Multidisciplinary Management of Hepatocellular Carcinoma Improves Access to Therapy and Patient Survival

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Background: Given the complexity of managing hepatocellular carcinoma (HCC), it is widely accepted that a multidisciplinary team approach (tumor boards) offers the best approach to individualize therapy. The aim of this study was to determine utilization of therapies and outcomes for patients with HCC, comparing those managed through our multidisciplinary tumor board (MDTB) to those who were not.

Methods: A database analysis of all patients with HCC managed through our MDTB, from 2007 until 2011, was performed. A database of all patients with HCC from 2002 to 2011, not managed through MDTB, was similarly created.

Results: A total of 306 patients with HCC, from 2007 to 2011 were managed through our MDTB, in comparison with 349 patients, from 2002 to 2011 who were not. There were no significant differences in baseline demographic data or model for end-stage liver disease at presentation. Patients managed through MDTB were more likely to present at an earlier tumor stage and with lower serum alpha fetoprotein (AFP) ($P = 0.007$). The odds of receiving any treatment for HCC was higher in patients managed through MDTB (odds ratio, 2.80; 95% confidence interval, 1.71-4.59; $P < 0.0001$) independent of model for end-stage liver disease score, serum AFP, and tumor stage. There was significantly greater survival of patients managed through MDTB (19.1 ± 2.5 vs. 7.6 ± 0.9 mo, $P < 0.0001$). Independent predictors for improved survival included management through MDTB, receipt of any HCC treatment, lower serum AFP, receipt of liver transplant, and T2 tumor stage.

Conclusions: Patients with HCC managed through a MDTB had significantly higher rates of receipt of therapy and improved survival compared with those who were not.

Key Words: tumor board, hepatocellular carcinoma, multidisciplinary

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BACKGROUND

Hepatocellular carcinoma (HCC) is a major global health problem, and the third leading cause of cancer-related mortality worldwide. The incidence of HCC in the United States has tripled during the past 20 years, largely attributed to hepatitis C viral infection acquired decades prior.[1] HCC is a complex disease, which occurs in the background of chronic liver disease. Its management therefore must simultaneously address challenges related to both tumor burden and underlying liver dysfunction. Up until recently, HCC was universally fatal, with a 5-year survival $< 10\%$.[2] The past 15 years, however, have witnessed significant advances in the management of HCC, which is now potentially curable, if detected early.[2] Liver resection, ablation, and liver transplantation are potentially curative treatments, with 5-year survival up to 70%. Intra-arterial therapy, such as transarterial chemoembolization, and systemic chemotherapy, with Sorafenib, have both been shown to prolong survival in patients with advanced HCC.[3–5] Given the complexity of managing HCC, as well as the plethora of potential treatment options available, it is widely accepted that a multidisciplinary team approach (or tumor boards), which includes hepatologists, oncologists, radiologists, surgeons, and pathologists, be utilized for the optimal management of patients with HCC.[6–8] This approach has been successfully utilized in the management of other cancers, for which the adoption of a team approach or "tumor board" has become commonplace.[6] However, it is estimated that less than half of physicians in the United States adopt this approach for evaluation and management of HCC, and patient utilization of potential therapies for HCC continues to remain suboptimal.[9] To date, a few studies have been published on the effect of this multidisciplinary paradigm on therapy utilization and outcomes in patients with HCC.[10,11] The aim of this retrospective study was to compare, in a single tertiary care center, the utilization of potential therapies and outcomes for patients with HCC who were managed through the multidisciplinary tumor board (MDTB) to a partially contemporaneous cohort who were not.

METHODS

An institutional MDTB was organized for patients with primary liver tumors in June 2007. The decision of whether a patient was discussed at our tumor board was at the discretion of the referring provider for the patient, and therefore subject to the provider's referring practices, based on their area of specialty, location of their practice, prior experience with patients with HCC, and knowledge of the tumor board. Individual cases with their corresponding imaging studies were reviewed at a weekly conference

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attended by transplant hepatologists, medical oncologists, hepatobiliary and transplant surgeons, pathologists, diagnostic, and interventional radiologists. The gamut of potential therapies offered includes surgical resection, liver transplantation, thermal ablation, intra-arterial therapies such as chemoembolization and/or radioembolization, systemic chemotherapy, stereotactic radiation, and comfort-based care. Decisions regarding the appropriate treatment modality were made based on patient factors, review of their cross-sectional imaging studies and/or histopathology, in context of their underlying liver dysfunction. The tumor board discussion was summarized in meeting minutes as well as tumor board encounters recorded in each patient's medical chart.

