Hepatic Arterial Therapy as a Bridge to Ablation or Transplant in the Treatment of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is a challenging malignancy as a result of the advanced course at presentation. Recent interventional advances have improved treatment of lesions unamenable to resection using drug-eluting microbeads delivered into the hepatic circulation. We hypothesize that the use of hepatic arterial therapy (HAT) will safely identify appropriate patients who can proceed to ablation and/or transplantation. We evaluated our open-label, multicenter, multinational, single-arm study including 240 patients with intermediate-staged HCC who received drug-eluting beads and were not initial candidates for transplantation or resection. We reviewed the resulting clinical data to determine factors leading to possible ablation or transplant. Of 240 patients undergoing HAT, 14 (5.8%) received ablation or transplant. We compared those receiving ablation or transplant with those receiving only HAT. Groups were similar regarding sex, age, median number of tumors (one; range, 1 to 25), Child's score, tobacco and alcohol abuse, and treatment type. Patients who were downstaged were more likely to have: hepatitis-related tumors (76 to 66%, $P = 0.02$), distinct lesions on imaging (92 to 76%, $P = 0.004$), and less than 25 per cent parenchymal involvement (84 to 59%, $P = 0.0001$). These patients typically had one tumor frequently in the left lobe (58.8 *vs* 30.9%, $P = 0.0001$), accessible through segmental arteries (47 *vs* 17%, $P = 0.001$), with increased segmental branch occlusion (57 *vs* 39%, $P = 0.02$). HAT should be considered a potential bridging therapy to eventual ablation or transplant in the multimodal treatment of HCC.

As the third leading cause of the world's cancer deaths, hepatocellular carcinoma (HCC) is a deadly malignancy.[1] With 48,500 new cases from 2000 to 2006, HCC is the ninth leading cause of cancer death in the United States, with a 5-year survival rate of at best 15 per cent for all stages.[2, 3] A total of 27,200 deaths from HCC are predicted in the United States over the next decade.[4] The only reliable method of cure for HCC remains surgical intervention.[5] Different modalities have been developed to supplement classical anatomical hepatectomy for HCC, including transplantation,[6–11] transarterial chemoembolization,[12, 13] and radiofrequency ablation (RFA)[14] based on the stage of the cancer and the performance status of the patient. RFA has been described as an alternative to resection, also increasing survival. Liver transplantation for lesions not exceeding certain anatomic criteria on imaging has also proven to be curative.

A newer adjunct to these modalities includes catheter delivered hepatic arterial therapy (HAT). This method of delivering microscopic beads into the hepatic circulation using an interventional technique has been proven to result in a decrease in tumor size and improved survival with minimal morbidity in patients with HCC.[15–17] In addition, HAT beads are frequently augmented with microdoses of chemotherapeutic agents such as doxorubicin or radiation-delivering ions like yttrium-90. Initially used as destination therapy for the treatment of HCC in patients with advanced tumor burden, HAT is now being used earlier in the disease management process as a method of decreasing tumor size in HCC with anatomically unfavorable lesions. The goal of this treatment is to reduce the size of the tumor burden to

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the point of potential surgical intervention, thereby effectively "downstaging" the patient to potentially receive RFA, transplant, or resection.[6–11, 18] The purpose of this study was to determine the role that HAT plays as part of downstaging in a cohort of patients undergoing treatment for HCC.

Methods

This prospective study analyzed the results of an ongoing evaluation for the treatment of liver tumors by different methods of HAT. This database is composed of patients with HCC enrolled in an open-label, multicenter, multinational single-arm observational registry. Patients were eligible if they were older than age 18 years, had a new diagnosis of HCC, and had tumors that were either multiple in number or deemed unresectable by the consulting surgeon. This evaluation was approved by the Institutional Review Board of each participating institution.

