

Predictors of intermediate-term survival with destination locoregional therapy of hepatocellular cancer in patients either ineligible or unwilling for liver transplantation

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Abstract: Intra-arterial or percutaneous locoregional therapies (LRT) are often employed to maintain potential liver transplant (LT) recipients with hepatocellular carcinoma (HCC) within T2/Milan criteria. Predictors of survival when LRT is used as destination therapy in those who are either ineligible or unwilling for LT remain poorly defined. We evaluated predictors of 3-year survival with destination LRT in a population of cirrhotic patients diagnosed with HCC, presenting within T2 criteria, and either ineligible or unwilling for LT. The cohort surviving 3 years had a significantly lower model for end-stage liver disease (MELD) score at HCC diagnosis (9.7 vs. 11.4, P=0.037) and MELD following initial locoregional therapy (10.7 vs. 13.3, P=0.008) compared to those not surviving three years despite similar demographic, tumor, and treatment variables. LRT as destination therapy results in modest intermediate term survival, with liver function at presentation and immediately following initiation of LRT predicting intermediate survival with this approach.

Keywords: Locoregional therapy; destination therapy; hepatocellular carcinoma (HCC); elderly

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Introduction

The incidence of hepatocellular carcinoma (HCC) has increased dramatically, with deaths secondary to liver cancer rising at a rate higher than that of any other malignancy (1). Importantly, HCC prevalence is predicted to increase among the geriatric population as efforts directed at birth cohort screening for chronic hepatitis C virus (HCV) and recognition of the global epidemic of Nonalcoholic Fatty Liver Disease (NAFLD) have led to increased screening (2). Curative therapies for HCC include segmental hepatic resection and liver transplant (LT), with 5-year overall survival rates ranging from 27 to 70 percent and 44 to 78 percent, respectively (3).

Elderly patients (age greater than 60) are often not deemed candidates for resection or LT due to coexisting cardiopulmonary disease, other organ dysfunction, or

psychosocial comorbidity that renders candidacy for operative therapy marginal. Locoregional therapies (LRT), including intra-arterial: transarterial chemoembolization (TACE) or transarterial radioembolization (Y-90); as well as percutaneous: radiofrequency ablation (RFA), microwave ablation (MWA), and external beam radiation therapy (EBRT), are often employed as “destination therapy” for patients who are not candidates for or are unwilling to undergo surgical resection or LT. Use in this context is in contrast to “bridging,” in which such therapy is employed to maintain or downstage potential LT candidates within T2/Milan criteria.

While data regarding predictors of response and survival en route to transplant have been described (4,5), less is known regarding utility and predictors of response to locoregional therapy when employed as destination therapy

in elderly populations. The aim of this investigation was to evaluate the use of locoregional approaches as destination therapy for HCC in an elderly population within criteria but either ineligible or unwilling for transplant and to investigate predictors of short (1-year) and intermediate (3-year) term survival.

Methods

Study design

This was a retrospective cohort study in which 123 patients over the age of 60 receiving destination locoregional therapy for HCC were reviewed and evaluated for predictors of 1- and 3-year survival. After institutional board approval, chart review was conducted on patients presenting to a university-based transplant clinic for diagnosis of HCC between January 2009 and January 2013.

Inclusion criteria

Inclusion criteria included: age greater than 60, HCC diagnosis made by multiphasic cross-sectional imaging (triphasic CT or MRI with Eovist), initial tumor burden within T2/Milan criteria, and use of locoregional interventions as destination therapy rather than bridging. When applicable, patients were offered transplant evaluation, though all were ultimately denied for various reasons by a multidisciplinary transplant committee.

Demographics, tumor and treatment variables

Patient demographics, liver disease factors, and tumor treatment characteristics were compared between the cohort surviving 3 years from initiation of locoregional therapy and the cohort that did not. Patient demographics included gender, age, ethnicity, whether LT evaluation was pursued, and reason for LT denial. Liver disease factors reviewed included etiology of cirrhosis and albumin, total bilirubin, INR, and creatinine at diagnosis, as well as model for end-stage liver disease (MELD) at diagnosis and after locoregional therapy. Tumor and treatment characteristics included number of lesions, AFP at diagnosis, presence of unilobar disease, and initial treatment modality.

