Comparison of Transarterial Chemoembolization in Patients With Unresectable, Diffuse vs Focal Hepatocellular Carcinoma

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Hypothesis: Transarterial chemoembolization (TACE) is beneficial for selected patients with unresectable hepatocellular carcinoma (HCC).

Design and Setting: A prospective comparison study in a tertiary hospital.

Study Period: November 21, 1995, to May 2, 2001, with a mean follow-up of 939 days.

Patients: A total of 157 TACE treatments were performed in 88 patients with unresectable HCC: 132 treatments in 69 patients with focal HCC (F-HCC) and 25 treatments in 19 patients with diffuse HCC (D-HCC).

Interventions: Transarterial chemoembolization consisted of selective catheterization and intra-arterial infusion of a mixture of doxorubicin hydrochloride, cisplatin, and mitomycin followed by embolization. Sequential treatments were performed for bilobar HCC.

Main Outcome Measures: Child-Pugh classification and clinical outcomes, including α-fetoprotein (AFP) response, length of hospital stay, readmission rate, and survival, were compared between patients with F-HCC and D-HCC following TACE using the χ² test, Fisher exact test, or t test (2-tailed, unpaired).

Results: Fifty-eight patients (84%) in the F-HCC group and 18 patients (95%) in the D-HCC group had cirrhosis. For those patients with cirrhosis, 58 (100%) in the F-HCC group and 14 (78%) in the D-HCC group had a Child-Pugh score of A or B (P = .002). The mean baseline AFP was higher in the D-HCC group: 55577 vs 7815 ng/mL in the F-HCC group (P = .001). Of the patients secreting AFP, 4 (29%) of 14 in the D-HCC group and 30 (68%) of 44 in the F-HCC group had a significant decrease in AFP 1 month following TACE (P = .01). The mean hospital stay was longer (3 vs 1.9 days; P = .001), and readmissions occurred more frequently (44% vs 9%; P < .001) in the D-HCC group. The mean survival rate was significantly higher in the F-HCC group: 425 vs 103 days (P < .001).

Conclusions: In patients with F-HCC, TACE is well tolerated and provides a survival benefit. However, there is no apparent benefit for patients with D-HCC. Importantly, tumor characteristics and hepatic reserve are essential criteria for successful TACE.

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Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide. Viral hepatitis B and C infections and cirrhosis are known risk factors. Most patients are diagnosed as having HCC late and have underlying liver disease that often precludes effective treatment. These patients have a poor prognosis and most will live less than 1 year after diagnosis.

The diagnosis of HCC is usually suspected based on radiologic imaging studies, such as computed tomography (CT), magnetic resonance imaging (MRI), and in some cases, angiography. Because of the vascular nature of these tumors, the radiologic findings are distinct. However, the radiologic features are frequently obscured by coexisting cirrhosis with regenerative nodules or other benign tumors. The diagnosis may be established by fine-needle aspiration or biopsy or by significant and/or serial elevation of the tumor marker, α-fetoprotein (AFP). There is consensus in the liver transplant community that an AFP level greater than 500 ng/mL is diagnostic and a level greater than 250 ng/mL is highly suspicious for HCC in a patient with cirrhosis and a hepatic mass on radiologic imaging. Seventy percent of HCC tumors secrete AFP.

Hepatocellular carcinoma can be classified into 3 types based on gross characteristics: nodular, massive, and diffuse.
PATIENTS AND METHODS

Consecutive patients who were diagnosed as having unresectable HCC or liver transplant candidates with suspected HCC who met the criteria for TACE treatment were included in this prospective comparison trial. The diagnosis of HCC was based on histologic evidence and/or radiologic imaging with a serum AFP value greater than 250 ng/mL. The diagnosis of HCC was confirmed histologically in 75 of 88 patients before TACE treatments. A biopsy was not performed in transplant candidates for fear of tumor seeding or in patients at increased risk for complications from this procedure. The HCC was confirmed in the explanted liver on the 5 patients who underwent liver transplantation at our center.

