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Multimodal therapy for hepatocellular carcinoma: A complementary approach to liver transplantation

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ABSTRACT

Objective. To evaluate the survival benefit of multimodal therapy for the treatment of HCC. **Background.** Orthotopic liver transplantation (OLT) is considered the treatment of choice for selected patients with hepatocellular carcinoma (HCC). However, donor organ shortages and patients whose HCCs exceed OLT criteria require consideration of alternate therapeutic options such as hepatic resection, radiofrequency ablation (RFA), ethanol injection (EI), transarterial chemoembolization (TACE), and chemotherapy (CTX). This study was performed to evaluate the survival benefit of multimodal therapy for treatment of HCC as complementary therapy to OLT. **Methods.** A retrospective review was conducted of HCC patients undergoing therapy following multidisciplinary review at our institution from 1996 – 2006 with a minimum of a 2 year patient follow-up. Data were available on 247/252 patients evaluated. Relevant factors at time of diagnosis included symptoms, hepatitis B (HBV) and C (HCV) status, antiviral therapy, Child-Pugh classification, portal vein patency, and TNM staging. Patients underwent primary treatment by hepatic resection, RFA, EI, TACE, CTX, or were observed (best medical management). Patients with persistent or recurrent disease following initial therapy were assessed for salvage therapy. Survival curves and pairwise multiple comparisons were calculated using standard statistical methods. **Results.** Mean overall survival was 76.8 months. Pairwise comparisons revealed significant mean survival benefits with hepatic resection (93.2 months), RFA (66.2 months), and EI (81.1 months), compared with TACE (47.4 months), CTX (24.9 months), or observation (31.4 months). Shorter survival was associated with symptoms, portal vein thrombus, or Child-Pugh class B or C. HCV infection was associated with significantly shorter survival compared with HBV infection. Antiviral therapy was associated with significantly improved survival in chronic HBV and HCV patients only with earlier stage disease. **Conclusion.** Multimodal therapy is effective therapy for HCC and may be used as complementary treatment to OLT.

Key words. Liver resection. Radiofrequency ablation. Chemoembolization. Liver transplantation.

INTRODUCTION

Worldwide, hepatocellular carcinoma (HCC) is one of the most common malignancies and causes of cancer deaths and in North America the incidence of HCC continues to rise.[1,2] Although the management of HCC has improved over the last several years, the prognosis remains relatively guarded.[3]

HCC arises in the setting of cirrhosis in 80-90 % of cases and is the leading cause of death among cirrhotic patients.[4] Many centres consider orthotopic liver transplantation (OLT) to be the gold standard of treatment for patients with HCC and cirrhosis. OLT not only removes the tumor(s) but also addresses the underlying cirrhosis. Several criteria have been proposed to identify HCC patients who are most likely to benefit from OLT. When considering OLT for HCC patients, the Milan Criteria recognize a single HCC tumor less than 5 cm in maximal diameter, or up to three tumors none more than 3 cm, as amenable to OLT with 5-year survival in excess of 70%.[5] Alternate proposals, including the San Francisco criteria and others, are utilized in some centers to determine eligibility for OLT in the setting of HCC.[6-8] HCC patients who exceed these criteria at time of

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diagnosis are typically not candidates for OLT and must rely on other forms of therapy. In addition, progression of HCC while awaiting OLT, such that listing criteria are eventually exceeded, may have a dropout rate exceeding 20% from OLT waiting lists resulting in poor survival rates based on intention-to-treat analysis.[9,10] In the transplant setting, alternative therapies to OLT are required:

1. To effectively treat HCC patients who exceed listing criteria for OLT, and
2. As a bridge to transplantation, to halt the progression of tumors and maintain candidacy for patients who are listed for OLT.

Although the results of OLT for HCC suggest this may be the preferable treatment for eligible patients, the worldwide shortage of organ donors limits its availability. This organ donor shortage results in a death rate approaching 30% of patients on a waiting list for OLT regardless of etiology. As an alternative, hepatic resection for HCC for patients with preserved liver function has been suggested as an effective alternative to OLT providing equivalent results.[11,12] Further, with the availability of other treatment modalities for primary therapy or for treatment of recurrences, long-term survival can be achieved even in the presence of recurrent disease.[3,13,14] Thus, multimodal therapy may be considered as an effective alternative approach to the management of patients with HCC regardless of their suitability for OLT.

