The Role of Tumor Ablation in Bridging Patients to Liver Transplantation

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Hypothesis: Treatment of hepatocellular carcinoma before liver transplantation can curb local tumor progression and thereby prolong patients’ transplantation eligibility.

Design: Retrospective case-control pilot study. Twelve of 39 patients receiving liver transplantation for hepatocellular carcinoma had treatment before transplantation. Pretreatment included radiofrequency ablation (n=8), percutaneous ethanol injection (n=2), both modalities (n=1), and tumor resection (n=1). Twelve control subjects without pretreatment who were age-, sex-, and score-matched on the Model for End-stage Liver Disease and Child-Turcotte-Pugh classification were selected. The primary outcome measure was the waiting period for transplantation.

Results: Patients with pretreatment waited on the transplant list significantly longer than their counterparts without pretreatment (median, 484 vs 253 days; \( P = .03 \)).

Conclusions: Treatment before transplantation with tumor ablation or resection is associated with a longer waiting period on the transplant list. This enables patients who might otherwise be removed from the list because of tumor progression to receive transplantation.

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and the most frequent solid organ tumor. It is one of the world's 10 most common tumors, and its burden on society is not inconsequential, accounting for more than 1 million deaths per year. There has been a steep rise in incidence in the United States to 2.4 cases per 100000 people, a rate that is expected to increase further in the coming years because of delayed consequences of the hepatitis C virus epidemic of the 1970s and 1980s.

Patients who have small tumors may be eligible for multiple treatment alternatives, including partial hepatectomy (PH). Although PH provides a chance of cure, only a small percentage of patients with HCC undergo resection. Contraindications to PH include limited liver reserve and tumor size and location, and the resectability rate in patients with underlying cirrhosis is as low as 10%. For most patients, other locoregional therapeutic options exist, including transarterial chemoembolization, percutaneous ethanol injection (PEI), and radiofrequency ablation (RFA). All of these treatments, including resection, are associated with a high rate of tumor recurrence, because the entire liver is at risk for HCC.

Liver transplantation offers the dual advantages of eradicating the tumor and replacing the diseased liver. This modality has become the treatment of choice, especially for patients with end-stage liver disease. Favorable outcomes with 5-year tumor-free survival in the range of 70% have been reported in recent studies for patients with stage I or II disease (ie, 1 nodule that is 2-5 cm or ≤3 nodules that are all <3 cm, without vascular invasion). The outcomes of orthotopic liver transplantation (OLT) in patients with stage III disease (ie, 1 nodule that is >5 cm or ≥3 nodules with at least 1 that is >3 cm) and higher have not been encouraging. Therefore, the United Network for Organ Sharing has adopted transplant listing criteria that exclude patients with stage III disease and higher.

Orthotopic liver transplantation remains problematic because of the limited availability of organs. Patients with tumor progression beyond stage II while awaiting appropriate donor livers contribute to a high rate of being rejected from the transplant list. Dropout rates of 23% in 6...
months and up to 40% in 12 months have been reported. When dropouts are included in the 2-year survival calculation, Llovet and colleagues have indicated that properly selected patients fare better with PH than OLT. Appropriate care for patients on the transplant list is controversial, and there is a lack of evidence-based recommendations.

Local tumor control while patients await OLT appears to hold promise to decrease the transplant list dropout rate in the era of an increasing waiting period. Recent suggestions of therapy while on the waiting list include PH, transarterial chemoembolization, and ablative techniques, but definitive studies are required. Although there are data that imply that RFA is safe in such a setting, no studies, to our knowledge, have compared the experience of patients who receive ablation as pretreatment with that of patients who do not. This study was undertaken to determine if such interventions intended as a bridge to OLT extend the waiting period for transplantation.

### METHODS

This was a retrospective case-control pilot study with a median follow-up of 18 months. Thirty-nine patients underwent OLT for end-stage liver disease associated with HCC between January 1999 and August 2003. All patients were placed on the transplant list and ultimately underwent transplantation at the same tertiary referral center.

Twelve patients were identified, each having had ablation or resection before transplantation. Methods of tumor ablation included RFA or PEI. Eight patients received RFA and 2 patients underwent PEI. One patient had both modalities of ablative therapy. Only 1 patient had resection of tumor before transplantation. Intraoperative ultrasonography was used for ablative therapy. Pathologic review of the explanted livers showed a mean±SD of 25%±38.6% (range, 0%-95%) residual tumor at the sites of previous ablation.

