Liver transplantation should be offered to patients with small solitary hepatocellular carcinoma and a positive serum alpha fetoprotein rather than resection

Jay A. Graham, M.D. a,*, Joseph K. Melancon, M.D. a, b, Kirti Shetty, M.D. b, Lynt B. Johnson, M.D., M.B.A. a, b

a Department of Surgery, and b The Transplant Institute, Georgetown University Hospital, 3800 Reservoir Road, Washington, DC 20008, USA

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Abstract

BACKGROUND: As debate continues as to what surgical modality should be offered to patients with hepatocellular carcinoma, the authors submit that serum $a$-fetoprotein (AFP) is an important variable to consider.

METHODS: Using the Surveillance, Epidemiology and End Results database, patients with solitary tumors within the Milan criteria were further stratified into 2 groups, those who underwent orthotopic liver transplantation (OLT) and those who underwent segmentectomy, lobectomy, or extended lobectomy (resection). Patients were further grouped according to serum AFP status (negative or positive). Relative survival was retrospectively evaluated for 3 years using the log-rank test.

RESULTS: In the AFP-negative group, resection (n = 165) offered equivalent survival compared with OLT (n = 116); 3-year survival was 73.8% and 81.6%, respectively ($P = .245$). In the AFP-positive group, 3-year survival for resection (n = 200) was 59%, while survival was 75.3% for OLT (n = 181), which showed a clear survival advantage ($P = .001$).

CONCLUSIONS: The results of this study demonstrate that patients with solitary hepatocellular carcinoma lesions within the Milan criteria and AFP-positive status should not undergo resection but rather be offered OLT.

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Published in 1996, the Milan criteria radically changed the dominant paradigm that previously guided therapeutic treatment of hepatocellular carcinoma (HCC).\(^1\) This landmark study countered the prevailing thought and showed that orthotopic liver transplantation (OLT) for limited HCC progression yielded curative outcomes. A United Network of Organ Sharing (UNOS) exception allowance soon followed and contributed to the resultant rate rise in OLT for HCC.\(^2\) However, the shortage of donor organs has limited the ability to perform OLT for all patients with disease. Moreover, this practice has brought to the forefront ethical concerns of fairness of organ distribution.\(^3\)

Consequently, there has been renewed interest in resection as a primary therapy for curative or bridge therapy.\(^4,5\) Recent studies promoting resection as a reasonable treatment option for early-stage HCC have also been buttressed by the Barcelona Clinical Liver Cancer (BCLC) staging system.\(^5,7\)
Updated in 2004, the BCLC staging system has sought to underscore the reality that widespread transplantation for HCC is untenable. Combining clinical staging and treatment strategy, the BCLC staging system provides an algorithm for clinicians for HCC. As such, Childs-Pugh score A patients with an absence of portal hypertension or hyperbilirubinemia and a single nodule <5 cm in size should be offered resection. Surrogate measures for the degree of liver disease, bilirubin, and portal pressure are the fulcrum for choosing between resection and OLT. Although these variables are important, we feel that specificity can be added to the decision-making process by incorporating the measurement of serum α-fetoprotein (AFP).

AFP is multimetric glycoprotein that is found in abundance in the fetus. Although many theories have been postulated regarding the role of AFP, its role remains unclear. Interestingly, in adults, increased levels of AFP are seen in only 4 situations: HCC, germ cell tumors, metastatic disease, and neonatal maladies. In HCC, the proliferation of hepatocytes and ultimate neoplastic transformation by upstream signaling defects increases the expression of AFP. In our translational approach, we use AFP to gauge survival in patients who have undergone either resection or transplantation. More important, we submit that AFP may be used as a prognostic factor for these patients.

Retrospectively using the Surveillance, Epidemiology and End Results (SEER) database, we identified patients with limited-disease HCC within the Milan criteria who were offered either resection or OLT. Assessing the preoperative serum AFP level, we further divided these groups. Evaluating these groups’ relative survival for 3 years (2004–2007) in 12-month intervals, it became clear that elevated AFP conferred a survival disadvantage. Further delineating solitary tumors within the Milan criteria, we demonstrated that the dismal 3-year survival of resected patients in this cohort with positive AFP status should preempt any discussion of resection and relegate these patients to expedient transplantation.

Methods

Data source

SEER*Stat software version 6.6.2 (National Cancer Institute, Bethesda, MD) was used to query the SEER program’s SEER*Stat Databases: Incidence – SEER 17 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2009 Sub (1973–2007 varying) – Linked to County Attributes – Total U.S., 1969–2007 Counties.