Tumors were classified based on gross radiologic findings. Unlike the classic gross classification, we stratified tumors into 2 distinct groups: focal (F) or diffuse (D). Patients with nodular or massive HCC were considered to have F-HCC, whereas those with diffusely infiltrating or multifocal (>3) tumors were classified as having D-HCC. Patients were considered to have AFP-secreting tumors if the baseline AFP value was greater than 50 ng/mL. This AFP baseline value was selected because of the high prevalence of viral hepatitis and cirrhosis in our patients.

Pretreatment evaluation consisted of the following: (1) medical history, (2) complete physical examination, (3) laboratory studies to assess renal, hematologic, and liver function, (4) serum AFP value, (5) assessment of portal vein patency by ultrasonography and CT or MRI scan, (6) hepatitis serologic testing, and (7) Child-Pugh classification. A list of exclusion criteria for TACE follows.

### Exclusion Criteria
- Extrahepatic metastasis
- Complete portal vein thrombosis
- Obstructive jaundice
- Severe comorbidity or infection
- Advanced liver disease
- Uncontrolled encephalopathy
- Total bilirubin level >5 mg/dL (85.50 µmol/L)
- Prothrombin time >16 seconds
- Intractable ascites
- Gastrointestinal varices >grade II

These criteria are based on our experience and did not always correspond with the Child-Pugh C classification.

Before treatment, visceral angiography was performed to assess the arterial blood supply to the liver and confirm portal vein patency. Selective catheterization was achieved and a mixture of doxorubicin hydrochloride (50 mg), cisplatin (100 mg), mitomycin (20 mg), and ethiodized oil (Ethiodol; Savage Laboratories, Melville, NY) was infused followed by embolization with polyvinyl alcohol particles (Ivalon; Unipoint, High Point, NC). For patients in most patients by tumor size, location, and/or underlying hepatic disease. Various types of local ablative therapies have been used for patients with unresectable HCC with some success. Transarterial chemoembolization (TACE) is a form of local ablation that uses regional chemotherapy and localized infarction.

Despite the worldwide use of TACE for many years, the efficacy of this treatment is controversial. Nonrandomized studies evaluating TACE treatment have shown improved quality of life and survival, whereas randomized studies have not demonstrated a survival benefit. These studies have generally compared TACE treatment in heterogeneous patients with heterogeneous tumors. Importantly, the efficacy of TACE on specific tumor types is unknown. Herein, we report a comparison of TACE in patients with focal vs diffuse HCC.

### RESULTS

From November 21, 1995, to May 2, 2001, 157 consecutive TACE treatments were performed in 88 patients with unresectable HCC. Seven patients in the F-HCC group were transplant candidates at the time of TACE treatment. The mean follow-up for this trial was 939 days, with a range of 58 to 2047 days. Table 1 outlines the demographic and clinical characteristics of the 2 treatment groups. In the F-HCC group, 30 patients received 1 TACE treatment, 26 patients received 2 treatments, and 13 patients had more than 2 treatments. In the D-HCC group, 13 patients had more than 2 treatments. In the D-HCC group, 13 patients had more than 2 treatments. In the D-HCC group, 13 patients had more than 2 treatments. In the D-HCC group, 13 patients had more than 2 treatments. In the D-HCC group, 13 patients had more than 2 treatments.

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### Table 1. Patient Demographics*

<table>
<thead>
<tr>
<th>Demographic</th>
<th>D-HCC</th>
<th>F-HCC</th>
<th>Value</th>
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<tbody>
<tr>
<td>No. of patients</td>
<td>19</td>
<td>69</td>
<td>...</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
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<td>64 ± 12</td>
<td>.95</td>
</tr>
<tr>
<td>Male/female</td>
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<tr>
<td>Cirrhosis</td>
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<td>58</td>
<td>.23</td>
</tr>
<tr>
<td>Child-Pugh classification</td>
<td>A or B</td>
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<td>58</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>16</td>
<td>61</td>
<td>.62</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>5</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>11</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Maximum tumor size, mean ± SD, cm</td>
<td>...</td>
<td>6.4 ± 3.9</td>
<td>...</td>
</tr>
<tr>
<td>Baseline AFP, mean ± SD, ng/mL</td>
<td>55 577 ± 83 386</td>
<td>7815 ± 26 026</td>
<td>.001</td>
</tr>
<tr>
<td>Baseline AFP &gt;50 ng/mL</td>
<td>14</td>
<td>44</td>
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<td>.30</td>
</tr>
<tr>
<td>No. of TACE treatments</td>
<td>25</td>
<td>132</td>
<td>...</td>
</tr>
</tbody>
</table>

