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Predicting hepatocellular carcinoma recurrence and survival

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Abstract

Background: Beta blockers can inhibit tumor growth and metastases, while necroinflammation can enhance these tumor properties.

Objective: To determine whether beta blockers and necroinflammatory disease predict tumor recurrence and/or overall survival following potentially curative therapeutic interventions for patients with hepatocellular carcinoma (HCC).

Methods: The medical records of 36 adults with non-metastatic HCC who had undergone surgical resections and/or radiofrequency ablation (RFA) were retrospectively reviewed. In addition to post-intervention beta blocker usage and serum alanine aminotransferase levels greater than 2xULN, other variables commonly associated with recurrences such as number and size of tumors, state of differentiation and vascular invasion were included in univariate and multivariate analyses for recurrence and survival.

Results: Vascular invasion (OR 29.3, 95% CI 2.6-33.6) and surgical resection (OR 0.19, 95% CI 0.04-0.90) emerged from univariate (p=0.003 and 0.03 respectively) and multivariate (p=0.005 and 0.048 respectively) regression as predictors of tumor recurrence whereas beta blocker usage (OR 0.03, 95% CI 0.04-0.9, p=0.03) and tumor recurrence (OR 6.7, 95% CI 1.6-28.1, p=0.026) correlated with overall survival.

Conclusions: Neither beta blocker usage nor serum ALT levels predict HCC recurrences, but beta blocker usage is associated with improved overall survival following potentially curative therapeutic interventions for HCC in adults.

Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer mortality worldwide [1]. Until recently, HCC was largely confined to developing nations where hepatitis B and C viral infections are endemic. However, increased immigration along with the rising prevalence of non-alcoholic fatty liver disease has resulted in HCC being diagnosed more frequently in developed nations [2-4]. Indeed, in Canada, the incidence of HCC is increasing at a rate higher than all other malignancies in females and second only to thyroid cancer in males [5].

Unfortunately, HCC treatment remains suboptimal. Aside from liver transplantation, surgical resection and radiofrequency ablation (RFA) are generally considered the only potentially curative therapeutic interventions. Recent studies suggest that both interventions are associated with similar results: three year recurrence rates of 40-50% [6-8]. The ability to identify those tumors most likely to recur is the focus of intensive research. To date, a number of predictor variables have been described, including: vascular invasion, number and size of lesions, state of tumor differentiation, etiology of the underlying liver disease, alpha fetoprotein, alkaline phosphatase, albumin and platelet levels [9-13]. Presumably, others have yet to be identified.

Recently, data have emerged indicating that adrenergic stimulation enhances tumor (including HCC) growth and invasion [14-16]. Conversely, adrenergic inhibitors such as non-selective beta blockers (BB) inhibit these tumor properties [16-18]. Also to be considered in terms of recurrence risks is the extent of the necroinflammatory activity of the underlying liver disease. Here, one would predict that the inflammatory cytokines and growth promoters released with liver injury/inflammation would increase the risk of HCC recurrence and growth [19]. Whether beta blocker usage and/or the presence of underlying active liver disease predict HCC recurrence and/or survival in humans has yet to be formally evaluated.

In this retrospective chart review, the medical records of patients who had undergone surgical resection or radiofrequency ablation for HCC were reviewed. Recurrence and overall survival rates were documented and interpreted in light of beta blocker use and the presence or absence of active underlying liver disease.

Materials and methods

Selection of HCC cases

Patients were selected by reviewing the records of two hepatobiliary surgeons responsible for the majority of surgical resections and/or RFA performed at a single, tertiary care centre in Winnipeg, Manitoba, Canada over the past 15 years (1996-2011). Inclusion criteria included adult patients (beyond the age of 18 years) of either gender and Childs-Pugh scores 5-15. Only cases with cytologic or histologic confirmation

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of HCC were selected. Patients with radiologic or histologic evidence of extrahepatic HCC, vascular invasion and those who died within 30 days of the procedure (i.e. procedure-related deaths) or proceeded to liver transplant within 3 months of therapeutic intervention were excluded from the study.

Data accrual

Demographics: Date of birth and gender were recorded for each patient.

Pretreatment information: In addition to the etiology, the activity of the underlying liver disease was recorded in a binomial manner (active or inactive). Active liver disease was considered present if serum alanine aminotransferase (ALT) values exceeded twice the upper limit of normal (>30 U/L). Also recorded were serum aspartate aminotransferase (AST), alkaline phosphatase (AP), albumin, alpha fetoprotein (AFP) and platelet counts. In the event that bloodwork on the day of treatment did not include all the variables noted, levels from the most recent previous bloodwork were recorded (within 6 weeks in all cases). Childs-Pugh scores prior to therapeutic interventions were also calculated.