We report here the results of patients undergoing multidisciplinary evaluation for multimodality treatment for HCC at our institution for the period of January 1996 to December 2006 with all patients subjected to a minimum one year follow-up. Overall survival was the primary endpoint in which survival following primary treatment with liver resection, radiofrequency ablation (RFA), ethanol injection (EI), transarterial chemoembolization (TACE), or chemotherapy (CTX) was analyzed.

METHODS

Data Collection

A retrospective review was conducted of patients diagnosed with hepatocellular carcinoma who underwent systematic multidisciplinary review and follow-up at Vancouver General Hospital between January 1996 and December 2006. Evaluation was carried out by a panel of surgeons, hepatologists and radiologists, most of whom who were also members of the liver transplant program. Patients with decompensated liver disease meeting the criteria for OLT and whose HCCs fell within the Milan criteria were referred for OLT and were not included in this analysis. The criteria used for establishing HCC diagnoses were those recommended by the American Association for the Study of Liver Diseases (AASLD).[15]

A total of 252 patients evaluated by this process were identified. Of those, complete data sets were available for 247 patients. All data were retrieved from institutional electronic databases at Vancouver General Hospital, the British Columbia Centre for Disease Control, and the British Columbia Cancer Agency, as well as from manual review of clinic and hospital charts. Details concerning tumor number, size, and presence or absence of portal vein thrombi, were retrieved from radiology reports of abdominal CT scan, MRI, or abdominal ultrasound studies. Details concerning primary and salvage treatment modalities were retrieved from operative and procedural reports. Child-Pugh classifications were calculated using standard criteria. TNM stages were calculated according to the American Joint Committee on Cancer TNM Staging Manual, 6th Edition. Dates of death were retrieved from the British Columbia Cancer Registry. Survival was calculated from date of diagnosis to date of death in deceased patients. Survival in living patients was calculated from date of diagnosis to the most recent clinic visit and/or visit to their family physician.

Hepatic Resection

Hepatic resection was performed primarily by an open approach as described elsewhere.[16]

Radiofrequency Ablation (RFA)

RFA was performed on tumors up to 3 cm in maximal dimension, using the methodology prescribed by the manufacturer (ValleyLab Inc). Ablations were performed percutaneously by an interventional radiologist under ultrasound or CT scan guidance unless they were subcapsular or adjacent to major vessels or portal pedicles. For subcapsular tumors, ablations were performed in the operating room either laparoscopically or as an open procedure, with intraoperative ultrasound guidance for probe insertion into HCC tumors. Tumours adjacent to major portal pedicles or hepatic veins were also performed in the operating room to minimize the heat dissipation effect.

Ethanol Injection (EI)

EI was performed either percutaneously under ultrasound or CT scan guidance by an interventional radiologist, or in the OR as either an open or laparoscopic procedure with intraoperative ultrasound guidance as for RFA. A 95% ethanol solution was injected into the centre of the tumor. The maximal tumor dimension was measured by ultrasound at the time of the procedure, and the injected volume of ethanol solution was calculated from the equation for the volume of a sphere using maximal tumor dimension as diameter.

Transarterial Chemoembolization (TACE)

TACE was performed by catheter-directed angiography of the hepatic artery. The branch of the hepatic artery supplying the HCC tumor was selectively catheterized and an admixture of lipiodol (20 mL) and doxorubicin (50 mg) was infused. The procedure was concluded with gelfoam embolization of the hepatic artery branch and angiographic confirmation of arterial exclusion of the tumor.

Chemotherapy (CTX)

Systemic CTX was provided using a doxorubicin-based protocol. Intravenous infusions of doxorubicin (60 mg/m^2 body surface area) were given as an intravenous bolus every 21 days for three to six cycles, as tolerated. Hematologic parameters were monitored. The doxorubicin dose was reduced to 75% of the target dose for absolute neutrophil count (ANC) of 1.0 – 1.5 x 10^9 / L, or platelet count of 70 – 100 x 10^9 / L. Bolus infusions were withheld for ANC < 1.0 x 10^9 / L or platelet count < 70 x 10^9 / L.

Statistical Analyses

Results are presented as mean ± standard deviation. Actuarial analysis of survival curves was performed using the Kaplan-Meier method and the log-rank test (Mantel-Cox). Pairwise comparisons within groups containing more than two factors were performed using the Gehan-Breslow test statistic. Contingency table analyses of the distribution of each factor across TNM stages were calculated using the Chi-Square statistic. All statistical analyses were performed using SigmaStat software, V3.5.