Although patients with benign tumors are presented at MDTB, only patients with a diagnosis of HCC are included in this study. The diagnosis of HCC was made based on the presence of accepted radiologic criteria[12–14] on dynamic imaging (computed tomography or magnetic resonance imaging) and/or histopathologic findings. A database analysis of all patients with HCC managed through our MDTB, since its inception up to December 31, 2011, with follow-up until May 31, 2013 was performed. Data for analysis included demographics, laboratory parameters at time of diagnosis and treatment, imaging findings, histopathology and/or surgical pathology, treatment rendered and follow-up information. For comparison, a database of all patients with a diagnosis of HCC managed at our institution in the model for end-stage liver disease (MELD) era (from February 2002 to December 31, 2011), as identified by International Classification of Diseases 9 code (155.0), but not managed through the MDTB, was similarly created and reviewed. The outcomes measured in this study include receipt of any therapy and patient survival. Outcomes were evaluated until May 31, 2013.

The Health Sciences Institutional Review Board of the University of Wisconsin School of Medicine and Public Health approved this study.

Statistical Analysis

Univariate analysis was performed comparing the HCC patients managed through MDTB with the HCC patients managed without MDTB. For categorical variables, χ^2 or the Fisher exact test were utilized and for continuous variables the Student *t* test was utilized.

Survival analysis was performed with Kaplan-Meier statistics and multivariable Cox Proportional hazards models were used to compare survival between the MDTB and the non-MDTB groups censoring for liver transplantation.

Two-tailed *P*-value of <0.05 were considered statistically significant.

RESULTS

From 2007 to 2011, a total of 306 patients with HCC were managed through the MDTB. In comparison, 349 patients were not managed through the MDTB (from 2002 to 2011), including 60 patients managed outside the confines of the MDTB in the interval from 2007 to 2011 when the MDTB was available in our center. Baseline demographic and tumor characteristics are shown in Tables 1 and 2, respectively. There were no significant differences in the baseline demographic data including age, sex, and MELD score at presentation between the 2 groups (Table 1).

TABLE 1. Baseline Demographic Data

Variables	MDTB (N = 306) (%)	Non-MDTB (N = 349) (%)	*P*
Age at presentation (mean ± SD) (y)	61 ± 9.4	62 ± 11.9	0.22
Sex (M:F)	254:52	272:77	0.13
Presence of cirrhosis	283 (92)	283 (73)	0.0005
Presence of chronic viral hepatitis	168 (55)	161 (46)	0.03
Total bilirubin at presentation	2.2 ± 3.9	2.1 ± 2.6	0.67
MELD score at presentation	12 ± 5.6	12.3 ± 5.7	0.61

F indicates female; M, male; MDTB, multidisciplinary tumor board; MELD, model for end-stage liver disease.

The patients in the MDTB cohort had less advanced HCC than the patients in the non-MDTB group, with more patients with T2 tumor stage, lower serum alpha fetoprotein (AFP) levels, and fewer patients with multifocal or extrahepatic disease (Table 2).

The rate of treatment was higher among the MDTB patients (75%) than in the non–MDTB-managed patients (61%), with an odds ratio in favor of treatment in the MDTB group of 2.80 (95% confidence interval, 1.71-4.59; $P < 0.0001$), which was independent of MELD score, serum AFP, total bilirubin and tumor stage (Table 3).

Comparison in the forms of treatment utilized in the 2 cohorts showed a shift in the MDTB cohort, compared with the non-MDTB group, to more use of thermal ablation (37% vs. 13%). Although rates of chemoembolization were similar in the 2 groups (21% vs. 17%), the utilization of radioembolization (15% vs. 2%) as well as combined multimodal treatment, which represents combination of locoregional therapies including ablation, chemoembolization or radioembolization, were higher in the MDTB group (12% vs. 2%). Patients referred to the MDTB were also more likely to receive liver transplantation (24% vs. 14%). There was a small shift away from primary surgical resection in the MDTB group, although the proportion of patients receiving surgery was small in both groups (10% vs. 16%). The rates of systemic

TABLE 2. Baseline Hepatocellular Carcinoma Characteristics

Variables	MDTB (N = 306) (%)	Non-MDTB (N = 349) (%)	*P*
Serum AFP (median) (ng/mL)	23.4	79.3	0.009
No. patients with T2 tumor stage	147 (48)	90 (26)	< 0.0001
Multifocal disease	78 (26)	123 (35)	0.008
Extra-hepatic disease	33 (11)	97 (28)	< 0.0001

MDTB indicates multidisciplinary tumor board.