Treatment information: The date and nature of the procedure (resection or RFA), number of tumors, largest tumor diameter, level of tumor differentiation (well/moderately/poorly differentiated) and where available, microscopic evidence of vascular invasion were recorded.

Post-treatment information: Follow-up was not protocol based, however in the majority of cases; post-treatment follow-up consisted of liver biochemistry testing every three months and abdominal imaging (ultrasound, CT or MRI) at 3, 6, 12 and every 6-12 month intervals thereafter. Recurrences were diagnosed on the basis of characteristic imaging findings, serum tumor markers and when indicated, confirmed histologically.

Patient medication post-treatment was recorded from the provincial government's drug program information network (DPIN) and doctors' discharge letters. Dates of death were also documented.

Statistical analysis

Statistical methods: Continuous variables were reported as means with standard deviations, medians and 95% confidence intervals. Categorical variables were reported as frequencies and percentages. Patients were classified according to their use of beta blockers as users or nonusers and based on their serum ALT levels as those with active or inactive liver disease in two separate analyses. Chi-square test of association (or F-test when warranted) was used to examine differences in clinical and histological factors (beta blocker use and disease activity). To assess for quantitative differences between the groups, Analysis of Variance (ANOVA) tests were performed. Univariate regression analysis was used to determine which factors were associated with tumor recurrence and overall survival. Factors found to be significant in univariate analysis were included in multivariate regression analyses. Statistical analysis was performed using SAS Version 9.1 (SAS Inc, Cary, N.C.). For all analyses, statistical significance was set at less than 5%.

Results

Study population

As indicated in Table 1, a total of 39 subjects who underwent surgical resection or RFA had cytologic or histologically confirmed HCC. Three patients (one surgical resection, one RFA and one both resection and RFA) were excluded due to deaths within 30 days of their procedure. The mean age of the study population was 61±9 years and 31 (86%) were male. The etiology of the underlying liver disease was viral hepatitis in 20 (56%). Of these, 6 (17%) were hepatitis B and 14 (39%) hepatitis C. Alcohol induced liver disease was present in 11 (31%), NASH in 2 (5.6%), cryptogenic cirrhosis in 2 (5.6%) and no diagnosis in 2 (5.6%). Of note, some patients had more than one etiology. The majority of patients had histologic or radiologic evidence of cirrhosis 20/36 (56%). Where data permitted (N=24), 16 (67%) were classified as Childs-Pugh A, 6 (25%) B, 1 (4.2%) borderline A/B and 1 (4.2%) borderline B/C.

Table 1. Baseline, clinical and demographic characteristics of 36 HCC study patients.

Variable	N	%/range
*Age (yr.) (Mean ± SD)	61 ± 9	39-79
Male	31	86
Underlying liver disease and related conditions:		
Viral hepatitis total:	20	56
hepatitis B	6	17
hepatitis C	14	39
Alcoholic	11	31
NASH	2	5.6
Cryptogenic	2	5.6
Incidental finding of HCC	2	5.6
Cirrhosis	20	56
Ascites	10	28

* the value is given as Mean ± SD

Table 2. Histopathology of HCC.

Variable	n	%
Number of lesions:		
1	23	64
2	8	22
3	2	5.6
4 or more	3	8.3
Differentiation:		
Poorly	4	17
Moderate	5	22
Well	14	61
Vascular invasion:		
Yes	14	61
No	9	39

HCC histology

HCC characteristics are provided in Table 2. Solitary lesions were present in 23 (64%), 2 in 8 (22%), 3 in 2 (5.6%) and more than 3 in 3 (8.3%) individuals. The mean diameter of the largest lesion was 3.6 ± 1.8 cm. The majority of HCC (61%) were well differentiated. Microscopic evidence of vascular invasion existed in 14/23 (61%) cases.

Therapeutic intervention

A total of 10 subjects (28%) had undergone surgical resections, 23 (64%) RFA and 3 (8.3%) both resection and RFA. Beta blockers were prescribed orally immediately after RFA and as soon as bowel sounds returned following surgical resections.

Patient outcomes

Patient outcomes are provided in Table 3. Mean follow-up was 1.4 ± 1.8 years (range: 0.2 to 6.0 years). Seventeen patients (47%)

Table 3. Outcomes of HCC patients treated with either surgical resection or radiofrequency ablation.

