation

One-hundred and nine patients underwent thermal ablation by either RFA (n = 50) or MWA (n = 59). There were no 'drop-outs' while waiting for ablation. The median tumour size was 2.4 cm (range 0.5 cm – 5 cm). Twenty-three patients (21.1%) were treated with combination TA and TACE. Follow-up imaging at 6-weeks post-treatment demonstrated residual viable tumour in 7 patients (6%), of whom 2 were retreated with TA and 1 underwent resection. The 7 patients with incomplete ablation were excluded from disease free survival and recurrence analyses.

Survival. The median follow-up time was 26.9 (range 0.4–107.9) months. The OS probability at 1, 3, and 5 years were 94.5%, 72.4% and 49.1%, respectively. 38 patients (34.9%) died

during follow-up. The main cause of death was tumour recurrence in 31 patients, 3-month treatment mortality accounted for 1 death (0.9%).

There was no difference in OS or DFS between patients that underwent RFA (n = 50) or MWA (n = 59; HR 1.72 and 1.44; p > 0.05).

Recurrence. Sixty-five recurrences were observed at a median of 14.0 (range 1.3–89.7) months following TA. The 1-, 3- and 5-year probability of HCC recurrence after ablation was 26.6%, 66.6% and 78.2%, respectively, with the DFS at 1, 3, and 5 years being 72.6%, 33%, and 19.2%, respectively.

Three patients (2.8%) underwent salvage LT following TA. Median time to recurrence post-TA was 7.6 (5.1–10.3) months. All 3 patients remained recurrence free at the end of the follow-up period, with a median overall follow-up time of 2.9 (2.5–3.1) years.

Survival and recurrence comparison

OS was higher at 5 years in the LT group, compared to LR or TA, but not at 1 and 3 years (Fig. 2a). The OS of patients undergoing LT was significantly longer than those patients within UCSF criteria that underwent LR (n = 131; HR 0.255, p < 0.001). OS between LR and TA were not different.

The LT group had higher DFS (Fig. 2b) and lower recurrence rates at 1, 3 and 5 years as compared to LR or TA, with no difference between the LR and TA groups.

Prognostic factors

Overall Survival: On univariate analysis, 8 baseline variables were associated with higher OS (Table 3). Three variables were found to be independent predictors of OS in the multivariate analysis (Table 4) – ECOG status: PS 2 compared to PS 0; (HR 3.3, $p = 0.048$), serum AFP (HR 1.00004, $p = 0.003$) and treatment group: LR compared to LT (HR 2.1, $p = 0.004$) or TA compared to LT (HR 2.1, $p = 0.003$).

Disease Free Survival: Ten variables were found to have prognostic value for DFS in the univariate analysis. In the multivariate analysis, treatment group was the only variable associated with DFS and recurrence among the entire cohort (Table 4).

Among LT and LR patients, macrovascular invasion or microvascular invasion on histology was associated with worse OS (HR 4.1, $p = 0.002$ and HR 1.8, $p = 0.022$, respectively) and DFS (HR 4.4, $p = 0.002$ and HR 1.6, $p = 0.021$, respectively), as well as higher likelihood of recurrence (HR 6.1, $p < 0.001$ and HR 1.7, $p = 0.019$, respectively).

Discussion

This is the first single-centre study to report ITT long-term outcomes of all three curative modalities, LT, LR and TA, used concurrently in consecutive patients presenting with HCC. Overall and DFS were significantly better among patients listed for LT, but was not significantly different between LR and TA. ECOG PS-2 and elevated serum AFP were independently associated with worse OS among all patients. Among those treated with LT and LR the presence of macrovascular or microvascular invasion was also associated with worse OS and DFS and a high rate of recurrence.

LR has traditionally been the treatment of choice for HCC in either patients without cirrhosis or patients with cirrhosis with well-preserved liver function and without significant portal hypertension. Long term survival is adversely influenced by the presence of portal hypertension, elevated bilirubin level, and tumour stage.[21,22] Five-year survival of 70% can be achieved in the best selected patients.[21–23] With one of the largest single-centre LR cohorts in the Western world, we demonstrated a 5-year OS of 54%. Most of the data for resection of HCC beyond BCLC stage A comes from Asia, reporting 5-year OS of 30–40%[22,24] and is even lower in CPS B patients with multiple tumours.[22] Recurrence occurs in approximately 50%–70% of patients treated with LR by 3 and 5 years, respectively.[25] We demonstrated similar recurrence rates of 55% and 62%.