*Data are presented as number of patients unless otherwise indicated. D-HCC indicates diffuse hepatocellular carcinoma; F-HCC, focal hepatocellular carcinoma; ellipses, data not applicable; AFP, α-fetoprotein; and TACE, transarterial chemoembolization.

Histologic grade is based on cellular differentiation, and the World Health Organization (WHO) classification describes 5 distinct histologic types. Growth patterns and histologic structure are known to affect prognosis.

Surgical removal, either with partial or total hepatectomy, represents the only potentially curable treatment. Unfortunately, surgical resection is precluded...
with bilobar HCC, sequential TACE treatments were performed at 1- to 2-month intervals. Patients were hospitalized following TACE until adverse effects were controlled with oral medications. After discharge from the hospital, patients were seen in the outpatient clinic weekly for 1 month and then monthly. Posttreatment evaluation consisted of an adverse symptoms questionnaire, physical examination, and biochemical studies to assess for hepatic, renal, and hematologic function during their hospital stay and outpatient clinic visits. The AFP value 1 month following TACE was compared with the baseline value. The AFP responders were defined as those who had a 25% or greater decrease in AFP value during this interval. Follow-up radiologic imaging was performed at 6 and 12 months and compared with baseline studies. Additional TACE treatments were performed if there was evidence of tumor growth, de novo tumors identified, or a progressively increasing AFP.

Clinical outcomes, including AFP response, length of stay, readmission rate, complications, and survival (mean, actual 1 year, and actual 2 year), were monitored and analyzed. Comparisons between the F-HCC and D-HCC groups were made with the χ² test for categorical variables, Fisher exact test for binary variables, and t test (2-tailed, unpaired) for continuous numerical variables. All tests of significance were 2-tailed with a significance level of .05.

Table 2

The comparisons of clinical outcomes following TACE are summarized in Table 2. Five patients with F-HCC underwent liver transplantation at our center after a mean waiting time of 267 days following the first TACE treatment. Four transplant recipients are alive without evidence of recurrent HCC at a mean follow-up of 841 days (range, 104-1777 days). One recipient died from the sepsis 3 days following the transplantation. Two other patients with F-HCC underwent transplantation at another center and were lost to follow-up. Five patients in the F-HCC group had surgical resection following TACE. These patients were not candidates for resection before TACE because of tumor size and proximity to major vascular structures. Following TACE, there was a reduction in tumor size, rendering them eligible for surgical resection. Patients who had undergone liver transplantation or surgical resection were excluded from the survival analysis. Eight patients (7 with F-HCC and 1 with D-HCC) were lost to long-term follow-up.

Hepatocellular carcinoma is a leading cause of morbidity and mortality worldwide. It is associated with cirrhosis in 60% to 90% of patients and most prevalent in regions with a high seroprevalence of hepatitis B virus infection. As the current hepatitis C epidemic, HCC is becoming increasingly common in the United States. Hepatocellular carcinoma is the most common malignancy seen at our liver disease center, which is located in a large, urban region with an ethnically diverse population. In our study, 76 (86%) of 88 patients had cirrhosis, and 77 (88%) had hepatitis B and/or C infections. Most patients were older than 60 years, and there was a 2.6:1 prevalence in men.