Variable	N	%/range
Follow up (yr)	1.4 ± 1.8	0.2 – 6.0
Death	17	47
Time to death (yr)	2.0 ± 1.7	0.5 - 6.0
Cause of death recorded	2	5.6
- Intra-abdominal hemorrhage	1	2.8
- Multiorgan failure	1	2.8
Recurrence	17	47
Liver transplant	3	8.3

died. The mean time to death was 2.0 ± 1.7 years (range 0.5-6.0 years). Causes of death were only recorded in two patients. These included variceal bleeding and multisystem failure. Seventeen subjects (47%) experienced recurrence but were alive at the time of analysis. Three (8.3%) patients proceeded to liver transplant.

A total of 11 (31%) subjects were prescribed beta blockers (all but one received non-selective beta blockers in dosages adjusted to decrease the resting pulse rate by 20-25% but not less than <55 bpm) following treatment and 9 (25%) subjects had biochemical evidence of active liver disease. The clinical, biochemical, tumor characteristics and therapeutic interventions of those receiving and not receiving beta blockers, as well as those with and without active liver disease are provided in Tables 4 and 5 respectively. There were no statistically significant differences in any of these categories when beta blocker recipients were compared to non-recipients. The same was true of patients with and without active liver disease.

Tumor recurrence

When the above variables were included in univariate regression analysis only vascular invasion (OR 29.3, 95% CI 2.6-36, p=0.006) and surgical resection (OR 0.19, 95% CI 0.04-0.90, p=0.036) predicted tumor recurrence. Both variables remained significant following multivariate regression (vascular invasion: OR 11.5, 95% CI 1.9-68.7, p=0.007 and surgical resection: OR 0.16, 95% CI 0.02-0.98, p=0.048).

Overall survival

When the above variables were included in univariate analysis for survival, only beta blocker use (OR 0.03, 95% CI 0.04-0.9, p=0.03) and tumor recurrence (OR 6.7, 95% CI 1.6-28.1, p=0.026) emerged as statistically significant predictors of outcome.

Discussion

The results of this study do not support the hypotheses that beta blocker usage decreases and underlying liver disease activity increases the risk of HCC recurrence following potentially curative therapeutic intervention in humans. However, the data do suggest that beta blocker usage may be associated with improved overall survival in such patients. The data also indicate that recurrences are significantly less common in subjects undergoing surgical resection as compared to RFA. Finally, the importance of vascular invasion as a predictor of HCC recurrence was confirmed.

That beta blocker usage was not associated with fewer HCC recurrences but rather, increased overall survival is in keeping with recent results from the authors' laboratory wherein malignant hepatocyte proliferative activity remained unaltered but cell migration/invasion was significantly attenuated following exposure to beta blockers [16]. These *in vitro* findings suggest that beta blockers do not inhibit tumor growth per se but do decrease their tendency to invade and metastasize. Given that tumor invasion and metastasis are the principal causes of death in HCC, one might have predicted the findings of no difference in tumor recurrence but prolonged survival in the present study. It should be noted however, that although not statistically significant perhaps due to the small number of subject involved, those prescribed beta blockers tended to have lower Childs-Pugh scores than non-users which could also explain the improved survival rates observed in this cohort.

Regardless of the mechanism(s) whereby beta blockers may be associated with a favourable survival outcome, this finding contributes to the debate of their role (if any) in patients with advanced liver disease. Specifically, recent reports (albeit contested) suggest that beta blocker usage is associated with decreased survival in patients with diuretic resistant ascites [20-22]. On the other hand, their value in preventing primary and recurrent portal hypertensive bleeding is well established, and the results of the present study, as well as an abstract describing a lower incidence of HCC in patients with hepatitis C and esophageal varices treated with beta blockers (versus variceal banding), would support their use in the majority of cases of advanced liver disease [18,23]. Clearly, further research in this important area is warranted.

Recent data indicate that surgical resection and RFA have similar efficacy in the management of small HCC [6-8]. Thus, it was somewhat surprising to find significantly fewer recurrences in those patients who had undergone resection compared to those treated with RFA. The most likely explanation for this finding is the fact that the majority of RFA cases were treated at a time when tumor diameters greater than 2cm were still considered potentially curative. Thus, despite radiologic evidence suggesting complete tumor eradication, residual tumor along the edges of ablated lesions almost certainly remained.