The efficacy of TA is dependent on tumour size, with the best long term results observed in patients with small tumours.[26,27] Patients with a single HCC $\leq$ 2 cm diameter treated by RFA have a reported 5-year OS of 47–68%, and a recurrence rate of 80% at 5 years.[28,29] In our study where consecutive patients treated with TA were included, not limited by single tumour or size $\leq$2 cm, we showed similar results with a 49% 5-year OS and 79% recurrence at 5 years. Post-ablation patients require close surveillance to facilitate early detection of marginal tumour recurrence in order to facilitate salvage treatment. In our series, of those patients who recurred post-ablation (n = 65) over half went on to have further curative treatments, including 4 patients (6.2%) who subsequently underwent LT.

When evaluating the outcomes after LT, it is important to use an ITT approach, as the presence of waiting list drop-outs significantly diminishes the long-term outcomes. Llovet and colleagues[21] were the first to quantify this in their study in 1999, where they showed that drop-out on the waiting list was the sole prognostic factor for worse OS among patients selected for LT, and a 23% drop-out rate resulted in 54% survival at 2 years, compared to 84% at 2 years among transplanted patients (p < 0.003). Their results also showed that the best resection candidates, those with no portal hypertension and normal bilirubin, had a better survival of 74% at 5 years when compared to LT (p = 0.02).[21] Since then, there have been more single-centre studies reporting long term outcomes following LT-listing or LR.[30–37] Six of these studies showed no statistically significant survival advantage of transplant listing when compared to immediate treatment with LR.[30–35] Most of these studies[30–33,35] demonstrated a relatively low 5-year ITT OS of 52% or less among the LT group, which is attributable to a relatively large proportion, between 31% and 33%, of LT patients being delisted,[30,31,35] as well as higher tumour recurrence

Table 3 Univariate analysis of predictors of overall survival, disease-free survival, and recurrence

Variables	Overall Survival (n = 444)		Disease-free Survival (n = 413)[b]		Recurrence (n = 413)[b]	
	Hazard Ratio	*p* value	Hazard Ratio	*p* value	Hazard Ratio	*p* value
Age (years)	1.02	0.007	1.03	0.001	1.03	0.001
Male Gender	0.89	0.515	1.05	0.772	1.16	0.436
Ethnicity						
Asian	1	–	1	–	1	–
European	1.11	0.633	0.77	0.165	0.72	0.099
MPI	1.38	0.144	0.96	0.816	0.95	0.784
Other	0.65	0.556	0.58	0.359	0.62	0.416
Primary Liver disease						
Alcohol	1	–	1	–	1	–
HBV	0.81	0.459	0.91	0.705	1.00	1.00
HCV	0.64	0.152	0.71	0.206	0.75	0.325
None	1.78	0.180	1.78	0.134	1.90	0.116
Other	0.91	0.782	0.97	0.911	0.92	0.809
Cirrhosis	0.78	0.143	0.77	0.076	0.71	0.031
Portal hypertension	0.88	0.415	0.67	0.004	0.62	0.001
MELD						
<9	1	–	1	–	1	–
9–15	1.10	0.599	0.82	0.229	0.72	0.064
>15	0.92	0.817	0.46	0.065	0.25	0.018
Platelet count (10^9/L)	1.001	0.290	1.001	0.024	1.002	0.008
ALBI grade						
1	1	–	1	–	1	–
2	1.006	0.973	0.75	0.048	0.74	0.048
3	0.61	0.137	0.28	0.001	0.13	0.001
Serum AFP (μg/L)	1.00002	0.093	1.00001	0.485	1.000	0.384
ECOG performance status						
0	1	–	1	–	1	–
1	1.02	0.929	1.13	0.486	1.04	0.826
2	2.8	0.043	1.13	0.496	1.07	0.926
Screen detected	0.67	0.045	0.64	0.01	0.59	0.003
Within UCSF criteria	0.56	0.003	0.54	0.001	0.52	0.001
Histological differentiation[a]						
Well	1	–	1	–	1	–
Moderate	1.39	0.347	1.37	0.280	1.59	0.174
Poor	2.71	0.004	2.62	0.001	3.39	0.001
Macrovascular invasion[a]	6.37	0.001	6.19	0.001	7.95	0.001
Microvascular invasion[a]	1.85	0.002	1.84	0.001	2.09	0.001
ITT Group						
LT	1	–	1	–	1	–
LR	2.09	0.001	6.00	0.001	9.27	0.001
TA	1.97	0.003	7.34	0.001	11.59	0.001