Treatment modality was based on imaging review and discretion of the interventional radiologists. Modalities employed included TACE, Y-90, RFA, MWA, and EBRT as described elsewhere (6,7).

Statistical analysis

Continuous variables were examined with Levene's test for equal variances and student's *t*-test. Categorical variables were examined using Fisher's exact test and Pearson's chi square analysis; $P < 0.05$ was considered as significant. Statistical Product and Services Solutions (SPSS, version 21, Chicago, IL, USA) was used for statistical analyses.

Results

Intermediate survival with destination HCC therapy and reasons for transplant ineligibility

One hundred and twenty-three patients with HCC met inclusion criteria, with 50/123 (40.6%) alive at 3 years. No significant difference existed between the cohort surviving 3 years and the remaining population with respect to age at presentation ($P = 0.232$), gender ($P = 0.065$), or ethnicity ($P = 0.503$) (Table 1). Forty-eight percent of the cohort surviving 3 years and 22% of the population that did not ($P = 0.030$) underwent evaluation for transplant and were ultimately denied listing for similar reasons, including (cohort alive at 3 years *vs.* not): severe cardiopulmonary disease (38.2% *vs.* 36.1%), active substance abuse (17.6% *vs.* 21.3%), psychiatric (8.8% *vs.* 12.7%), unwilling (26.5% *vs.* 12.9%) and other (8.8% *vs.* 17%) ($P = 0.764$) (Table 1).

Tumor characteristics/treatment modalities

No significant difference was found between the two groups in terms of tumor characteristics including number of lesions at diagnosis ($P = 0.156$), AFP at diagnosis ($P = 0.898$), and presence of unilobar disease ($P = 0.540$). Initial treatment modality employed, including TACE, Y-90, RFA, MWA, bland transarterial embolization, and EBRT, was also not found to be significant ($P = 0.760$) (Table 2).

Liver disease factors and intermediate survival

No significant differences existed between groups with respect to liver disease factors including etiology of liver disease ($P = 0.113$), albumin ($P = 0.376$), bilirubin ($P = 0.354$), or creatinine at diagnosis ($P = 0.708$). However, INR at diagnosis was significant ($P = 0.024$) (Table 3). In addition, the cohort surviving 3 years had a significantly lower MELD score at HCC diagnosis (9.7 *vs.* 11.4, $P = 0.037$) and MELD following initial locoregional therapy (10.7 *vs.* 13.3,

Table 1 Demographics

Characteristic	Alive at 3 years (n=50)	Not alive at 3 years (n=73)	P
Gender (male)	64%	79%	0.065
Ethnicity			0.503
White	48%	62%	
African American	14%	6.8%	
Hispanic	34%	25%	
Other	4%	6.8%	
Age at HCC diagnosis	66.3±4.99	67.5±6.08	0.232
Evaluation for OLTx	48%	22%	0.030
Reason for denial			0.764
Outside of Milan criteria	32%	36%	
Cardiopulmonary disease	38.2%	36.1%	
Substance abuse	17.6%	21.3%	
Psychiatric condition	8.8%	12.7%	
Other concomitant malignancy	8.8%	17%	
Unwilling	26.5%	12.9%	

HCC, hepatocellular carcinoma.

Table 2 Tumor and initial treatment factors

Variable	Alive at 3 years (n=50)	Not alive at 3 years (n=73)	P
Number of lesions	1.7±1.09	2.0±1.18	0.156
AFP at diagnosis	152±446.22	166±626.10	0.898
Unilobar disease	76%	70%	0.540
Initial treatment modality			0.760
Transarterial chemoembolization	36%	41%	
Transarterial radioembolization	42%	41%	
Radiofrequency ablation	14%	6.8%	
Microwave ablation	2%	4.1%	
Bland transarterial embolization	2%	6.8%	
External beam radiation therapy	4%	0%	

P=0.008) (Table 3).