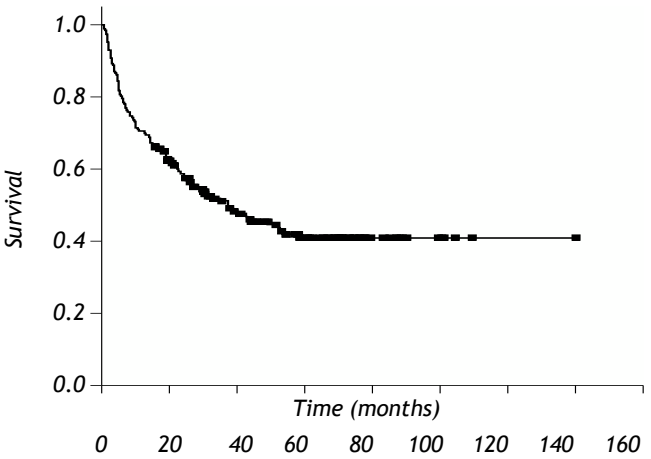

Figure 1. *Overall survival.*

Table 1. Analysis of patient characteristics with corresponding numbers of patients and mean survival (months).

Characteristics	n	Mean Survival (months)
GENDER		
Male	199	64
Female	48	89
AGE		
< 50 yrs	49	76
50-70 yrs	129	74
> 70 yrs	69	50
SYMPTOMS		
No	177	92
Yes	70	31
VIRAL STATUS		
Negative	54	45
Positive	193	82
VIRAL TYPE		
B	151	75
C	42	60
ANTIVIRAL THERAPY		
No	131	78
Yes	62	68
PORTAL VEIN STATUS		
Intact	226	81
Thrombus	21	20
CHILD-PUGH		
A	214	83
B	28	24
C	5	33
TNM		
STAGE 1	140	83
STAGE 2	42	55
STAGE 3	52	42
STAGE 4	13	9

RESULTS

Overall Survival

Overall survival is depicted in Figure 1. A total of 247 patients are represented, with 129 deaths during the observation period and 47 patients followed beyond 60 months. Mean actuarial survival was 77± 4 months.

Patient Demographics

Patient demographics are demonstrated in Table 1. Pair-wise comparisons of mean survival for patient characteristics in relation to TNM stage identified presence or absence of symptoms, viral status, portal vein thrombus, and Child-Pugh stage as having significant influence on survival.

Survival curves of patients with TNM stages I through IV are presented in Figure 2. There was a statistically significant difference in observed mean overall survival among the four groups (stage I, 83 months; stage II, 55 months; stage III, 42 months; stage IV, 9 months: overall $p < 0.001$). Pairwise multiple comparisons between TNM stages revealed significant differences in survival between stages I versus III ($p = 0.010$), stages I *versus* IV ($p = 0.009$), stages II versus III ($p = 0.017$), and stages II versus IV ($p = 0.013$). No significant differences in mean survival were observed for stages I versus II ($p = 0.357$) or stages III *versus* IV ($p=0.082$). Of note, patients with regional metastatic lymphadenopathy based upon either radiological or pathological assessment had a median survival of 5 months (Figure 3), while patients with metastatic disease had a median survival of 2 months (data not shown).