After obtaining informed consent, the patients underwent hepatic arterial cannulation through an interventional technique. They received doxorubicin-eluting bead embolization (LC Bead), yttrium-90 embolization (Sirr-sphere or Therasphere), or a combination to the vasculature of the tumor. This decision was made by the treating physician at each institution. After this treatment, patients were re-evaluated between 3 and 6 months through repeat imaging to determine the degree of response. Response to therapy was determined by modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria.[19] If patients had residual disease, they received further HAT if the anatomy was favorable. Otherwise, they underwent chemotherapy as per the local standard of care. If the patients were able to be "downstaged," that is, their tumors were now of a lower American Joint Committee on Cancer (AJCC) stage, they were offered more aggressive treatment. If patients met Milan criteria for transplantation (single tumor less than 5 cm or three tumors less than 3 cm) or were then surgical candidates after HAT, these options were offered.

We compared risk factors, tumor characteristics, and clinical outcomes between patients undergoing surgical treatment with curative intent after HAT *versus* those who did not receive surgery. *Post hoc* analyses were performed using chi square, independent *t* test, Fisher exact test, and log rank testing. All statistical analyses were performed using PASW/SPSS (IBM, Somers, NY).

Results

Two hundred forty patients in this cohort underwent 421 individual sessions of HAT for intermediate stage (AJCC Stage IIB to Stage III) HCC. Of these patients, 14 (5.83%) were able to undergo subsequent operative treatment. Specifically, two patients underwent liver transplantation after being downstaged to tumor dimensions matching the Milan criteria; the remaining 12 patients underwent liver RFA. The two groups were similar in terms of median age (67 nonoperative *vs* 63 operative), gender composition (72.1% male *vs* 76.9% male), tobacco use (29.9 *vs* 30.7%), and alcohol abuse (24.7 *vs* 23.1%) (Table 1).

Each patient's hepatic history for risk factors and overall staging systems, including Child's Pugh score and Okuda classification, were similar (Table 2). Those patients undergoing surgery had a higher rate of hepatitis C-related disease (66.7 *vs* 35.8% , $P = 0.034$). None of the operative patients had portal venous thrombus compared with 16.0 per cent of the nonoperative patients. There was no difference in the Child's score of the groups; Class A (58.4 *vs* 71.4%), Class B (37.0 *vs* 28.6%), and Class C (4.6 *vs* 0%), respectively ($P = 0.5$). A significantly higher proportion of operative patients had a lower Okuda score (grade of 1: 66.2 *vs* 92.3%, $P = 0.038$).

Patients were classified according to anatomical considerations of parenchymal disease burden based on radiographic appearance on CT imaging using a combined, triple-phase hepatic protocol. Initial classification was assigned based on the borders of each tumor within the parenchyma. If tumors were well separated from other lesions by surrounding normal-appearing parenchyma, they were classified as "distinct." Conversely, if the border between lesions was indistinct, they were classified as "numerous." Patients undergoing surgery had a higher incidence of distinct HCC lesions compared with those who did not (76.7 *vs* 92.3%, $P = 0.004$). In addition, the operative group had a significantly lower degree of parenchymal involvement as stratified by quartiles (less than 25% involvement, 59.6 *vs* 84.6%, $P = .0001$). The median

TABLE 1. *Patient Characteristics*

Characteristics	Nondownstaged (n = 226)	Radiofrequency Ablation/ transplant (n = 14)	*P*
Age (years) (median, range)	67 (27–88)	63 (51–78)	
Gender (%)	72.1% male	76.9% male	
Medical history			
Cardiac	41 (18.1%)	1 (7.1%)	0.293
Vascular	19 (8.4%)	0 (0%)	0.258
Pulmonary	35 (15.5%)	1 (7.1%)	0.396
Diabetes	70 (31.0%)	1 (7.1%)	0.058
Alcohol	58 (25.7%)	2 (14.3%)	0.340
Tobacco	70 (31.0%)	3 (21.4%)	0.451
Hypertension	110 (48.7%)	7 (50.0%)	0.923