### RESULTS

The results are summarized in Table 1. Patients with and without pretreatment had median ages of 52 and 54 years, respectively. Each group had 10 men and 2 women. The mean MELD and Child-Turcotte-Pugh scores were 10.5 and 7.0, respectively, in the group with pretreatment and 11.5 and 8.1 in the group without pretreatment. Although control subjects were not matched to patients based on tumor size, there was no significant difference in the size of the largest dimension of their tumor (median, 2.45 vs 2.50 cm; \( P = .53 \)). The primary outcome measure was days on the transplant waiting list. Patients receiving pretreatment waited on the transplant list significantly longer than their counterparts who did not receive pretreatment (median, 484 vs 253 days; \( P = .03 \)).

Eleven (55%) of 20 patients enrolled before February 2002 received pretreatment, and of the remaining 4 patients enrolled after that time, 1 received pretreatment. The median waiting period for transplantation before February 2002 was 517 and 307 days \( (P = .08) \) for the groups with and without pretreatment, respectively. The median waiting period after that date was 149 and 92 days \( (P = .25) \) for the 2 groups, respectively. The reduction in sample size in the subanalyses precluded achieving statistically significant results.

There were no significant complications associated with ablative therapy. Pathologic review of the explanted livers showed a mean±SD of 25%±38.6% (range, 0%-95%) residual tumor at the sites of previous ablation. The distribution of residual tumor is presented in the Figure. All but 1 patient had residual tumor on microscopic evaluation. One patient in the pretreatment group died 4 months after transplantation because of aplastic anemia. There were 2 HCC recurrences in the matched controls after transplantation and none in the pretreatment group \( (P = .48) \).

### COMMENT

Many treatments now exist for patients with HCC and well-compensated liver function; however, none, to our knowledge, have been evaluated in randomized controlled studies. Most clinicians agree that ultimately these patients need OLT; however, treatment of tumor...
progression in the interim period is variable, and dropout rates from the transplant list are as high as 40%.19,20 We evaluated whether pretreatment mostly with RFA affected the length of time patients remained on the transplant list compared with those without pretreatment.

Patients in this pilot study who received pretreatment before OLT remained on the transplant list significantly longer than their matched control subjects not receiving pretreatment (median, 484 vs 253 days; \( P = .03 \)). These extra days are vital to increasing the probability for an OLT match in today’s era of increasing need for organs in short supply.

After the implementation of the MELD score in February 2002, subanalyses of that data showed that the waiting period dropped to about one third of the previous waiting period. When each group, before and after February 2002, was further subdivided into those who received pretreatment and those who did not, we concluded that there was a similar distribution of patients and controls. In addition, a similar trend of waiting periods was observed regardless of whether the patient was listed before or after February 2002; the waiting period of those receiving pretreatment was 40% longer.

Ablation appears to be a safe, well-tolerated procedure, as no increase in posttransplant morbidity was observed among patients compared with controls. When RFA was used as the primary local ablative therapy, histologically proven residual disease was found in 91% of the explanted livers. Of these, viable tumor occupied on average 40% of the ablated sites. The reported local recurrence rate varies significantly in the literature and has been as high as 79% among patients whose explanted livers were examined microscopically.22 Although most studies of local recurrence are based on imaging results (ie, computed tomography, magnetic resonance imaging, and positron emission tomography), few histologic analyses have been conducted beyond a year from the time of ablation. Our findings are unique because of the long duration (ie, percutaneous, open, or laparoscopic), tumor size, and proximity of tumor to vessels.

Although it is accepted that patients with HCC need OLT, the timing of it is controversial. Should available organs be reserved for the sickest patients? Is there a role for pretransplant therapy? Graziadei et al27 documented that patients meeting United Network for Organ Sharing criteria and receiving pretreatment with transarterial chemoembolization to arrest tumor progression were able to remain on the transplant list, with excellent outcome after OLT. Belghiti and colleagues28 showed in a comparative study that PH extended the time on the transplant list a mean of 20 months and was an effective treatment, yielding no decrease in long-term survival after OLT. Had these patients been placed on the transplant list before the intervention, PH would have extended their ability to wait to 600 days. The Center for the Study of Liver Disease in Hong Kong described a series of 135 patients with 5-year survival of 70% when PH was the primary therapy followed by salvage OLT for HCC recurrence.29 Finally, another study18 of PH before OLT asserts an increase in the ultimate transplantation rate to 10.7% on a 24-month waiting list.