A large number of variables have been identified as predictors of HCC recurrence following potentially curative interventions. This retrospective study was not designed to test all such variables however; data on vascular invasion, number and size of lesions, state of tumor differentiation, etiology of the underlying liver disease, alpha fetoprotein, and serum alkaline phosphatase, albumin and platelet levels were available. Of these, only vascular invasion emerged from univariate and multivariate analyses as a predictor of HCC recurrence. Despite recent reports, patients with hepatitis C and multiple (≥3) tumors were not identified as predictor variables [12,13]. Presumably, the small number of patients with these features (N=17 and 3 respectively) contributed to this finding. Why the other variables (for which data existed in most cases) did not associate with outcome requires further study.

There are a number of significant limitations to this study that warrant emphasis. First, the sample size was small. Second, the experimental design renders it susceptible to all the limitations associated with retrospective analyses including enrolment and data collection bias, incomplete data sets, variable management over time etc. Third, the data was derived from a single centre. Fourth, no fixed follow-up protocol was in place, and therefore it was not possible to accurately document time to recurrence in the various cohorts. Fifth, all RFAs were performed during an open operative procedure which is more invasive and associated with increased morbidity than the present standard of percutaneous RFA [24]. Sixth, provisions were not in place to determine whether patients were taking their beta blockers as prescribed. Seventh, the definition of active underlying liver disease was arbitrary (ALT ≥ twice the upper limit of normal) and may not

Table 4. Clinical, biochemical and histologic features of beta blocker users and nonusers with HCC.

	Beta Blockers (N=11)		No Beta Blockers (N=25)		
Variable	**n**	**%/range**	**n**	**%/range**	**P**
Male	8	73	23	92	0.12
Age (years)	61 ± 9	50 - 76	60 ± 10	39 - 79	0.83
Follow-up (years)*	2.9 ± 3.1	0.2 – 6.0	1.0 ± 1.3	0.25 – 5.2	0.84
Underlying liver disease and related conditions					
Viral hepatitis total:	6	55	14	56	0.94
--HBV	2	18	4	16	0.88
--HCV	4	36	10	40	0.84
Alcoholic	3	27	8	32	0.78
NASH	1	9.1	1	4.0	
Cryptogenic	0	0	2	8.0	
Incidental finding of HCC	1	9.1	1	4.0	
Cirrhosis	5	46	15	60	0.42
Ascites	4	36	6	24	0.44
Active disease	2	18	7	28	0.53
ALT	63 ± 54	14 - 176	66 ± 60	7 - 273	0.83
GGT	95 ± 62	34 - 186	192 ± 225	19 - 1043	0.15
AST	72 ± 64	19 - 228	61 ± 49	10 - 207	0.56
Alkaline Phosphatase	116 ± 60	68 - 242	126 ± 54	32 - 266	0.62
AFP	303 ± 818	4 - 2761	354 ± 1003	2 - 5091	0.87
Platelets	112 ± 50	53 - 196	136 ± 68	59 - 360	0.27
INR	1.3 ± 0.2	1.0 - 1.7	1.2 ± 0.8	1.0 - 1.6	0.26
Albumin	32 ± 5	25 - 39	34 ± 7	13 - 44	0.33
Total Bilirubin	24 ± 27	5 - 106	14 ± 7	7 - 34	0.12
Creatinine	79 ± 20	57 - 126	84 ± 54	52 - 347	0.65
C-P score (from recorded data only)**					
Class A	6	86	12	63	0.52
Class B	1	14	5	26	
Borderline A/B	0	0	1	5	
Borderline B/C	0	0	1	5	
HCC characteristics					
Largest lesion (cm)	3.6 ± 2.1	1.5 – 8.0	3.5 ± 1.6	1.0 – 9.5	0.84
Number of lesions	1.3 ± 0.7	1 – 3	1.9 ± 1.3	1 – 6	0.27
Vascular invasion***	4	75	10	56	0.32
Number of lesions: 1	8	73	15	60	0.74
2	2	18	6	24	
3	1	9.1	1	4.0	
4 or more	0	0.0	3	12.0	
Differentiation (from recorded data)****					
- Poor	3	43	1	6	0.10
- Moderate	1	14	4	25	
- Well	3	43	11	69	
HCC treatment					
Resection only	3	27	7	28	0.72
RFA only	7	64	16	64	0.72
Both Resection and RFA	1	9.1	2	8.0	
Outcome					
Recurrence	3	27	14	56	0.11
Death	2	18	15	60	**0.02**
Liver transplant	1	9.1	2	8.0	
Time to death (yr)	3.5 ± 3.5	1.0-6.0	1.8 ± 1.4	0.5-5.0	0.40

*Calculated from the recorded data only (4 beta blocker users and 19 nonusers)

**Calculated from the recorded data only (6 beta blocker users and 18 nonusers)

***Calculated from the recorded data only (5 beta blocker users and 18 nonusers)

****Calculated from the recorded data only (7 beta blocker users and 16 nonusers)

Table 5. Clinical, biochemical and histological characteristics of HCC patients with active and without active inflammation.

