PAPER

Twenty-Year Experience With Liver Transplantation for Hepatocellular Carcinoma

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Hypothesis: Liver transplantation (LT) has become the optimal treatment for stages I and II hepatocellular carcinoma (HCC). Based on our 20-year experience, changes in staging, techniques, and patient selection have improved survival over the past 20 years. Herein, we determine if pre-LT treatment for HCC alters the long-term outcomes in patients with HCC.

Design: Outcomes study.

Setting: Tertiary referral center.

Patients: We retrospectively reviewed prospectively collected data in a cohort of 92 patients who underwent LT for HCC between 1983 and 2003.

Main Outcome Measures: Patient demographics, tumor stage in the explant liver, patient survival, and tumor recurrence data were analyzed.

Results: The average follow-up was 1052 (range, 0-6491) days. The average tumor size was 3.6 cm; 40% of tumors were multifocal and 60% unifocal. Of the 92 patients, 26% were classified as stage I; 42%, stage II; 24%, stage III; and 8%, stage IV. The overall 5-year survival rate was 50%, the 10-year survival rate was 32%, and the 15-year survival rate was 27%. Improvements in staging in the last 5 years reduced the number of patients with stages III and IV HCC from 39% to 19% and increased the 5-year survival rate to 69%. Tumor recurrence was relatively rare (13%); however, recurrence resulted in a poor prognosis (75% mortality rate; $P=.02$). The average time to recurrence was 458 (range, 179-1195) days.

Conclusions: Liver transplantation for HCC results in excellent long-term survival for patients with stages I and II HCC, with relatively few patients dying from tumor recurrence. Improvements in preoperative staging have resulted in increased 5-year survival rates. Further refinements in pre-LT staging may increase the effectiveness of LT for HCC.

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HEPATOCELLULAR CARCINOMA (HCC) is the most common primary liver tumor encountered worldwide.[1] Although most prominent in south Asia and Africa, recent data suggest that the incidence is increasing in Western countries, including the United States, the United Kingdom, and Europe.[2-4] The early experience with liver transplantation (LT) for HCC had relatively poor results, and LT was largely abandoned in most centers.[5,6] However, numerous recent studies suggest that LT can have excellent results when limited to patients with stages I and II disease.[5,6] In the United States, the current liver allocation system for patients with HCC is limited to patients with stage I or II disease.[7,8] Multiple studies[6,8-10] have demonstrated that when LT is limited to patients with single lesions smaller than 5 cm or as many as 3 lesions each smaller than 3 cm, patient survival is comparable to the survival of patients who undergo LT for benign disease. One study[11] has shown acceptable results in patients with more advanced disease by limiting LT to patients with well-differentiated tumors.

The relative scarcity of cadaveric donor organs limits the application of LT for HCC.[6] Disease progression that causes patients to be removed from the waiting list is also a major concern. Living-donor adult liver transplantation (LDALT) has been proposed as a way to increase the number of available organs and reduce the time that patients with HCC must wait for organs.[7,12,13] However, LDALT places healthy donors at risk.[7,12,13] As the use of this technique has become more widespread, donor morbidity and mortalities have been

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reported,[14,15] and the benefits to the recipient have to be carefully weighed against the risks to the donor.[7,12-15] Apart from the risks to the donor, several studies[7,12,13] have suggested that LDALT provides a better outcome compared with cadaveric LT because of shortened waiting times, and many experienced centers have shown excellent results using LDALT in patients with HCC. Gondolesi et al[12] also suggested LDALT as a way to provide organs for patients whose tumors have grown beyond stages I and II. Beginning in 2002, the application of a new organ-allocation system in the United States using the model for end-stage liver disease (MELD) has shortened waiting times for cadaveric organs in patients with HCC.[7] The proper role for LDALT after MELD continues to be a topic of debate.

Disease progression precluding the use of LT is still a major problem.[7,12] Numerous adjuvant therapies, including radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), transarterial chemoembolization (TACE), and surgical resection, have been used to limit tumor progression while patients await LT.[16-20] However, few data exist on the overall effectiveness of these therapies in patients with HCC. Many studies[16-20] have shown that these therapies can be safely administered before LT, but there is little evidence that these therapies either reduce patient dropout or provide a long-term survival benefit after LT.