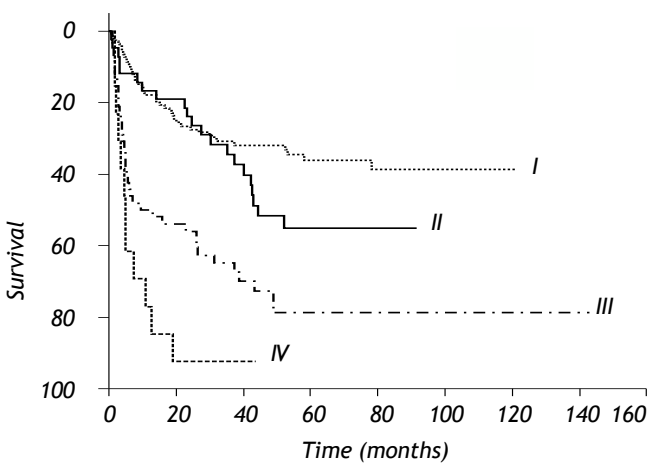

Figure 2. *TNM Stage.*

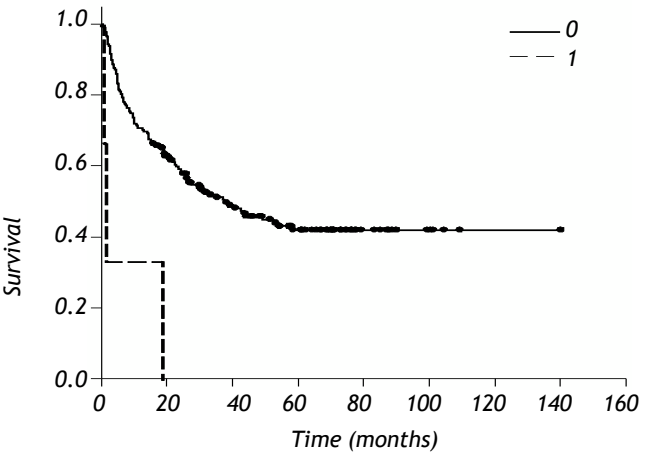

Figure 3. TNM: N-Score.

Symptoms

The presence of symptoms at time of diagnosis was associated with a significantly shorter survival. Of the 247 patients, 177 were asymptomatic at time of diagnosis, with HCC detected during surveillance imaging for known viral hepatitis or cirrhosis. HCC was detected in the remaining 70 patients during the course of investigations prompted by symptoms of abdominal pain, malaise, or weight loss. Among asymptomatic patients, mean survival was 92 months, compared with 31 months in the symptomatic group ($p < 0.001$; Table 2). Chi-square contingency table analysis of the distribution across TNM stages of asymptomatic versus symptomatic patients revealed a significant difference between the two groups (Table 2). There was a clustering of asymptomatic patients in stages I and II, and symptomatic patients in stages III and IV, suggesting that symptomatic presentation was associated with higher stage disease. However, the shorter survival associated with the presence of symptoms was also observed in earlier stage disease. As shown in Table 2, when asymptomatic versus symptomatic patients were matched by TNM stage, there was a trend towards longer survival in asymptomatic versus symptomatic patients with stage I (86 *versus* 58 months; $p = 0.111$) and stage IV disease (28 *versus* 6 months; $p = 0.083$); and significantly longer survival was observed among asymptomatic *versus* symptomatic patients with stage II (63 *versus* 10 months; $p = 0.001$) and stage III disease (60 *versus* 19 months; $p = 0.023$).

Table 2. Analysis of patient characteristics across TNM stages. Mean survival (months) presented in bold in each cell that corresponds to a factor crossed with a TNM stage. Number of patients per cell in small font in parentheses. Intervening columns labeled 'p' present p-values for pair-wise comparisons of the cells (ie each TNM Stage) to the left. Overall p-value for comparison of each patient factor across all TNM stages presented in the right-most column. Contingency table analyses of the distribution of each factor across TNM stages were calculated using the Chi-Square statistic. Statistical comparisons are detailed in Results.

	TNM STAGE									
	I	p	II	p	III	p	IV	p	ALL	p
SYMPTOMS										
No	86 (115)	0.111	63 (36)	0.001	60 (24)	0.023	28 (2)	0.083	92 (177)	0.001
Yes	58 (25)		10 (6)		19 (28)		6 (11)		31 (70)	
VIRAL TYPE										
B	94 (90)	0.001	63 (24)	0.045	24 (31)	0.828	14 (6)	0.997	75 (151)	0.005
C	49 (22)		32 (11)		73 (8)		11 (1)		60 (42)	
PORTAL VEIN										
Intact	82 (139)	0.540	56 (41)	0.248	49 (36)	0.068	7 (10)	0.868	81 (226)	0.001
Thrombus	49 (1)		23 (1)		16 (16)		17 (3)		20 (21)	
CHILD-PUGH CLASS										
A	88 (123)	0.001	61 (36)	0.005	46 (43)	0.034	6 (12)	0.174	83 (214)	0.001
B	25 (13)		26 (5)		16 (9)		44 (1)		24 (28)	
C	41 (4)		3 (1)		-	-	33 (5)			
ALL	83 (140)		55 (42)		42 (52)		9 (13)		77 (247)	

HBV/HCV Serology and Antiviral Therapy

The survival of HBV/HCV seropositive *versus* seronegative patients is presented in Table 2. Patients with HBV/HCV seropositivity had a longer observed mean survival compared with seronegative patients (82 *versus* 45 months), a difference which approached but did not reach statistical significance ($p = 0.07$). Among HBV/HCV seropositive patients, patients with HBV had a median survival of 75 months compared 60 months for patients with HCV ($p=0.005$, Table 2). The use of antiviral therapy (lamivudine, interferon, and/or ribaviran) was not associated with significantly improved survival except for those patients with earlier stage disease (data not shown).