If pretreatment is determined to be appropriate, which modality, PH or ablation, is most effective? Ablative techniques as pretreatment are not well studied.18 Llovet et al18 demonstrated that PEI increased the rate of OLT by greater than 10% at 1 year. There are rare reports of the use of RFA during the waiting period for transplantation. Restaging and treating occult nodules with RFA has been shown to be beneficial in reducing the dropout rate.30 Also, in a case series by Fontana et al,22 RFA was an effective bridge to OLT therapy for 15 of 23 transplants.

**Table 2** compares the local recurrence rate following RFA in contemporary series, including 2 studies that included pathologic data from explanted livers.8,22,25,26 Compared with conventional imaging techniques, microscopic analysis provides much greater sensitivity in detecting small-volume disease. Other factors contributing to postablation recurrence include RFA technique (ie, percutaneous, open, or laparoscopic), tumor size, and proximity of tumor to vessels.

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**Table 2. Local Tumor Recurrence Rate Following Radiofrequency Ablation (RFA) in Contemporary Series**

<table>
<thead>
<tr>
<th>Source</th>
<th>Technique of Ablation</th>
<th>Follow-up, No. of Months From Time of RFA</th>
<th>Detection Method</th>
<th>Local Recurrence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrison et al,8 2003</td>
<td>Percutaneous, open</td>
<td>Median, 10</td>
<td>Radiologic</td>
<td>36 (18/50)</td>
</tr>
<tr>
<td>Fontana et al,22 2002</td>
<td>Percutaneous</td>
<td>Median, 3</td>
<td>Radiologic</td>
<td>58 (7/12)</td>
</tr>
<tr>
<td>Machi et al,25 2001</td>
<td>Open, laparoscopic, percutaneous</td>
<td>Mean, 20.5</td>
<td>Radiologic</td>
<td>22 (14/64)</td>
</tr>
<tr>
<td>Wood et al,24 2000</td>
<td>Open, laparoscopic, percutaneous</td>
<td>Median, 9</td>
<td>Radiologic</td>
<td>18 (15/84)</td>
</tr>
</tbody>
</table>


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plant candidates. As there is a paucity of comparative data on the subject, our pilot study documenting an extended waiting period with the use of ablative techniques encourages us to examine the questions further.

Alternative explanations for a comparatively longer waiting period in the pretreatment group were considered. It is possible that the matched controls received OLT faster because of deterioration of liver function and an associated advancement of priority status on the transplant list, suggesting that the key difference is not extension of the waiting period in the pretreatment group, but rather shortening of the waiting period in the control group. Although possible, we believe that this scenario is unlikely given that the ablative therapy in the pretreatment group would be prone to cause liver parenchymal damage and be associated with possible deterioration more so than nonintervention. Furthermore, the MELD scores of the 2 groups were equivalent at the time of enlistment for transplantation.

Patients in this pilot study were selected from the population of those successfully transplanted. An important question regarding ablative therapy is whether it enables patients who would otherwise be dropped from the list to remain on the transplant list after receiving RFA or PEI. We have shown that patients who receive pretreatment remain on the list longer than their counterparts who do not receive any pretreatment; however, we have not answered the question of whether ablation prevents dropout from the waiting list. An improved study design to address the role of ablation would include all patients who were originally listed for transplantation, comparing the rates of successful transplantation and time-to-event data between similar groups. An analysis of all pretreatments (PH, RFA, and PEI) as a follow-up to this pilot study is now under way. Conclusions of that study, in combination with this study’s results showing that ablation is associated with a longer term on the waiting list, will help determine the feasibility of randomized controlled trials to definitively establish the role of pretreatment modalities in this patient population.

CONCLUSIONS

Treatment before transplantation with tumor ablative therapy or limited resection is associated with a longer waiting period on the liver transplant list. This may be one reason why patients who might otherwise be removed from the list because of tumor progression can be successfully transplanted. Pretreatment with RFA or PEI is safe and effective in bridging certain patients with HCC to transplantation, but when used as the primary therapeutic modality, RFA is associated with a high rate of histologically proven recurrence.

Accepted for publication April 9, 2004.

This paper was presented at the 75th Annual Meeting of the Pacific Coast Surgical Association; February 15, 2004; Maui, Hawaii; and is published after peer review and revision. The discussions that follow this article are based on the originally submitted manuscript and not the revised manuscript.

We acknowledge the contribution of Lois Yamamoto for assistance in study coordination.