The evaluation and diagnosis of HCC are becoming more standardized. Current radiologic techniques can detect these vascular tumors with a high degree of sensitivity and specificity. The presence of an elevated AFP value raises the suspicion for HCC. Unfortunately, hepatic inflammation and regeneration will also increase AFP levels, and thus the level of AFP needed for diagnosis is unclear. We obtained AFP levels in all patients and found that 79 (90%) of 88 had levels greater than 10 ng/mL. However, only 58 patients (66%) had levels greater than 50 ng/mL, and 51 (58%) had levels greater than 100 ng/mL. The clinical triad of a hepatic mass, viral hepatitis and/or cirrhosis, and an AFP level greater than 250 ng/mL is diagnostic of HCC. Histologic confirmation is no longer essential for all patients with HCC before treatment. In fact, a fine-needle biopsy may be contraindicated in patients who are candidates for liver transplantation or surgical resection.

Tumor histologic grade and type are known to affect prognosis. Seventy-five (85%) of our patients had histologic confirmation of HCC, and most of these patients had well-differentiated or moderately differentiated tumors. Because numerous patients had fine-needle aspirates at outside institutions, assessment of histologic grade and type was not consistent. Thus, we did not correlate these variables with clinical outcome.

The gross classification of HCC in most patients is based on radiologic findings. We included patients with nodular and massive HCC in the F-HCC group since these tumors, regardless of size, represented focal lesions distinct from the surrounding liver parenchyma. The mean
size of tumors in our patients was substantial at 6.4 cm, with a range of 2 to 18 cm. Patients with diffusely infiltrating tumors, or more than 3 tumors, were classified as having D-HCC. The multifocality of these tumors in the setting of cirrhosis made it difficult to determine the exact number of tumors present and the extent of parenchymal involvement. Angiography confirmed the diffuse or multifocal nature of the tumors in the D-HCC group. Using this criteria, only 19 (22%) of 88 patients had D-HCC. Radiologic findings alone were not adequate to distinguish the subtypes of nodular HCC as described by the Liver Study Group of Japan.26 Stratifying patients into 2 groups based on gross radiologic criteria proved simple and reproducible.

Most patients with HCC are not candidates for surgical resection and potential cure. Local ablative treatment modalities have been developed to control HCC without the need for major surgical intervention. Transarterial chemoembolization is one such treatment that has been used for many years, particularly in Asia.27 The advantages of TACE include being readily available and minimally invasive. However, the efficacy of TACE remains controversial because of the discrepancy between randomized and nonrandomized studies. These studies evaluated the clinical benefit of TACE in heterogeneous patients with heterogeneous tumors.16-21 We evaluated the outcomes of TACE in 2 groups of similar patients with different gross tumor characteristics.

The clinical results of this study demonstrate the significant risks and lack of benefits from TACE in the D-HCC group. None of the patients with D-HCC lived more than 10 months, and all died of tumor progression and hepatic failure. Clearly, these patients had more advanced liver disease even though 78% had Child-Pugh class A or B disease. Because of the extent of tumor burden and distribution, we believed that patients with D-HCC were not candidates for local ablation (eg, radiofrequency ablation, cryosurgical ablation, or percutaneous ethanol injection therapy) with the exception of TACE. Although the risk of liver failure and subsequent death in patients with cirrhosis who undergo TACE is well known, we believed that TACE was the only potentially effective treatment option for these patients.19 However, our data demonstrate the significant morbidity and mortality associated with TACE in patients with D-HCC. It is our belief that in patients with D-HCC the tumor burden and hepatic function impairment are often underestimated. We believe a 16% mortality for a palliative procedure is unacceptable, and thus we currently do not advocate TACE in patients with D-HCC regardless of Child-Pugh score. Furthermore, we are unaware of any effective treatment modality for these patients.

In patients with F-HCC, TACE was well tolerated, and only 1 (1%) of 69 patients died (of liver failure) following a second treatment. One patient developed ischemic cholecystitis following TACE to the right lobe of his liver and required a cholecystectomy. Otherwise, adverse effects were related to the procedure and were transient and easily managed. The survival in patients with F-HCC was significantly better than in patients with D-HCC. Approximately one third of patients with F-HCC were alive 2 years following TACE without any other treatment modality. These data compare favorably with published reports on the natural history of HCC in untreated patients.2

Importantly, 7 patients with F-HCC eventually underwent complete hepatectomy and orthotopic liver transplantation. Five of these patients underwent transplantation at our center after a mean waiting time of 267 days (range, 149-443 days) following TACE treatment. Four of these 5 patients recovered from the transplantation, and none of them have developed recurrent HCC. Given the shortage of donor organs and the protracted waiting time, TACE is an important treatment modality to help control tumor growth in patients with HCC who are awaiting liver transplantation.