Portal Vein Thrombus

Survival of patients with patent versus portal vein thrombi (occlusive or non-occlusive) is presented in Table 2. Portal vein status was determined from radiologic reports of abdominal ultrasound, CT scan, or MRI imaging. However, histological studies to determine if the thrombus was bland or neoplastic in nature were not uniformly available. The observed mean survival of patients with patent portal veins was significantly longer than in patients with a portal vein thrombus (81 *versus* 20 months; $p < 0.001$). Chi-square contingency table analysis of the distribution of patients with patent versus portal vein thrombi across TNM stages is presented in Table 2, and reveals a significant ($p < 0.001$) difference between the two groups. There is a clustering of patients with patent portal vein in TNM stages I and II, and patients with portal vein thrombi in TNM stages III and IV.

Child-Pugh Class

Due to the relatively small number 5 of Child-Pugh class C patients and the inadequate power of the test statistic if this small group was considered separately, data from class B and C patients were therefore combined. The observed mean survival of Child-Pugh class A patients was significantly longer than Child-Pugh class B + C patients (83 *versus* 24 months; $p < 0.001$). Chi-square contingency table analysis of Child-Pugh class A *versus* B + C patients revealed no significant difference in the distribution of patients across TNM stages between the two groups, suggesting no correlation between Child-Pugh class and TNM stage of disease at diagnosis (Table 2).

Primary Treatment Modality

The primary modalities for treatment of HCC were hepatic resection, RFA, EI, TACE, CTX, and observation (Table 3). Survival curves for each of these primary modalities are presented in Figure 4. There was a statistically significant overall difference in observed mean survival among the six primary modalities (resection, 93 months; RFA, 66 months; EI, 80 months; TACE, 47 months; CTX, 25 months; observation, 31 months: overall $p < 0.001$). As shown in Table 4, multiple pairwise comparisons between primary modalities revealed significantly longer survival for each resection/ablative primary modality (resection, RFA, EI) compared with each medical modality (TACE, CTX, observation). Chi-square contingency table analysis of the distribution of each primary modality across TNM stages revealed a significant overall difference ($p < 0.001$) among the six groups. In general, the resection/ablative primary modalities were preferentially applied at earlier stages of disease, while medical or palliative primary modalities were preferentially applied at later stages. However, this does not entirely account for the observed differences in survival between resection/ablative *versus* medical/palliative primary modalities. Survival analyses of primary treatment modalities for stage-matched patients revealed significant overall differences for stage I ($p < 0.001$) and stage II ($p = 0.041$) disease. Furthermore, multiple pairwise comparisons confirmed significantly longer survival observed for

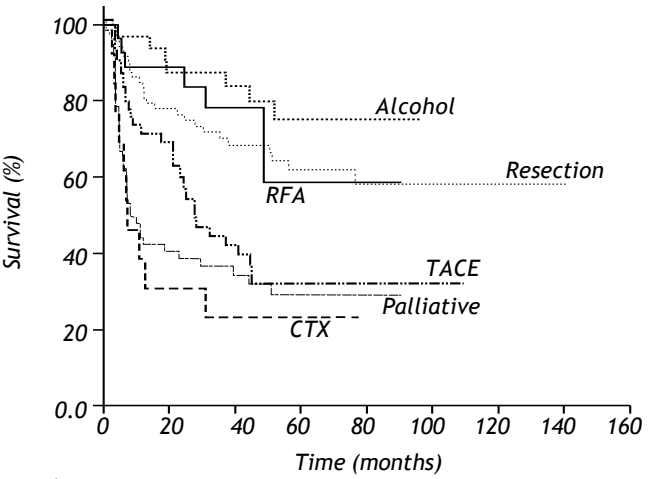

Figure 4. *Primary therapy.*

Table 3. Correlation of primary modality of treatment with numbers of patients (percentage in parentheses) and patient characteristics.