Study population

Cases of HCC were extracted from the SEER database on the basis of site and morphology (International Classification of Diseases for Oncology, 3rd Edition, Hist/behave, malignant codes 8170/3 [Hepatocellular carcinoma, NOS], 8171/3 [Hepatocellular carcinoma, fibrolamellar], 8172/3 [Hepatocellular carcinoma, scirrhous], 8173/3 [Hepatocellular carcinoma, spindle cell variant], 8174/3 [Hepatocellular carcinoma, clear cell type], and 8175/3 [Hepatocellular carcinoma, pleomorphic type]) for those patients first diagnosed and/or treated between January 1973 and December 2007.

The study was further refined to include patients who had undergone resection or OLT using the SEER surgery primary site codes available from 2004 to 2007 (Therapy.RX Summ—Surg Prim Site (1998+)). More important, only patients within the Milan criteria were selected using the collaborative staging (CS) codes {Extent of Disease – CS.CS tumor size (2004+) = 0–499}, {Stage – TNM,Derived AJCC T, 6th ed (2004+) = T1,T2}, and {Extent of Disease – CS.CS mets at dx (2004+) = 0}. As such, patients within the Milan criteria had <5 cm and T1-staged or T2-staged tumors without any evidence of metastasis.

Surgical treatment was broadly grouped into 2 categories: segmentectomy or lobectomy and extended lobectomy (resection) (Therapy.RX Summ—Surg Prim Site = 20–25,30,36–37,50–52,60) and OLT (Therapy.RX Summ—Surg Prim Site = 61). These 2 groups were further divided into 2 arms according to serum AFP level. Serum AFP ≥500 ng/mL was considered positive {Extent of Disease – CS.CS site-specific factor 1 (2004+) = 10}, while a lower value of serum AFP was considered negative {Extent of Disease – CS.CS site-specific factor 1 (2004+) = 20}.

Statistical analysis

The actuarial method of Kaplan and Meier was used to measure the survival duration without adjustment for heterogeneity with 95% confidence intervals. Relative survival was adjusted for the general survival of the US population for that race, sex, age, and date at which the age was coded. Survival was assessed at 12-month intervals up to 3 years, and duration was compared using log-rank analysis with chi-square validation.

Results

Positive serum α-fetoprotein levels in patients with hepatocellular carcinoma within the Milan criteria portend worse survival in both resection and orthotopic liver transplantation groups

After selecting for patients who met the aforementioned criteria, 258 subjects were identified in the resection AFP-negative group. Of note, 38 patients were excluded from this grouping because of second or later primaries or database entry incongruence, for a total of 220 patients (Table 1). The 3-year relative survival rates in this group were 92.3%, 82.2%, and 67.6% in successive years. In
the resection AFP-positive group, 337 patients were identified after 63 subjects were excluded because of second or later primaries or database integrity issues. The 3-year relative survival rates were 84.7%, 72.3%, and 58.1%, significantly different from the AFP-negative group \( (P = .001; \text{Fig. 1A}) \).

Similarly, the OLT AFP-negative and AFP-positive groups had roughly the same numbers of subjects in the cohort. There were 209 patients in the AFP-negative group and 399 patients in AFP-positive group after 21 and 38 patients were excluded for second or later primaries or database integrity issues (Table 1). Strikingly, the 3-year relative survival rates in the OLT AFP-negative group were 94.4%, 88.9%, and 85.6% and in the OLT AFP-positive group were 92.6%, 83.7%, and 74.1%. Interestingly, there was a survival disadvantage in the OLT AFP-positive group compared with the OLT AFP-negative group, with a significant difference \( (P = .001; \text{Fig. 1B}) \).

**Orthotopic liver transplantation offers a distinct survival advantage compared with resection for all patients within the Milan criteria regardless of \( \alpha \)-fetoprotein status**

Comparing resection and OLT in both AFP-negative and AFP-positive groups, transplantation had a survival advantage \( (P = .001; \text{Figs. 2A and 2B}) \). Although 3-year relative survival was lower at 74.1% in the OLT AFP-positive group compared with 85.6% in the OLT AFP-negative group, when comparing these outcomes with the respective resection groups, the survival benefit was the same at 8%.

**The orthotopic liver transplantation survival advantage is decidedly greater in patients with solitary nodules of hepatocellular carcinoma within the Milan criteria and serum \( \alpha \)-fetoprotein positivity compared with resection**

Positive serum AFP conferred a worse prognosis in patients with solitary tumor nodules within the Milan criteria who underwent resection compared with OLT. After selecting strictly for T1 HCC tumors <5 cm in size, 200 patients were identified. The respective 3-year relative survival rates were 88.2%, 75.9%, and 59% in the resection T1 AFP-positive group. In contrast, 3-year relative survival rates in the OLT T1 AFP-positive group were 95.9%, 88.8%, and 75.3%, with 181 subjects identified. Comparing 3-year relative survival in these AFP-positive patients, it is clear that OLT offered a significant difference in patient longevity \( (P = .001; \text{Fig. 3B}) \). Moreover, at 3 years, there was a difference of 16.3% relative survival between resection and OLT.