In conclusion, tumor characteristics are important criteria for successful TACE. Transarterial chemoembolization is efficacious in patients with F-HCC regardless of tumor size, provided patients have adequate hepatic reserve. However, there is no apparent clinical benefit of TACE in patients with infiltrating or multifocal (>3 tumors) HCC. The morbidity and mortality associated with TACE in patients with D-HCC are substantial and should be avoided.

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REFERENCES


DISCUSSION

Mark S. Talamonti, MD, Chicago, Ill: As a new member of the Western Surgical Association, I would also like to compliment Dr Lopez and his colleagues for taking on the task of re-viewing what is essentially a nonsurgical procedure. I am reminded of Dr Richardson's presidential address yesterday about the so-called cognitive specialties vs the surgical specialties. If one reviews the world literature on chemoembolization, you will find that the most critical and analytical assessments of this procedure have been done by surgeons. Our medical colleagues in the so-called cognitive specialties have addressed such profound questions as whether it is important to add cisplatinum or mitomycin to the chemotherapy cocktail, whether we should use Ivalon sponges or little metal coils vs big metal coils for the embolization part of the procedure, while the surgeons are left to address such simple and humble questions as, is it safe, and does it work?

So what have we learned from Dr Lopez's presentation? First, proper patient selection is absolutely crucial to avoid complications and deaths. The selection parameters and exclusion criteria outlined in their presentation and in his manuscript are absolutely essential to avoid excessive morbidity and treatment-related deaths.

Secondly, patients with diffuse or multifocal hepatocellular carcinoma are poor candidates for local or regional therapies and should not undergo chemoembolization. No surprise there.

Thus I have 3 questions that are directed at the group of patients with focal hepatocellular carcinoma. First, what were your treatment end points? Our experience with a similar group of patients was recently published, and we found that the patients with the most sustained and durable responses were the ones with tumors less than 4 cm in size and who had undergone at least 4 or more chemoembolizations per tumor. Thus, can you tell us if there were any differences in response rates or survival among the patients with focal hepatocellular carcinoma based on differences in their chemoembolization treatments?

Secondly, several of your patients had transplants or resections after chemoembolization. You mentioned that extensive necrosis was seen in some of the transplant specimens. In our experience we have found that the degree of response to chemoembolization may be a prognostic predictor for survival and disease-free intervals in patients who have undergone chemoembolization. I was wondering if you could give us any update on that information.

Finally and from a very clinical perspective, when I am in the clinic with my residents and I see these patients come in, I go through this elaborate algorithm of decision making. I decide whether or not they are candidates for surgical resection, candidates for transplant, and if not, then I am left with the majority of patients as you mentioned, who may be candidates for some locoregional ablative form of therapy. And now I have choices between chemoembolization, radiofrequency ablation, ethanol ablation, and I was wondering in your review of these patients if you can give us some insights in terms of the decision-making algorithm or the decision-making tree you go through and how chemoembolization plays or does not play in the role with these other ablative modalities.

Theodore X. O'Connell, MD, Los Angeles, Calif: I thought this was a good paper, but I have several problems with the conclusions drawn. Because it is not randomized and prospective and really has no controls, it is very difficult to come to the conclusions that Dr Lopez has. There is no doubt that it is ter-rible to have diffuse hepatocellular carcinoma (HCC), and any kind of treatment is probably not very worthwhile. But that is not really proven by the paper because you don't have a group with no treatment controls in those with the diffuse hepatocellular carcinoma. On the other side, Dr Lopez came to the conclusion that TACE is good for focal HCC, but again it is very hard to draw that conclusion unless you have a control group with no treatment to prove that TACE is better than the no treatment control. Certainly in the studies done around the world when it was done in a randomized prospective way, there...
is no survival benefit to TACE and this should probably only be done as a bridging procedure for liver transplant.