Mean Age ± SD	RFA 60 ± 12	Resect 61 ± 14	EI 60 ± 12	TACE 61 ± 11	CTX 62 ± 9	Obs 64 ± 12	All Patients 61 ± 12
Gender							
Male	20 (74 %)	60 (82 %)	27 (84 %)	36 (77 %)	8 (62 %)	48 (87 %)	199 (81 %)
Female	7 (26 %)	13 (18 %)	5 (16 %)	11 (23 %)	5 (38 %)	7 (13 %)	48 (19 %)
Symptoms							
No	25 (93 %)	56 (77 %)	29 (91 %)	28 (60 %)	5 (38 %)	34 (62 %)	177 (72 %)
Yes	2 (7 %)	17 (23 %)	3 (9 %)	19 (40 %)	8 (62 %)	21 (38 %)	70 (28 %)
Viral status							
Negative	1 (4 %)	23 (32 %)	4 (13 %)	8 (17 %)	5 (38 %)	13 (24 %)	54 (22 %)
B	20 (74 %)	42 (57 %)	23 (72 %)	30 (64 %)	6 (46 %)	30 (55 %)	151 (61 %)
C	6 (22 %)	5 (7 %)	4 (13 %)	8 (17 %)	2 (15 %)	10 (18 %)	35 (14 %)
B + C	0	3 (4 %)	1 (3 %)	1 (2 %)	0	2 (4 %)	7 (3 %)
Portal Vein Status							
Patent	27 (100 %)	73 (100 %)	31 (97 %)	41 (87 %)	10 (77 %)	44 (80 %)	226 (91 %)
Thrombus	0	0	1 (3 %)	6 (13 %)	3 (23 %)	11 (20 %)	21 (9 %)
Child-Pugh Class							
A	25 (93 %)	71 (97 %)	28 (88 %)	40 (85 %)	10 (77 %)	40 (73 %)	214 (87 %)
B	2 (7 %)	2 (3 %)	4 (12 %)	7 (15 %)	3 (23 %)	10 (18 %)	28 (11 %)
C	0	0	0	0	0	5 (9 %)	5 (2 %)
TNM Stage							
I	21 (78 %)	58 (79 %)	26 (81 %)	9 (19 %)	2 (15 %)	24 (44 %)	140 (57 %)
II	4 (15 %)	8 (11 %)	6 (19 %)	17 (36 %)	0	7 (13 %)	42 (17 %)
III	2 (7 %)	6 (8 %)	0	19 (40 %)	7 (54 %)	18 (33 %)	52 (21 %)
IV	0	1 (1 %)	0	2 (4 %)	4 (31 %)	6 (11 %)	13 (5 %)

Table 4. Comparison of Primary Treatment Modalities. Holm-Sidak pair-wise comparisons of mean survival as a function of primary treatment modality (see Figure 6, legend). Significant interactions presented as yes with p-values in minor font and parentheses. For each pair-wise comparison, the modality associated with longer survival is presented in the left-most column, and the modality with shorter survival in the top row. Nonsignificant interactions presented as no with p-values.

PRIMARY THERAPY	EI	RFA	TACE	Observation	CTX
Resection	No (0.11)	No (0.42)	Yes (0.0003)	Yes (< 0.0001)	Yes (< 0.0001)
EI	-	No (0.53)	Yes (0.0002)	Yes (< 0.0001)	Yes (< 0.0001)
RFA	-	-	Yes (0.005)	Yes (< 0.0001)	Yes (0.0001)
TACE	-	-	-	no (0.02)	No (0.09)
Observation	-	-	-	-	No (0.52)

Table 5.

SYMPTOMS	TNM STAGE									
	I	p	II	p	III	p	IV	p	ALL	p
PRIMARY THERAPY										
RFA	74 (21)	0.001	32 (4)	0.041	50 (2)	0.232	-	0.348	66 (27)	0.001
Resection	86 (58)		40 (8)		75 (6)		5 (1)		93 (73)	
EI	84 (26)		54 (6)		-		-		80 (32)	
TACE	44 (9)		64 (17)		19 (19)		11 (2)		47 (47)	
Chemo	45 (2)		-		26 (7)		9 (4)		25 (13)	
Observe	43 (24)		21 (7)		25 (18)		10 (6)		31 (55)	
SALVAGE THERAPY										
RFA	106 (13)	0.054	55 (2)	0.214	-	0.480	-	-	102 (15)	0.013
Resection	54 (3)		-		-		-		54 (3)	
EI	68 (7)		40 (1)		-		-		65 (8)	
TACE	91 (6)		59 (4)		74 (1)		-		89 (11)	
Chemo	44 (3)		34 (2)		48 (2)		-		47 (7)	

each surgical/ablative modality compared with each medical/palliative modality for stage I and stage II disease (Table 5). Meaningful stage-matched comparisons of survival by primary treatment modality in stages III and IV disease were confounded by the small number of those patients who received surgical/ablative primary treatment modalities.