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REFERENCES


DISCUSSION

Robert R. Selby, MD, Los Angeles, Calif: For practical purposes, there is only one curative therapy for HCC in the cirrhotic liver, and that is liver transplantation. The converging problems of liver donor unavailability and cirrhotic liver unresectability create a dilemma that has left us struggling for interim therapies that would allow us to bridge the time to transplantation without allowing tumor progression. Add to that the development of a new form of intrahepatic therapy, RFA, whose utility and efficacy are not completely defined, and we have the ingredients of a very timely paper.

In that context, this paper is quite germane. It takes a retrospective look at cirrhotic patients with HCC who have been closely matched physiologically and who have comparable tumor sizes. Both the controls and the pretreated patients have gone on to transplantation. The primary end point is the time from candidate listing to liver transplantation, with the secondary end points of pretreatment morbidity and efficacy. The conclusions of the paper are that pretreatment results in patient transplantability that persists a long time following pretreatment and that this pretreatment is safe.

The MELD and CTP scores of patients at listing were quite low, which I assume means they were listed for HCC rather than liver failure. My first question is what were the MELD and CTP scores at transplantation? Were patients transplanted for liver failure or for time spent on the waiting list? Here, you have 2 groups of patients who were transplanted, and I group waited twice as long as the other. What is the explanation? Did patients with pretreatment demonstrate any radiologic progression while they were waiting, or did the tumors remain inert? Was there radiologic tumor progression in the controls? Rather than just knowing that there was 25% viable tumor in the treated sites of the explanted liver, I would like to know more pathologic information. What were the histologic and radiologic tumor stages of transplanted patients for both subsets? If they were similar at the outset, what were they at transplantation? In the beginning, you established a comparison between the 2 groups, but you have not completely developed that comparison. Although it is impressive that pretreated patients were still transplantable for cure at 484 days, how do we know that the same would not have been true in the control group?

Early in the paper, you say that tumor progression leads to a high dropout rate. But in your matched controls, there was no dropout since it was a retrospective study, and you defined controls that went on to transplantation. I think that in your study design you should pick a primary end point that reflects the ability of your therapy to control local tumor progression and spend more effort on the comparative pathologic data between the groups. Although the results in the study imply, they do not necessarily justify your conclusion, and although that data may be available, it has not been completely elucidated here.

Lastly, just a comment about the nature of RFA. In my mind, this is a spatially 2-dimensional therapy, even when employed intraoperatively. I believe that most failures result from inadequate application due to the difficulty to appreciate the 3-dimensional aspects of tumors on ultrasound imaging, either intraoperatively or in the radiology suite. Perhaps stereotactic localization and treatment, such as neoadjuvant therapy with external beam radiation (CyberKnife), may offer improved control with low morbidity, although I am not yet aware of any trials. Have you any knowledge of such practice?

Ryutaro Hirose, MD, San Francisco, Calif: I have some issues that have been expressed by Dr Selby. You could still examine all of the patients that were listed, even in a retrospective fashion, and look at your dropout rate of patients that were either treated or not treated. I don’t know that that is a favorable end point for anybody to wait longer for their transplant. I don’t think that is actually something that is a good thing to happen to someone waiting for a liver transplant. I also have some questions about the modalities of treatment. Several patients had ethanol injection, 1 person had resection, and the rest had RFA. How many patients were done by interventional radiologists in terms of the RFA vs surgeons, either laparoscopically or open? I believe that the laparoscopic approach often provides superior results than those performed by interventional radiologists.

Also, there have been data that suggest that percutaneous ethanol injections have a higher recurrence rate than RFA. In addition, there have been several studies that give us mixed messages about the role of resection in these patients with cirrhosis, whether it’s a good thing or a bad thing. I want to know how the authors would decide which modality a patient should have. They also did not mention transarterial chemoembolization, which we think is also another modality by which these patients can be bridged towards transplantation. I also want to know what the authors think of the role of living donor transplantation in these patients. And finally, I would like to know whether patients ought to be downstaged. We realize that, with Mazzaferrro’s criteria if you use them, you get very good results. There is no argument with that. But there is a question of whether someone who is slightly outside those bounds can be downstaged either with RFA or resection and whether those patients might not qualify then for liver transplantation as well.

Paul D. Hansen, MD, Portland, Ore: I am intrigued by the converging issues that have been expressed by Dr Selby. You could still examine all of the patients that were listed, even in a retrospective fashion, and look at your dropout rate of patients that were either treated or not treated. I don’t know that that is a favorable end point for anybody to wait longer for their transplant. I don’t think that is actually something that is a good thing to happen to someone waiting for a liver transplant. I also have some questions about the modalities of treatment. Several patients had ethanol injection, 1 person had resection, and the rest had RFA. How many patients were done by interventional radiologists in terms of the RFA vs surgeons, either laparoscopically or open? I believe that the laparoscopic approach often provides superior results than those performed by interventional radiologists.