TABLE 2. *Hepatic History*

Factor	No Surgery	Surgery	*P*
Hepatitis	151 (66.8%)	10 (71.4%)	0.781
Hepatitis B	15 (9.4%)	0 (0%)	0.265
Hepatitis C	57 (35.8%)	8 (66.7%)	0.034
Portal vein thrombosis	36 (16.00%)	1 (7.1%)	0.374
Child's score			
A	128 (58.4%)	10 (71.4%)	0.513
B	81 (37.0%)	4 (28.6%)	
C	10 (4.6%)	0 (0%)	
Okuda class			0.129
1	145 (66.8%)	13 (92.9%)	0.028
2	64 (29.5%)	1 (7.1%)	
3	8 (3.7%)	0 (0%)	
Distinct lesion on imaging	161 (73.5%)	12 (92.3%)	0.004
Liver involvement			0.0001
Less than 25%	117 (57.4%)	12 (85.7%)	
26–50%	69 (33.8%)	1 (7.1%)	
51–75%	15 (7.4%)	1 (7.1%)	
76%	3 (1.5%)	0 (0%)	
Number of lesions (mean, SEM)	2.46 (0.301)	2.08 (0.529)	0.734
1	88 (55.0%)	8 (66.7%)	0.638
2	31 (19.4%)	1 (8.3%)	
3+	41 (25.6%)	3 (25.0%)	
Extrahepatic disease	22 (9.8%)	0 (0%)	0.218
Alpha fetoprotein (mean, SEM)	16,300 (11,593)	7,642 (6,781)	0.850

TABLE 3. *Treatment Factors*

Factor	No Surgery	Surgery	*P*
Number of treatments (mean) (SEM)	1.765 (0.0756)	1.500 (0.174)	0.388
1	124 (54.9%)	8 (52.1%)	0.479
2	60 (26.5%)	5 (35.7)	
3+	42 (18.6%)	1 (7.1%)	
Treatment type			
LC Bead	354 (87.6%)	14 (87.5%)	1.00
Sirr-spheres	6 (1.5%)	0 (0%)	
Therasphere	44 (10.9)	2 (12.5%)	
Right lobe treatment	194 (48.0%)	5 (31.3%)	0.188
Left lobe treatment	125 (30.9%)	10 (58.8%)	0.0001
Middle lobe treatment	34 (8.4%)	0 (0%)	0.226
Segmental treatment	70 (17.3%)	8 (50%)	0.001
Doxorubicin dosing			0.135
75 mg	114 (39.9%)	2 (18.2%)	
100 mg	30 (10.5%)	3 (27.3%)	
150 mg	142 (49.7%)	6 (54.5%)	
Branching			0.02
Lobar	168 (55.6%)	5 (35.7%)	
Segmental	114 (37.7%)	8 (57.1%)	
Subsegmental	20 (6.6%)	1 (7.1%)	
Flow occlusion			0.034
Complete	132 (42.7%)	7 (53.8%)	
Near complete	77 (24.9%)	6 (46.2%)	
Partial	100 (32.4%)	0 (0%)	
Bead size			
100–300	204 (50.5%)	9 (56.3%)	0.652
300–500	152 (37.6%)	6 (37.5%)	0.992
500–700	31 (7.7%)	2 (12.5%)	0.482

number of liver tumors present on imaging was also lower in the operative group (Table 2).

The number of HAT treatments was lower the operative group (one treatment: 55.5 *vs* 69.2%, $P = 0.4$). The types of treatment delivered, however, were the same between groups (81.0 *vs* 76.9% LC Bead). In patients undergoing surgery, the majority of the treatments occurred in the left lobe (30.9 *vs* 58.8%, $P = 0.0001$) *versus* the right lobe in the nonoperative group (48.0 *vs* 29.4%, p =. 2). The operative group had an overall higher dosage of doxorubicin associated with the LC Beads (54.5 *vs* 49.7% with 150 mg doxorubicin, $P = 0.1$). Bead size was conserved between the groups (Table 3).

On angiography, a greater portion of the operative group had lesions more directly accessible. This was gauged by the ability to cannulate the segmental and subsegmental arteries supplying each lesion as opposed to the main lobar artery only (54.0% lobar *vs* 35.7% lobar, $P = 0.02$). The rate of complete or near occlusion of these arteries was also increased in the operative group (68.8 *vs* 100%, $P = 0.034$). Those patients receiving surgical treatment experienced a significant increase in overall survival (OS; $P = 0.006$) and disease-specific survival (DSS; $P = 0.012$) on log rank analysis with no patients developing death as a result of disease after 120 months (Figs. 1 and 2).