Abbreviations: MPI, Maori and Pacific Island; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-stage Liver Disease; ALBI, Albumin-Bilirubin; AFP, Alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group; UCSF, University of California, San Francisco; ITT, intention-to-treat; LT, liver transplant; LR, liver resection; TA, thermal ablation.

[a] TA patients excluded.

[b] 23 LT delisted patients, 1 peri-operative LT death and 7 incomplete TA patients excluded.

Table 4 Multivariate analysis of predictors of overall survival, disease-free survival, and recurrence

Variables	Overall Survival (n = 444)		Disease-free Survival (*n = 413*)[b]		Recurrence (n = 413)[b]	
	Hazard Ratio	*p* value	Hazard Ratio	*p* value	Hazard Ratio	*p* value
Age (years)	1.01	0.193	1.01	0.153	1.004	0.591
Ethnicity						
Asian	1	–	1	–	1	–
European	1.3	0.244	1.14	0.528	1.08	0.718
MPI	1.6	0.061	1.34	0.135	1.32	0.173
Other	0.3	0.203	0.66	0.590	0.65	0.586
Cirrhosis	–	–	1.21	0.374	1.22	0.364
hypertension	–	–	1.39	0.133	1.39	0.143
MELD						
<9	1	–	1	–	1	–
9–15	1.3	0.189	1.18	0.376	1.07	0.720
>15	1.1	0.783	1.71	0.280	1.22	0.762
Platelet count (10^9/L)			0.99	0.844	0.99	0.888
ALBI grade						
1	–	–	1	–	1	–
2	–	–	1.0009	>0.99	1.02	0.914
3	–	–	1.05	0.919	0.81	0.770
Serum AFP (μg/L)	1.00004	0.003	1.00003	0.145	1.00002	0.248
ECOG performance status						
0	1	–	–	–	–	–
1	1.1	0.818	–	–	–	–
2	3.3	0.048	–	–	–	–
Screen detected	0.8	0.415	0.74	0.160	0.71	0.117
Within UCSF criteria	0.8	0.293	0.87	0.513	0.86	0.515
Histological differentiation[a]						
Well	1	–	1	–	1	–
Moderate	0.8	0.520	0.99	0.974	1.26	0.578
Poor	1.4	0.372	1.47	0.269	1.97	0.106
Macrovascular invasion[a]	4.1	0.002	4.4	0.002	6.09	<0.001
Microvascular invasion[a]	1.8	0.022	1.62	0.021	1.7	0.019
ITT Group						
LT	1	–	1	–	1	–
LR	2.1	0.004	9.74	<0.001	13.1	<0.001
TA	2.1	0.003	10.1	<0.001	12.7	<0.001

Abbreviations: MPI, Maori and Pacific Island; MELD, Model for End-stage Liver Disease; ALBI, Albumin-Bilirubin; AFP, Alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group; UCSF, University of California, San Francisco; ITT, intention-to-treat; LT, liver transplant; LR, liver resection; TA, thermal ablation.
[a] TA patients excluded.
[b] 23 LT delisted patients, 1 peri-operative LT death and 7 incomplete TA patients excluded.

rates of 31%–50% among patients transplanted.[31,35] In one study 15% of the LT group died due to graft failure which contributed to 54% of all LT deaths.[33] Two studies demonstrated superior survival in the ITT LT group when compared to LR.[36,37] In the study by Sapisochin *et al.*,[36] patients who were assigned to the LT group had significantly better OS after 4 years of follow-up. This difference persisted at 10 years with an overall survival of 49% among patients who underwent LT compared to 33% in the LR group (p = 0.002). The later OS advantage among LT patients was similar to our findings, reflecting the high incidence of metachronous tumours following LR.