Salvage Treatment Modality

In the face of persistent or recurrent HCC following therapy with a primary treatment modality, one of the following salvage treatment modalities (primary treatment modality for recurrence of initial disease) was used: hepatic resection, RFA, EI, TACE, or CTX. Survival curves for each of these salvage modalities are presented in Figure 5. There was a statistically significant overall difference in observed mean survival among the five salvage modalities (resection, 54.0 months; RFA, 102 months; EI, 65 months; TACE, 89 months; CTX, 47 months: overall p = 0.013).

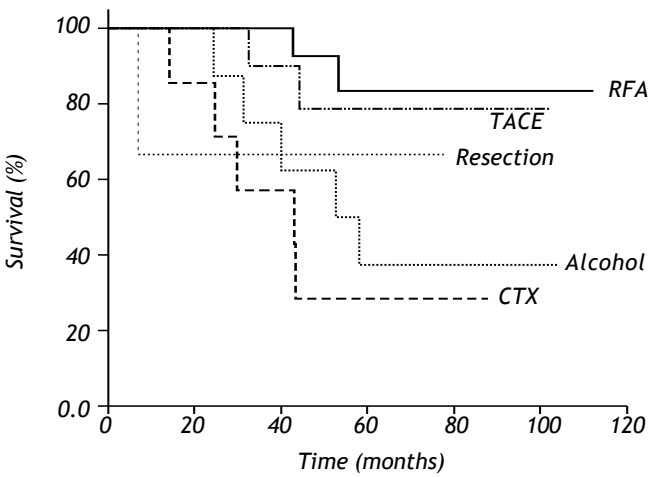

Figure 5. Salvage therapy.

DISCUSSION

In general, patients with HCC falling within defined criteria in setting of end-stage liver disease should be considered for transplantation.[5,10,17] However, there is controversy about the optimal

therapy for patients with HCC who have adequate liver function. This debate is generated by the satisfactory results of treatment for HCC by hepatic resection and ablation therapy, as well as the severe shortage or organs available for transplantation. With longer OLT waiting times for patients with HCC, there may in fact be a decreasing survival rate according to the intention-to-treat principle.[9,10,17] It is with these considerations that our program concurrently evaluates patients with HCC for either transplantation or consideration of potential multimodal therapy for their disease process. Factors considered were eligibility for OLT based upon underlying liver disease as assessed by Child-Pugh and MELD (Model for End-stage Liver Disease) score, and HCC stage including determination of OLT eligibility using the Milan criteria.

The organ donation rate in our region varies between 6-12 per million. The number of referrals for transplantation far exceeds the capacity to perform OLT, and the death rate of patients on the waiting list for OLT ranges between 20-30% regardless of underlying diagnosis. Unless patients with HCC first met the criteria for OLT based upon liver function they were evaluated for alternative forms of therapy by a multidisciplinary panel of surgeons, hepatologists and radiologists. Because of this approach, a comparison of OLT outcomes for HCC with multimodal therapy in these patients was not possible. Of the 252 patients undergoing systematic review, complete follow up was available on 247 patients.

Compilation of studies from other centres have reported 5 year survival data in the range of 60-70% for those patents transplanted within the Milan Criteria, with 50% 5 year survival for those patients undergoing resection . Intention-to-treat studies generally suggest survival figures in the range of 47-71% at 5 years although treatment of small tumours has resulted in a 79% 32 month survival.[7,10,17,18,19] We found that patients undergoing hepatic resection had a mean survival of 93.2 months, with 5 year survivals comparable to reported results of liver transplantation. Other therapeutic modalities used for "curative intent" included radiofrequency and ethanol ablation which had statistically equivalent results to liver resection patients albeit for smaller lesions or earlier stage disease. Ablation techniques were performed by percutaneous, laparoscopic or open approaches and were generally applied in patients with lesions <3 cm, or for those patients in whom it was felt the perioperative mortality precluded liver resection. Patients who were considered palliative, i.e., patients with unresectable or non-ablatable HCCs based on size or multifocal presentation, were considered for TACE, systemic chemotherapy, or observation only. During the time of this study, Sorafenib therapy was not generally available. As expected, these patients had significantly decreased survival compared to resection or ablation therapy with no significant survival differences between these palliative approaches. Patients undergoing therapy with "curative intent" who developed recurrences were re-evaluated on an individual basis and considered for any of the available treatment modalities as salvage therapy. Similarly, patients undergoing chemoembolization whose disease stabilized were reconsidered for resection or ablation therapy depending upon the status of their underlying liver function. Using this strategy of multimodal therapy (including salvage therapy), the mean overall survival for this entire group of patients was 76.8 months with a 5-year survival approaching that of liver transplantation with several patients survival approaching 10 years with or without recurrent tumour.