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The second issue is that between 1998 and 2003 there was tremendous change in RFA devices. We started out with a 50-W 3-cm device, and we now use a 200-W 7-cm device with saline infusion. That should greatly affect our ability to successfully ablate the tumor. I am wondering if the author could comment on their change in devices used over time. Did they notice better results as time went on?

John P. Roberts, MD, San Francisco: Everybody is trying to figure out in the transplant community and probably in the nontransplant community whether to ablate and wait or ablate and then transplant when an organ becomes available. Ablate and wait means that you wait and see if there is a recurrence, and ablate and transplant is when you transplant them based on their stage. The priority of transplantation is unclear...
for those patients who have been ablated, primarily because we
don't know if they have cancer still. Should they be prioritized
for transplantation at the same risk as a patient who is not ab-
lated? That's the area in which we lack clarity.

There was a study from Virginia, fairly similar, in which
they found a 25% risk of having recurrence of tumor at the ab-
lation site and another 25% risk of having tumor elsewhere in
the liver. I was wondering if we could hear about tumor at the
ablation site vs tumor elsewhere in the explanted liver, be-
cause I think this would help us understand the ablate and wait
vs the ablate and transplant issue.

Susan L. Orloff, MD, Portland: I agree with many of the
questions from the audience. They are some of the questions
that I had, and I think this is a very interesting topic to dis-
cuss, especially for those of us involved in liver transplanta-
tion. What are the specific reasons for no pretreatment in the
group of patients that were not pretreated? Most programs, I
believe, treat the patients that have tumors (pretransplant), and
why were these patients specifically not treated? That would
be important to know.

Dr Yeung: I want to thank the discussants for many in-
sightful comments regarding our study, which represents the
first phase of a series of planned studies to examine the value
of tumor ablation as a bridging modality in patients awaiting
liver transplantation for HCC.

The aim of ablation treatment is to halt disease progres-
sion and thereby to extend patients' eligibility on the waiting
list, as our data would support. Additionally, we would expect
a decrease in the dropout rate for the treated group and ulti-
imately be able to achieve equal or better long-term survival fol-
lowing transplantation. These latter hypotheses will be an-
swered in the subsequent phase of the study.

Dr Selby asked about possible reasons for the observed dif-
fferences in the waiting periods between the treated and un-
treated groups. As indicated in the presentation, there are a num-
ber of possibilities besides increasing the duration of eligibility
secondary to a decreased dropout among those treated with ab-
lation. For example, those in the untreated group may have more
severe liver disease, although this is unlikely since both groups
were matched for their MELD scores. Alternatively, there could
be a delay to transplantation due to complications or recovery
from ablation. Again, this is not supported by the observed me-
dian hospital stay of less than 24 hours following percutane-
ous or laparoscopic RFA and by the lack of significant postop-
erative morbidity. Lastly, there may be psychosocial issues in
the treated group that could delay their time to transplant. How-
ever, this should not affect our calculation of the waiting pe-
riod from the time of listing, when these issues have already
been worked out. Of these possible explanations, we favor the
interpretation that pretransplant therapy is effective in reduc-
ing disease progression and maintaining eligibility status for
transplant.

Drs Hirose and Hansen accurately pointed out that local
recurrence following RFA depends on a variety of factors, in-
cluding the techniques employed. In our series, the ablations
were equally divided between percutaneous, open, and laparo-
scopic approaches. The first of these was conducted by our ra-
diologists and the latter 2 by our surgeons. The numbers in each
group are too small for meaningful comparison. However, I think
that our higher recurrence rate is more related to (1) the method
detection, microscopic vs gross imaging techniques; (2) length
of the follow-up period, ours approaching 1½ years; and (3)
the number of ablation sessions. Our patients received only one
ablative procedure as long as their tumors remained within trans-
plant criteria. Other factors such as size of lesions, evolving tech-
nology, and reporting bias would all contribute to the highly
variable rates of recurrence reported in the literature. Several
recent posttransplant series have consistently found over 50%
local recurrence following RFA. Improvements in tumor tar-
\ing, heat distribution (especially for the larger lesions), and
methods of real-time assessment of the ablation zone are much
needed to achieve better outcomes in local control.

Finally, stemming from the paucity of evidence, it is highly
desirable to conduct prospective analyses to determine the real
impact of pretransplant tumor-directed therapies on the long-
term survival of this population.