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TABLE 3. Hepatocellular Carcinoma Treatment Data

Variables	MDTB (N = 306) (%)	Non-MDTB (N = 349) (%)	*P*
Any treatment	228 (75)	212 (61)	0.0001
Radiofrequency ablation	114 (37)	47 (13)	< 0.0001
Chemoembolization	63 (21)	59 (17)	0.16
Radioembolization	47 (15)	6 (2)	< 0.0001
Multimodality locoregional therapy	38 (12)	8 (2)	0.004
Resection	32 (10)	57 (16)	0.02
Systemic chemotherapy	33 (11)	57 (16)	0.11
Liver transplantation	72 (24)	48 (14)	0.0001

MDTB indicates multidisciplinary tumor board.

TABLE 4. Multivariate Survival Analysis (From Presentation)

Variables*	Hazard Ratio for Mortality	95% CI	*P*
Sex	0.902	0.647-1.257	0.543
Age	1.0	0.989-1.012	0.942
Presence of cirrhosis	0.652	1.036-2.635	0.035
MELD score at presentation	1.061	1.030-1.094	0.0001
AFP at presentation	1.000	1.000-1.000	0.014
T2 stage	0.626	0.426-0.919	0.017
HCC-specific treatment	0.281	0.191-0.415	0.0001
Tumor board	0.722	0.551-0.946	0.018
Ablation	1.022	0.739-1.413	0.895
TACE	0.926	0.664-1.290	0.649
Radioembolization	1.178	0.761-1.826	0.462
Liver transplantation	0.109	0.066-0.181	0.0001
Systemic chemotherapy	1.231	0.833-1.819	0.297

*Additional variables controlled for in multivariate analysis include number of nodules, bilobar involvement, multifocal disease, vascular involvement, extrahepatic disease and total bilirubin level at presentation.

CI indicates confidence interval; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; TACE, transarterial chemoembolization.

chemotherapy in both groups were similar (11% vs. 16%); various chemotherapy regimens were reportedly used; however, the rates of Sorafenib use among the 2 cohorts were similar (data not shown).

In a univariate analysis, patients managed through MDTB had an overall greater survival (19.1 ± 2.5 mo) compared with those managed without MDTB (7.6 ± 0.9 mo) with $P < 0.0001$ (Fig. 1).

In multivariable survival analysis, independent predictors of improved survival include receipt of any HCC treatment, utilization of MDTB, receipt of liver transplantation, lower serum AFP at presentation and T2 tumor stage (Table 4). Utilization of MDTB remained an independent predictor of improved survival in multivariable analysis even after stratifying patients in the cohorts based on their tumor stage at presentation (Tables 5, 6).

DISCUSSION

The management of HCC is complex because the vast majority of HCC occurs in the background of chronic liver disease and treatment needs to be individualized, addressing the dual challenges posed by the underlying liver dysfunction and tumor burden. For these reasons, and multimodal therapies now available to treat HCC, it is widely recommended that patients with HCC should have their care directed through a MDTB.[6–8] A typical MDTB comprises of transplant hepatologists, oncologists, hepatobiliary and/or transplant surgeons, interventional radiologists and pathologists. However, despite the widespread consensus on the appropriateness of MDTBs, there have been few studies examining patient outcomes using this MDTB paradigm. A retrospective study of 121 patients with HCC who were evaluated by an MDTB at a Veterans Affairs Medical Center between November 2003 and November 2006, and compared with a historical cohort reported improved uptake of both palliative and curative treatments, and prolonged survival, in the patients managed through a MDTB.[10] In another single center in the United States, a retrospective review of management of 167 patients with HCC found that the 97 (58%) who were presented to a tumor board were more likely to receive treatment with ablation, resection or liver transplantation, and were less likely to develop tumor progression or metastasis.[11] In multivariate analysis, presentation to the tumor board was independently associated with better survival.

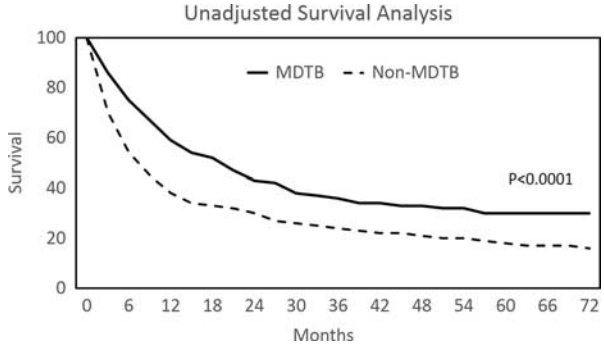

FIGURE 1. Kaplan-Meier survival analysis (unadjusted) of MDTB and non-MDTB cohorts. MDTB indicates multidisciplinary tumor board.