In contrast, patients with HCC T1 tumors within the Milan criteria who underwent transplantation did not enjoy the same survival benefit in the negative serum AFP group compared with resection. Moreover, 3-year relative survival between resection and OLT with negative serum AFP suggests equivalence between the 2 treatment arms \( (P = .245; \text{Fig. 3A}) \). One hundred sixty-five patients with T1 HCC lesions were identified in the resection arm, with 3-year relative survival rates of 93.3%, 87.7%, and 73.8%, respectively. OLT conferred 3-year relative survival of 92.6%, 83.5%, and 81.6%, with 116 subjects identified. As such, there was no significant difference in 3-year relative survival between the treatment groups in patients with T1 tumor lesions.

**Resected T2 hepatocellular carcinoma tumors have lower survival rates regardless of serum \( \alpha \)-fetoprotein level compared to orthotopic liver transplantation**

Interestingly, for T2 lesions, the survival advantage reverted back to favoring transplantation. In the AFP-negative group with T2 tumors, 55 patients in the resection group and 93 patients in the OLT group were identified. Three-year survival rates were 88.6%, 63%, and 46.2% for resection and 96.7%, 95.4%, and 90.1% for OLT, demonstrating a significant different \( (P = .001; \text{Fig. 4A}) \). In the AFP-positive group, 137 resected patients and 218 transplanted patients were identified. Three-year relative survival rates in the resection arm were 79.1%, 66.9%, and 55.5%, and rates in the OLT arm were 89.4%, 79.1%, and 72.1% \( (\text{Fig. 4B}) \). This difference was statistically significant \( (P = .001) \).

**Comments**

Historically, serum AFP was initially touted as a biomarker for HCC surveillance in high-risk patients. However, its sensitivity of only 60% and specificity of 75% have made it a suboptimal screening test for HCC. Moreover, the current American Association for the Study of Liver Diseases guidelines deemphasize the utility of AFP in the diagnosis of HCC.\(^\text{12}\)

Given the rather dismal efficacy of serum AFP surveillance, clinicians have recently begun to assess the usefulness of AFP after the diagnosis of HCC has been made.
More important, serum AFP has been used to assess mortality. Recently, Mailey et al\textsuperscript{13} demonstrated that higher levels of AFP predict worse survival after OLT. Moreover, elevated AFP levels showed prognostic value for disease-free survival and likelihood of recurrence.\textsuperscript{14,15} Although there is no proven biologic understanding of why higher levels of serum AFP may increase mortality, increased HCC tumor burden has been linked to robust expression of AFP and decreased survival.\textsuperscript{16}

Given these findings, perhaps the lack of utility of serum AFP lies in its principled application. It is clear from numerous studies that screening serum AFP is imprecise. This is unacceptable given the severe consequences of misdiagnosis, and as a result, the use of serum AFP for HCC detection has fallen out of favor. However, the misapplication of serum AFP should not condemn its utility but rather prompt an opportunity for identification of areas that its measurement might prove useful.

Our findings demonstrate a clear role for serum AFP assessment. Counter to the paradigm, in this study we assessed the prognostic quality of serum AFP in patients who have already been diagnosed with HCC.
important, serum AFP was used to evaluate relative survival in patients within the Milan criteria who underwent either resection or transplantation. We believe that this use of serum AFP may prove to be practical in guiding therapy for HCC.

The advent of the Milan criteria of Mazzaferro et al.1 reshaped the surgical approach to HCC. Before their inception, the dismal survival of patients transplanted with HCC prompted a de facto moratorium of liver graft use for this disease.17 However, after the publication of this seminal work in 1996, there was a dramatic increase in transplantation for HCC. The enthusiasm of achieving a 5-year survival of 82% by offering OLT for limited disease prompted UNOS to offer exception points for HCC. Initially, UNOS awarded 24 Model for End-Stage Liver Disease points to patients diagnosed with HCC, and as a result the rate of OLT rose exponentially.

The appeal of transplantation for HCC is obvious. Total hepatectomy removes tumor burden and eliminates the nidus of HCC, cirrhotic parenchyma. However, not all patients with HCC have liver field defects, which has raised concerns over the equanimity of organ distribution. In response, UNOS recently decreased the Model for End-Stage Liver Disease exception points to 20 for patients with HCC. Predictably, this has increased the wait-list times for...

Figure 3  (A) Survival comparing T1 HCC tumors in the resection AFP-negative group and OLT AFP-negative group. (B) Survival comparing T1 HCC tumors in the resection AFP-positive group and OLT AFP-positive group.