Discussion

This analysis describes a unique subset of patients with intermediate-stage HCC who were able to be downstaged to surgical therapy. It has been previously demonstrated that patients with intermediate-stage HCC benefit from HAT. Anecdotal experience shows response to HAT has either been fairly rapid and significant or patients have failed this modality utterly, leading to an "all or none" attitude toward HAT. That is, patients have been grouped by response into "responder" with good clinical outcomes or "nonresponders," who showed no benefit with HAT. However, this study presents a third subset of patients, those who were able to be downstaged with HAT and subsequently undergo definitive treatment. By using HAT as a bridge to other forms of treatment, more patients can be effectively "recaptured" who would otherwise have a very poor prognosis.

The group identified as a target for this treatment strategy within this cohort is, on inspection, the subset of patients that one would empirically expect to be candidates for downstaging. The majority of the lesions in the operative candidates were solitary and in the left lobe, leading to more favorable anatomic considerations for surgery after HAT as well as angiographic treatment. The lesions were more readily

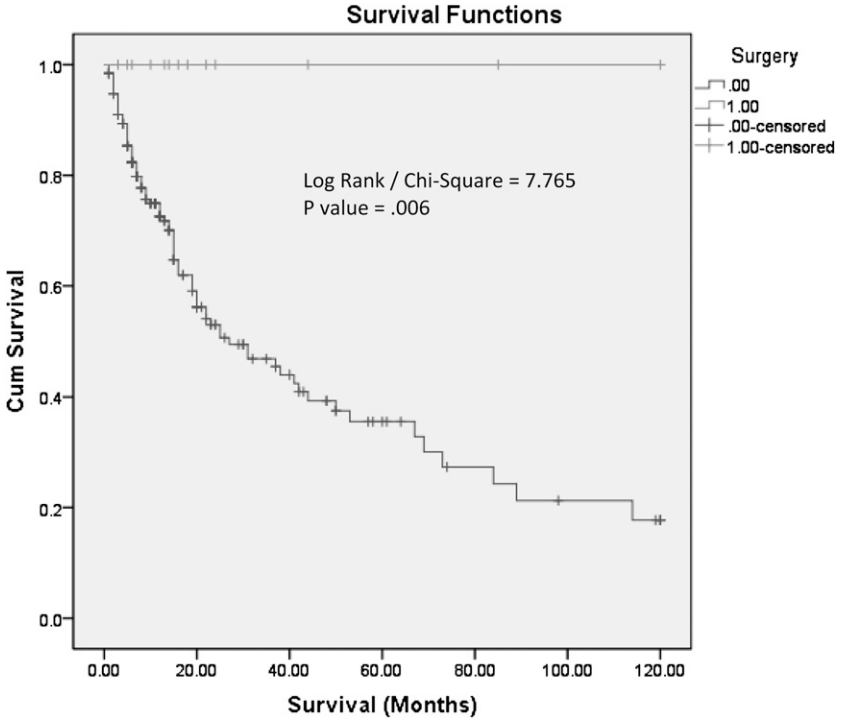

FIG. 1. Overall survival stratified by surgical therapy.