In our study, we present outcomes of a large cohort of patients with HCC managed through our MDTB from 2007 to 2011, comparing them to outcomes of patients with HCC who were not managed through a MDTB at our institution. We have expanded this comparison cohort by including patients evaluated in the interval from the adoption of the MELD score to prioritize patients with HCC on the liver transplant waiting list (ie, 2002) until 2007. Thus, we had 2 groups of roughly the same size. There are no significant differences in the baseline demographic data among the 2 groups (Table 1). Patients managed through the MDTB were more likely to be diagnosed at an earlier tumor stage, have lower serum AFP, and were less likely to have multifocal or extrahepatic disease at time of presentation (Table 2). These differences are likely in part due to improved screening of at-risk patients with earlier recognition of HCC and heightened awareness among clinicians of the value of referral to the MDTB. There may also have been selection biases after the institution of the MDTB, which are difficult to gauge, such as the frequent shifts during the study interval in allocation of

TABLE 5. Multivariate Survival Analysis of HCC T1 or T2 Stage (From Presentation)

Variables*	Hazard Ratio for Mortality	95% CI	*P*
Sex	1.17	0.693-1.976	0.558
Age	1.0	0.989-1.012	0.201
Presence of cirrhosis	2.156	0.727-6.396	0.166
MELD score at presentation	1.024	0.963-1.088	0.452
AFP at presentation	1.000	1.000-1.000	0.002
HCC specific treatment	0.247	0.098-0.627	0.003
Tumor board	0.58	0.367-0.918	0.02
Ablation	1.44	0.743-2.791	0.28
Resection	0.52	0.229-1.184	0.119
Liver transplantation	0.095	0.047-0.193	0.0001

*Additional variables controlled for in multivariate analysis include number of nodules, bilobar involvement, multifocal disease, vascular involvement, extrahepatic disease and total bilirubin level at presentation.

CI indicates confidence interval; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease.

MELD exception points to patients with HCC on the waiting list, or changing physician attitudes to futility of treating HCC in patients with advanced disease.

While recognizing the potential for hidden differences in the 2 cohorts, we believe that it is notable that the odds of receiving any HCC-specific therapy was higher in patients managed through the MDTB, irrespective of MELD score, total bilirubin, serum AFP, and most importantly tumor stage. Moreover, more patients received curative or palliative treatments, and many (12% vs. 2%) patients went on to receive >1 modality of treatment.

In our study, the survival outcome in patients referred to the MDTB was significantly improved overall even after correction for tumor stage at presentation (Tables 4–6). Undoubtedly, this result is open to biases. The favorable result in the MDTB cohort may be due in part to lead-time bias. Moreover, as we are comparing the MDTB cohort with historical controls, the data may be influenced by improvements in the delivery and efficacy of treatment modalities over time, which in turn, may have influenced the improved survival of patients. Despite this limitation, there were similar treatments offered for HCC, including liver transplantation, between these 2 eras. Taken together with 2 smaller studies referenced above, we believe the cumulative data supports the contention that concerted, multimodality therapy for HCC improves patient survival.

TABLE 6. Multivariate Survival Analysis of HCC T3 Stage or Beyond (From Presentation)

Variables*	Hazard Ratio for Mortality	95% CI	*P*
Sex	0.82	0.57-1.19	0.82
Age	1.0	0.99-1.015	0.70
Presence of cirrhosis	1.05	0.71- 1.54	0.82
MELD score at presentation	1.088	1.062-1.115	0.0001
AFP at presentation	1.000	1.000-1.000	0.47
HCC specific treatment	0.351	0.259-0.476	0.0001
Tumor board	0.716	0.551-0.931	0.012
Ablation	0.679	0.438-1.053	0.084
Resection	0.412	0.257-0.659	0.0001
Liver transplantation	0.102	0.048-0.218	0.0001

*Additional variables controlled for in multivariate analysis include number of nodules, bilobar involvement, multifocal disease, vascular involvement, extrahepatic disease and total bilirubin level at presentation.

CI indicates confidence interval; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease.

It is increasingly recognized that poor communication between specialists and generalists hampers the provision of good care to patients with complex liver disease, and that these patients need coordinated multidisciplinary approaches to management.[15] A MDTB facilitates multimodal treatment for these complex patients with HCC by enabling improved communication among the matrix of professionals involved in the care of these patients, and patient follow-up. At a very practical level, it saves the patient the cost, time and anxiety of having to attend serial clinics and successive new specialists in the pursuit of a clinical plan, with potential for duplication of investigations and delayed or contradictory therapy. As shown in our study, the MDTB enables more patients to receive treatment, who in the past were likely to go untreated.

In summary, HCC remains a challenging clinical problem, with rising incidence in many areas, including the United States. Our study shows that a multidisciplinary approach to coordinate, individualize and optimize care for these complex patients improves rate of treatment utilization, including both curative and palliative therapies for HCC, and improves patient survival. Future prospective studies are needed to further study how to improve outcomes of patients with HCC.

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