Figure 4  (A) Survival comparing T2 HCC tumors in the resection AFP-negative group and OLT AFP-negative group. (B) Survival comparing T2 HCC tumors in the resection AFP-positive group and OLT AFP-positive group.
transplantation, which are already constrained by the limited availability of organs.

In this evolving milieu, practitioners have sought to reengineer the use of hepatectomy as a primary means of curative or bridge therapy. Notably, there are many dissenting views that contend that resection of HCC is associated with higher recurrence rates. Kamiyama et al. published data that demonstrated 55% recurrence rates and 5-year survival of 50% in patients resected with HCC. Also, Bismuth et al. published a series of 68 noncirrhotic patients with HCC who underwent resection whose collective 5-year survival rate was 40%. Nonetheless, these studies do not implicitly exclude tumors beyond the Milan criteria and for this reason are not easily applied to patients with limited disease. Moreover, recent data have shown that 5-year survival approaches 70% in resected patients with solitary lesions <5 cm in size and with margins of >1 cm.

Recent staging systems such as the BCLC classification attempt to codify the notion of possible resection for early disease. Proposed in 1999, the BCLC staging system purports that patients with single nodules <5 cm in size and the absence of portal hypertension or hyperbilirubinemia should be offered resection. We propose that in addition to portal hypertension and hyperbilirubinemia, serum AFP should also be considered in making a decision between resection and OLT in patients with limited HCC. Notably, though, the SEER database does not allow for reliable assessment of cirrhosis. As such, our claim would be bolstered if these data were available, making the argument more strident for inclusion into the BCLC algorithm. Furthermore, we acknowledge that comparing patients with similar degrees of cirrhosis may offer a more stringent query. Therefore, there is an assumption that patients that are resected will have minimal cirrhosis compared with those who have been transplanted. Nevertheless, our findings do lend themselves to questions of refinement over liver allocations schemas.

In this study, we began by selecting patients according to the Milan criteria. Specifically, the Milan criteria describe a focus of HCC of <5 cm for a single lesion or multiple lesions involving no more than 3 lesions, with the largest measuring ≤3 cm. In this study, we used T1 and T2 tumors of the tumor-node-metastasis staging system that were <5 cm in size to approximate tumors within the Milan criteria. A T1 tumor is classically described as a solitary lesion without vascular invasion, and T2 tumors can be classified as solitary lesions with vascular invasion or multiple tumors <5 cm in size. As noted, the definition of T2 tumors lies slightly afield of the definition of the Milan criteria, but our use of T1 and T2 to recapitulate the Milan criteria is well accepted in the surgical community. Nevertheless, we demonstrate that in T1 HCC tumor lesions, there is a distinctive survival advantage for OLT when serum AFP is >500 ng/mL.

Strikingly, in the serum AFP-negative group, there was no statistical difference in survival between resection and OLT for T1 tumors. The resection group had a 3-year survival of 73.6%, and the OLT group’s survival was 81.6%. In contrast, patients in the resection AFP-positive group had dramatically lower 3-year survival of 59%, while OLT AFP-positive patients’ 3-year survival was 75.3% for T1 lesions. From these data, we show that positive serum AFP portends worse survival regardless of the choice of surgical therapy. This can also be observed as a generalized trend for Milan criteria tumors (T1 and T2 lesions). However, the decreased 3-year survival in the AFP-positive resection group for T1 tumors was extremely low at 59%. In these AFP-positive patients, there was a significant difference between the resection and OLT groups, whereas in the AFP-negative group for T1 tumors, there was no benefit to either treatment. These findings seem to support the principle that resection within the Milan criteria for solitary lesions can achieve results approaching transplantation in carefully selected patients. As such, negative serum AFP can be used to bolster the clinical decision making that supports resection in early-stage HCC.

More important, however, we clearly demonstrate that patients with T1 HCC within the Milan criteria with AFP-positive status should not undergo resected but rather be offered OLT. The stark 3-year survival in patients resected with positive AFP should give pause to clinicians. Although a link between high levels of AFP and disease severity is only speculative, our data demonstrate that pursuing transplantation is in the interest of the patient. To this end, we submit that the variable of serum AFP should be incorporated into an algorithm such as BCLC to guide best practice for solitary lesions.

Interestingly, the lack of predictive value of serum AFP for T2 tumors seems to further support the BCLC classification system, which contends that patients with multiple tumors should undergo transplantation, not resection. However, for single nodules <5 cm in size, we purport that much as the consideration of portal hypertension and hyperbilirubinemia help steer surgical therapy, serum AFP can be used to further enhance the evaluation of limited-stage HCC. It is our conjecture that with this type of model, we can begin to approach equanimity for organ distribution for patients with HCC.

References

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