Discussion

Inherent to a global trend towards an increasing average lifespan comes an increasingly elderly population diagnosed

with HCC (8). This has given rise to ongoing debate as to the most appropriate treatment strategies for this population. Numerous treatment options are available, with transplant allocation determined based on a comprehensive assessment of candidacy and individual fitness for surgery. Available treatment options include potentially curative

Table 3 Liver disease factors

Variable	Alive at 3 years (n=50)	Not alive at 3 years (n=73)	P
Etiology of cirrhosis			0.113
Viral	66%	42%	
NASH	20%	25%	
EtOH	6%	22%	
Autoimmune	0%	4.1%	
Cryptogenic	8%	6.8%	
Albumin (g/dL) at diagnosis	3.4±0.63	3.3±6.4	0.376
Total bilirubin (g/dL) at diagnosis	1.2±1.35	1.4±1.10	0.354
INR at diagnosis	1.2±0.17	1.3±0.43	0.024
Creatinine (mg/dL) at diagnosis	1.1±0.77	1.11±0.85	0.708
MELD at diagnosis	9.7±4.49	11.4±4.54	0.037
MELD after initial locoregional therapy	10.7±3.82	13.3±6.83	0.008

MELD, model for end-stage liver disease

therapies such as LT or surgical resection, ablative techniques, chemoembolization, radioembolization (Y-90), stereotactic radiation, and chemotherapy. There is significant interest in developing effective and durable treatment regimens for those who do not undergo LT or surgical resection. Elderly patients often are not candidates for surgery and there is increasing prevalence of HCC and liver-related morbidity in this population.

Advances in LRT and techniques have allowed for effective treatments with notable anti-tumor or oncostatic effect, safety, and minimal invasiveness (when compared to surgery), and represent an alternative therapeutic option (9). Per guidelines by the American Association for the Study of Liver Disease (AASLD) (10) and others (11), locoregional therapy, specifically TACE, is recommended as a first-line therapy for non-curative, nonsurgical management of patients with large multifocal HCC.

Prior studies have evaluated the efficacy and safety of locoregional therapy, with TACE having been shown to improve patient survival compared to supportive care alone in those with unresectable HCC (12,13); however, these studies have focused predominantly on the use of TACE and have not evaluated the possible benefit of using newer modalities such as radioembolization with yttrium-90. It has previously been established that LRT are effective in patients awaiting transplantation. This study aimed to determine features that are predictive of 3-year, intermediate-term survival in patients undergoing locoregional therapy for HCC as

a destination therapeutic approach, focusing specifically on patients 60 years of age and older who are unwilling or unable to undergo surgical treatment.

Our results suggest that patient demographic factors do not have a significant impact on intermediate-term survival and that rather host liver function at diagnosis of HCC and immediately following locoregional therapy (represented by the MELD score) are more predictive. This appears to have been largely driven by an elevated INR in our cohort. This is in contrast to what was previously found in a study by Sato *et al.*, which suggested that age greater than 70 was associated with significant mortality following treatment with locoregional therapy, specifically RFA (14). Two previous studies, however, found that advancing stage of HCC, not age of the patient, influenced patient survival when stratified by treatment subgroups (15,16). Our results echo these findings and additionally show that a wider range of treatment modalities may be applicable given that no significant difference was observed in terms of survival among the various locoregional techniques used.

Though this study included a large number of HCC patients over the age of 60 with a long-term follow-up period, and included a wide array of treatment modalities, it is not without limitations. First, a selection bias may be inherent given that data was pooled from a single center. In addition, results were based on initial treatment session despite many patients undergoing multiple treatment sessions and/or modalities. Prospective trials would be

beneficial to further support our findings.

Destination therapy may be increasingly employed in the elderly population and our results suggest that locoregional approaches as “destination therapy” for patients with HCC presenting within transplant criteria who are either ineligible or unwilling result in modest intermediate-term survival (roughly 40%). Liver function at presentation and immediately following initiation of locoregional therapy, rather than demographics, tumor characteristics, or treatment modality are robust predictors of survival at 3 years. Further prospective studies are needed to assess optimization of candidate selection and modality-specific regimens with this approach.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the committee of Banner Health (#0004299) and waiver of informed consent was obtained for this retrospective study.

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