In our study, patients listed for LT have a survival advantage at 5 years when compared to LR and TA, despite a delisting rate of 16%. The 5-year OS was 73% from time of listing (i.e. ITT) and 87% from time of transplant. If the supply of donor organs were unlimited LT would be the treatment of choice for cirrhotic patients within transplant criteria and otherwise eligible, as LT appeared to provide the lowest rate of HCC recurrence and best chance of long-term survival. The long-term complications of LT including immunosuppression were not measured in our study, however the metric of OS does incorporate death from any cause, not just those related to cancer recurrence.

There was no statistically significant difference in OS and DFS between LR and TA. Two randomized controlled trials[38,39] from China have shown similar OS and DFS among RFA and LR patients with solitary HCC $\leq$5 cm[38], or up to 2 HCCs each <4 cm.[39] One previous randomized controlled trial comparing RFA and LR reported superior OS and DFS after LR for HCC within Milan criteria but the conclusions are limited by concerns regarding patient selection, ablation technique, sample size, and differences in loss to follow-up between the RFA and LR groups.[40] Previous retrospective studies have also produced variable conclusions.[41–46] Overall, recent evidence suggests TA is a cost-effective, low morbidity and potentially non-inferior treatment alternative to LR for patients with small (<3 cm) tumours.[26,27,41–43]

Patients treated with LR or TA have a high risk of tumour recurrence within the diseased remnant liver and this was the leading cause of death after LR or TA in our study. We demonstrated a 62% and 78% chance of tumour recurrence at 5 years among patients treated with LR and TA, respectively. Regular surveillance after LR or TA for margin recurrence or the development of metachronous tumour is therefore important. In a recent study by Bhangui *et al.*[47] one third of patients with recurrence following LR were able to undergo salvage LT and these patients achieved short and long-term outcomes comparable to those who underwent primary LT. Moreover, it has been shown that a second resection strategy for patients deemed resectable and transplantable at both the time of primary resection and recurrence can achieve similar 5-year OS to the salvage LT strategy, although salvage LT still achieve better DFS.[48]

Our study has a number of limitations. The study focused on patients who were judged eligible for curative treatment whereas the majority of patients with a new diagnosis of HCC are beyond curative treatment. Treatment allocation was based on a combination patient-related, liver-related and cancer-related factors. The three treatment groups are therefore not directly comparable. Multivariate analysis may account for some but not all of these factors. Treatment allocation is necessarily constrained by the availability of donor organs for LT and New Zealand had a relatively low deceased donor rate of approximately 10 per million per annum during the study period.[49] Histology was reported in patients undergoing LR or LT, we were unable to include the TA group as tumour biopsy was not routinely acquired. LT and LR were mature surgical treatments throughout the study period, but thermal ablation was a technique in evolution. There was also a transition from RFA to MWA, a number of approaches used (percutaneous, laparoscopic and open) and some larger tumours treated with combination therapy (TACE/ablation). Advances in intra-procedural imaging may reduce the incidence of incomplete ablation that leads to the problem of lesion recurrence. Furthermore, the confidence intervals around survival estimates for TA beyond 3 years are wide due to relatively low number at risk.

The unique aspects of the study are that it describes long term outcome in a large consecutive series of patients managed in a single institution that provides a national service that offers all potentially curative treatment modalities. Salient aspects of the New Zealand environment include endemic levels of HBV as well as HCV infection in the population and a relatively low deceased donor rate (circa 10/million/annum), which has in turn driven treatment allocation towards non-transplant options whenever feasible. The best outcomes in terms of recurrence and survival were obtained with transplantation and it is reasonable to suppose that some patients who were within transplant criteria but treated with resection or ablation for pragmatic reasons experienced higher rates of recurrence as a result. This raises the interesting and challenging question of whether it would be more effective to offer such patients transplantation in future or to expand criteria as the supply of organs increases and/or demand for transplantation for decompensated HCV decreases. These are questions that each jurisdiction must address based on their own unique circumstances, informed using longitudinal data analysed on an intent-to-treat basis, as described here.

In summary, this study reports ITT analysis of consecutive patients with HCC treated with curative intent in a single institution where all curative modalities were able to be offered. We have demonstrated that patients listed for LT had the lowest recurrence rate and best chance of long term survival but LT is constrained by organ availability as well as cancer and patient-related eligibility criteria. OS and DFS were comparable between LR and TA but both treatments are associated with high rates of tumour recurrence in the long term. Regular surveillance of these patients is necessary to enable salvage treatments, including salvage LT, to be offered to eligible patients.

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Conflict of interest

None declared.

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