Jean-Nicolas Vauthey, MD, Houston, Tex: It is very important that we revisit hepatic arterial embolization. There are at least 4 randomized studies that have not shown an improvement in survival, and I think the effort to better define the patients that can benefit from the procedure is worthwhile. Now regarding this effort, I would like to ask Dr Lopez if he could characterize these patients a little bit better for us in terms of size differences, in terms of patients who have multiple vs single tumor, or presence of vascular invasion which you can assess by current imaging, and it is important to point out that you can use fine-needle aspiration and assess the grade of these patients. Has it been done, and are these patients with diffuse tumors patients with higher grade tumors? Are we looking at different biology?

Dr Lopez: Dr Talamonti raised several important issues, but first let me start by saying our interest in hepatocellular carcinoma stems from the fact that it is the most common malignancy seen at our liver disease center, and as Dr Talamonti mentioned, the great majority of patients are not candidates for transplantation or surgical resection. Thus we are left to try and determine what treatment modality, if any, is best for the individual patient. I am going to start with Dr Talamonti’s third question regarding this decision making. At our center, those patients with tumors less than 3 cm without evidence of vascular invasion, essentially stage I and II, are considered transplant candidates, and we work to prepare these patients for that eventual procedure. Unfortunately, tumor growth will preclude some of them from this life-saving procedure.

Other patients are stratified into those who are surgical candidates, and again this will include mainly patients who are Child-Pugh class A with sufficient hepatic reserve. Patients with small tumors are usually candidates for some type of surgical treatment, whether it be a radiofrequency ablation, cryosurgical ablation, or resection. Patients with larger tumors and cirrhosis are considered for nonoperative treatment such as chemoembolization. This group represents the majority of patients seen at our center. In our patient population, almost 90% of our patients have viral hepatitis and/or cirrhosis, and the mean tumor size was 6.4 cm.

Dr Talamonti mentioned the end point for patients with focal tumors. There are 2 end points: one is symptomatic relief. Some of the patients with focal lesions, even large lesions, are relatively asymptomatic and it is hard to say that we are actually alleviating their symptoms. Eventually, they all will become symptomatic, and so it is more accurate to say we hope to delay the onset of symptoms. The main end point is survival. I believe TACE does extend survival in selected patients. It is important to look at the historical controls; however, I understand the comments about the prospective randomized trials. Clearly several of these trials indicated a trend toward better patient survival with chemoembolization; and the key, as Dr Vauthey brought up, is patient selection. Due to small numbers of patients and early deaths, these trends were not statistically significant and therefore, these studies concluded TACE did not extend survival, although it did improve patient symptoms. I would argue with that conclusion to say that it really depends on the type of patient that we are selecting and the type of tumor we are treating. Patients with focal lesions, however large, seem to respond well to TACE.

Dr Talamonti raised a question of the histology in explanted livers. This is an important point. Five of the patients in the focal group went on to transplantation at our center, and an additional 5 went on to liver resection. In those patients, when we examined the resected specimens, you saw extensive necrosis of the tumors and sparing of adjacent hepatic parenchyma. So clearly I believe that arterial embolization, whether or not you add chemotherapeutic drugs, had a beneficial effect on tumor growth.

Dr O’Connell raised the issue of the lack of controls. While I understand his concern, it has been very difficult in our experience to convince patients to enter a treatment arm where there is no treatment. I think that we are at the point where it is almost unethical to ask patients to be in the control group. We know the natural history of this disease, and I find it difficult to convince patients to forego any treatment.

Dr Vauthey asked about tumor size and characteristics. These characteristics are based on radiologic findings. We did not separate patients based on tumor size but included all patients with focal lesions into one group. This included patients with massive tumors of 15 to 18 cm. We also included patients with vascular invasion as long as the main portal vein was patent. Again, our goal was to see how many patients who were not candidates for surgical treatment would benefit from this nonsurgical treatment. We did not stratify patients based on tumor grade since this information was not available for all patients. Hepatomas that are infiltrating or multifocal have a different tumor biology characterized by aggressive growth and unresponsiveness to any therapy.