Since patients with HCC represent a heterogeneous group of patients, subgroup analyses were performed to determine if there were subsets of patients who could be clinically identified as being at high risk for failure of a multimodal therapy approach. It was not surprising to note that a more advanced TNM stage correlated with a worse outcome. Since OLT has been shown to result in disease-free survival of stage III and IV equivalent to earlier stage disease, it is reasonable to preferentially list patients for OLT who have tumours of 5 cm or less who are stage III or IV.[5,20,21] Patients with nodal or distant metastases did poorly in this study. These patients similarly do not fare well following OLT. A higher Child-Pugh score led to a worse prognosis again supporting a role for preferential treatment by OLT. However, these patients would have already been considered for OLT based upon their compromised liver function, but those patients whose tumour status exceeded the Milan criteria would not be considered transplant candidates.

Symptomatic patients who presented with constitutional symptoms as the reason for initiating investigations had a worse prognosis regardless of tumour stage. Most of the patients with symptoms had more advanced disease, but even symptomatic patients who presented at an earlier stage demonstrated a trend to a worse outcome. Patients with portal vein thrombus also had a worse outcome again regardless of stage even though it was not

histologically determined if the tumour thrombi represented tumour extension or bland thrombus only. While there were a few patients with early stage HCC who had portal vein thrombi, most of the patients were later stage tumours suggesting that a portal vein thrombus is associated with an advanced stage of disease. Unfortunately, patients undergoing OLT with macroscopic (and microscopic) vascular invasion also have poor 5 year disease-free survival rates.[22,23]

Seventy-eight percent of the patients presenting with HCC had either hepatitis B (61%) or hepatitis C (17%) as their underlying liver disease. Whereas in the Western hemisphere approximately 50-80% of HCC may occur in the setting of HCV cirrhosis, a greater percentage of our patients had underlying HBV infections, reflecting the location of our program as a hub of travel immigration with southeast Asia where HBV prevalence is high. Compared to the other causes of underlying liver disease, patients with viral etiology had a significantly better outcome compared to patients with other underlying liver diseases. This outcome was further compounded if the patients received anti-viral therapy with early stage cancer, supporting a role for viral suppression therapy in this setting.[24,25]

As the vast majority of HCC tumors arise in cirrhotic livers, implementation of surveillance programs with serial imaging of the liver for early detection of HCC in high-risk cirrhotic patients has been suggested to attempt identification and treatment of HCC at an earlier stage of disease, which is associated with a more favorable prognosis.[26] The data from this current study provides support for strategies for early detection of HCC such as aggressive screening programs, particularly in the hepatitis B and C populations. Detection and treatment of early stage HCC obviates the need for OLT consideration. Patients with HBV or HCV should also be strongly considered for antiviral therapy where possible given the evidence that patients with hepatitis B infection who are treated with antiviral therapy have a reduced incidence of HCC development and the data demonstrating improved survival in patients who had been treated with viral suppression therapy in early stage disease.

Based on the results from this study, we believe that multidisciplinary assessment and management of patients with HCC by multimodal therapy yields satisfactory intermediate to long term patient survival. Patients who are managed with a "curative' intent by resection or ablation have 5- and 10-year survival rates equivalent to OLT. This approach can therefore be considered in situations where donor organ availability is problematic, and is justifiable as an alternative to OLT in patients with otherwise good liver function. Patients who develop recurrent disease should be reconsidered for multimodal therapy as this may lead to long-term survival either in the presence or absence of recurrent disease.

ABBREVIATIONS

- **HCC.** Hepatocellular carcinoma.
- **OLT.** Orthotopic liver transplantation.
- **RFA.** Radiofrequency ablation.
- **EI.** Ethanol injection.
- **TACE.** Transarterial chemoembolization.
- **CTX.** Chemotherapy.

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