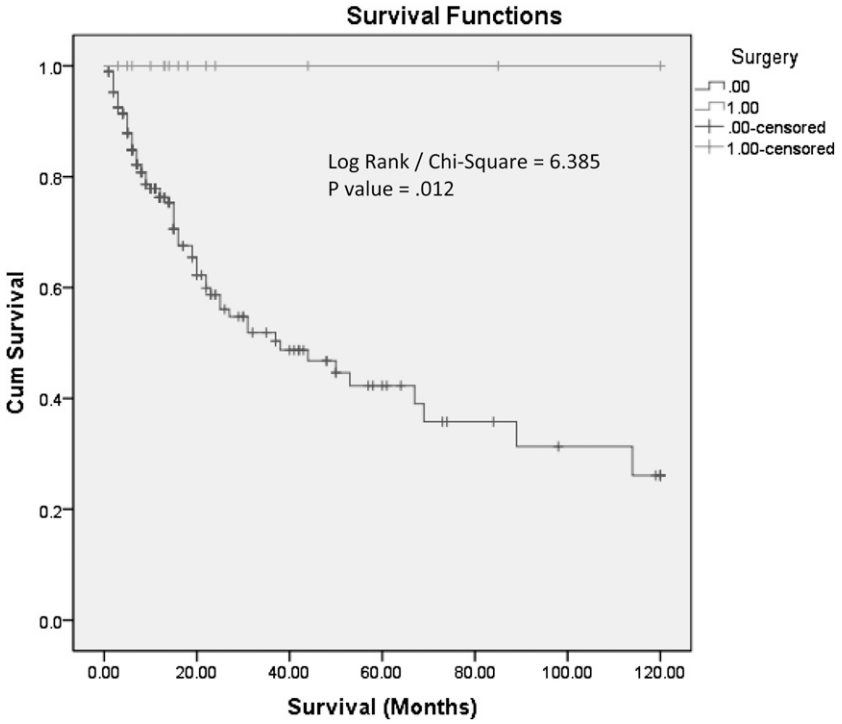

FIG. 2. Disease-specific survival in hepatocellular carcinoma stratified by surgical therapy.

accessible through cannulation of smaller contributing arteries as opposed to lobar branches. As such, these lesions would receive a more concentrated dose of HAT drug than those that are accessible through a lobar artery. The size of these arteries also led to an increase the rate of complete or near complete occlusion, further enhancing the effectiveness of the delivered HAT.

A confounder to this may be the dosage of doxorubicin that was delivered. Although 36.4 per cent of the nonoperative group received the lowest dose of doxorubicin, only 14.3 per cent of the operative group

received this dose. The contribution of the higher dose of doxorubicin to the effect of HAT in the operative group without a larger sample size cannot be determined. This is especially true because these data would need to be further stratified by total number of treatments, number of tumors treated as well as other factors. Subsequent investigation will be needed as HAT for HCC continues and outcomes are observed based on doxorubicin dosing.

The majority of focus for downstaging HCC has been with the goal of transplantation in mind. Several studies[6–11, 18] have attempted to achieve response using HAT such that patients were then eligible for transplantation through Milan criteria or other proprietary determinants. Although two of the 14 patients identified as surgical candidates in our study underwent transplantation, the remaining 14 patients underwent ablative therapy. Graziadei et al. describe successful transplantation in 41 of 48 patients with HCC after transcatheter arterial chemoembolization (TACE).[18] However, the patients enrolled already had met Milan criteria for transplantation. The role of HAT in this population was more of a maintenance therapy while waiting for transplantation than in our population, where RFA was an additional therapeutic end point.

Otto and colleagues[6] describe the use of TACE in a population of 62 patients exceeding Milan criteria. Of these patients, 27 were able to undergo transplantation after two rounds of TACE lipiodol and mitomycin. To qualify for transplantation, patients had to have regression of disease after initial TACE as defined by RECIST criteria. This proportion is significantly higher than those reported within our study. However, this population included patients of lower stage who were excluded from our cohort, potentially lowering our rate of transplantation.

Yao et al.[7] showed similar results from a group of 61 patients exceeding T2 criteria. Of these patients, 57 per cent underwent transplantation. These patients underwent pretransplant downstaging through TACE and RFA. These results have been replicated with the University of California–San Francisco criteria with a resulting transplant rate of 33.1 per cent for all stages.[9] Similar results were obtained by Ravaioli et al. with the proprietary Bologna criteria with downstaging; they report a transplant rate of 67 per cent with no difference in survival between those downstaged patients and those not downstaged. Jang et al. report similar success with downstaging using epirubicin or cisplatin with Lipiodol, resulting in transplantation in 41 per cent of all 386 patients presenting with tumor burdens outside the Milan criteria. Our analysis differs greatly from the previous work with downstaging in that we have analyzed only the ability of HAT to act as a downstaging mechanism. Although many of our patients did receive RFA, this was performed before HAT.

Although these results show significant promise for HAT as a therapy modality and bridge to transplantation, they do not make specific mention of the role of RFA as destination therapy. Ablation has been proven to be a successful treatment modality in the treatment of HCC. Many patients undergoing HAT will either not meet transplant criteria after treatment or be otherwise poor transplant candidates secondary to concomitant cardiopulmonary disease. The role of ablation as destination therapy for patients with HCC undergoing HAT should be seen as a complement to transplantation and a potential end point of treatment. Further investigation and consensus are needed to develop HAT as a supplementation for HCC treatment.

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