	Active (N=9)		Not Active (N=27)		
Variable	**n**	**%/range**	**n**	**%/range**	**P**
Male	8	89	23	87	0.78
Beta blockers use	2	22	9	33	0.53
Age (years)	61 ± 9	54 -79	60 ± 10	39 - 79	0.82
Follow-up (years)*	2.4 ± 2.5	0.2 – 6.0	0.9 ± 1.2	0.2 – 5.2	0.06
Underlying liver disease and related conditions					
Viral hepatitis total:	9	100	11	41	0.002
--HBV	3	33	3	11	0.12
--HCV	6	67	8	30	0.05
Alcoholic	1	11	10	37	0.14
NASH	0	0	2	7.4	
Cryptogenic	0	0	2	7.4	
Incidental finding of HCC	0	0	2	7.4	
Cirrhosis	2	22	18	67	0.02
Ascites	1	11	9	33	0.20
ALT	141 ± 57	60 - 273	35 ± 15	7 - 58	0.000001
GGT	237 ± 294	37 - 1043	133 ± 134	19 - 578	0.13
AST	128 ± 64	45 - 228	40 ± 15	10 - 73	0.000015
Alkaline Phosphatase	124 ± 49	61 - 226	123 ± 58	32 - 266	0.94
AFP	266 ± 427	6 - 1344	373 ± 1092	2 - 5091	0.66
Platelets	109 ± 28	61 - 166	136 ± 72	53 - 360	0.28
INR	1.2 ± 0.2	1.0 - 1.6	1.2 ± 0.2	1.0 - 1.7	0.51
Albumin	33 ± 6	23 - 44	34 ± 7	13 - 43	0.49
Total Bilirubin	17 ± 6	8 - 26	18 ± 19	5 - 106	0.82
Creatinine	99 ± 83	53 - 347	76 ± 16	52 - 126	0.15
C-P score (from recorded data only)**					
Class A	3	60	13	68	0.13
Class B	1	20	5	26	
Borderline A/B	0	0	1	5.3	
Borderline B/C	1	20	0	0	
HCC characteristics					
Largest lesion (cm)	4.1 ± 2.5	1.5 – 9.5	3.3 ± 1.3	1.0 – 7.5	0.16
Number of lesions	1.7 ± 1.0	1 – 4	1.7 ± 1.2	1 – 6	0.84
Vascular invasion***	5	63	9	60	0.91
Number of lesions: 1	5	56	18	67	0.65
2	3	33	5	19	
3	0	0	2	7.4	
4 or more	1	11	2	7.4	
Differentiation (from recorded data)****					
- Poor	1	20	3	17	0.98
- Moderate	1	20	4	22	
- Well	3	60	11	61	
HCC treatment					
Resection only	2	22	8	30	0.71
RFA only	6	67	17	63	0.71
Both Resection and RFA	1	11	2	7.4	
Outcome					
Recurrence	4	44	13	48	0.85
Death	5	56	12	44	0.56
Liver transplant	2	22	1	3.7	
Time to death (yr)	2.8 ± 2.5	1.0 - 6.0	1.6 ± 1.3	0.5 – 5.0	0.21

*Calculated from the recorded data only (7 active and 16 not active disease)
**Calculated from the recorded data only (5 active and 19 not active disease)
***Calculated from the recorded data only (8 active and 15 not active disease)
****Calculated from the recorded data only (5 active and 18 not active disease)

have reflected inflammatory activity, but rather aminotransferase elevations associated with cirrhosis. Moreover, even in the absence of cirrhosis, serum ALT levels do not always reflect underlying hepatic necroinflammatory disease [25-27]. Eighth, we were not able to ascertain whether any of the 10 patients with ascites belonged to the subgroup of patients with diuretic resistant ascites in whom beta blocker usage has been associated with adverse outcomes. Finally, in most cases, what was diagnosed as recurrent disease on radiologic

imaging was not confirmed histologically.

Despite the above limitations, the results of this retrospective study are informative in that they suggest beta blocker usage in this setting is not associated with adverse outcomes, and may indeed improve overall survival in cirrhotic patients who undergo potentially curative therapeutic interventions for HCC.

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