During the last 20 years, the use of LT in patients with HCC has evolved considerably. New therapies have been developed to control the tumor prior to LT.[16-20] There have also been considerable advances in the ability to stage tumors using radiography prior to LT.[21] Many advances, such as the application of stringent staging criteria and the use of new surgical techniques, have improved outcomes for patients with HCC who undergo LT. In this report, we review our 20-year experience with LT in patients with HCC and determine if pre-LT treatment for HCC alters the long-term outcomes.

METHODS

We performed a retrospective review of prospectively collected data on all patients with a concomitant diagnosis of HCC who underwent primary LT performed by a single team of surgeons between January 1983 and January 2003. Routine preoperative screening and staging was performed using either ultrasonography and/or multiphase high-speed computed tomography. Pre-LT biopsy was performed only in patients who underwent pre-LT therapy. Patients with HCC were eligible for cadaveric whole organs, cadaveric split livers, and, after 1998, LDALT. Patients with HCC who received cadaveric organs after February 2002 were allocated organs using the MELD. Post-LT immunosuppression therapy consisted of a combination of prednisone, mycophenolate mofetil, and tacrolimus or cyclosporine. The prednisone dose was rapidly tapered over 4 to 6 weeks in the majority of patients. Mycophenolate mofetil administration was usually stopped between 3 and 6 months. Patients who received LDALT grafts also received daclizumab (1 mg/kg) immediately after surgery and again on postoperative day 4. Post-LT tumor surveillance consisted of triphasic computed tomographic scans performed every 3 months.

Patients were selected for pre-LT therapy at the discretion of the evaluating surgeon or hepatologist. Percutaneous RFA was administered with introducer sheaths guided by real-time computed tomography and ultrasonography. Star Burst Semi flex needles (RITA, Mountainview, Calif) were used for ablation, and ablations were performed in each lesion and along each tract as well. Percutaneous ethanol injection was guided by real-time ultrasonography. Experienced liver oncologists observed the administration of TACE. Surgical resections were done by experienced hepatobiliary surgeons who were also part of the LT team.

We analyzed the following demographic and clinical data: age, sex, primary liver diagnosis, type of LT, operative time, and blood product use. The stage, size, and focality of the tumor were determined by analysis of the liver explant. The explanted liver was examined by an experienced liver histopathologist. Patient survival rates, tumor recurrence, and time to recurrence were also analyzed. Continuous variables were analyzed using the Student *t* test, and categorical variables were analyzed using the χ^2 or Fisher exact tests. Survival curves were determined using the Kaplan-Meier method and compared using log-rank analysis. A *P* value of less than .05 was considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS

During the 20-year study period there were 92 patients (72 men and 17 women) who underwent LT for HCC. The average follow-up was 1052 (range, 0-6491) days. The average age in the cohort was 53 (range, 28-68) years. The causes of liver failure were the following: hepatitis C, 51 patients (55%); cryptogenic cirrhosis, 8 patients (9%); alcoholic cirrhosis, 10 patients (11%); hepatitis B, 7 patients (8%); HCC, 7 patients (8%); hemochromatosis, 4 patients (4%); glycogen storage disease, 2 patients (2%); and primary sclerosing cholangitis, nonalcoholic steatohepatitis, and amyloid, 3 patients (3%). The average number of days before LT was 405 (range, 1-3222). There was no significant difference in the time spent on the waiting list between the years from 1998 to 2001 (pre-MELD) and from 2002 to 2003 (post-MELD).

TYPES OF LT

Seventy-eight patients (84%) received whole cadaveric organs, 13 patients (14%) received right lobes from living donors, and 1 patient (1%) received the right lobe from a cadaveric split. The average time of surgery was 6.1 (range, 3.1-11.7) hours.

TUMOR DATA

The tumors were staged at review of the explant liver as follows: stage I, 26%; stage II, 42%; stage III, 24%; and stage IV, 8%. Of the tumors, 40% were multifocal and 60% were unifocal. The average size of the largest tumor was 3.6 (range, 0.8-11.0) cm. All the patients were node negative at the time of LT. Of the patients who received pre-LT treatment, the liver explants in only 2 patients (2%) were tumor free. In all the remaining pretreated patients (13 [86%] of 15), viable tumor cells were identified in their liver explant (**Table 1**).

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SURVIVAL AND RECURRENCE RATES

The overall survival rates were 50% at 5 years, 32% at 10 years, and 27% at 15 years (**Figure 1**). There was no significant difference in survival between patients who received LDALT and those who received cadaveric organs. Tumor stage was strongly associated with survival: patients with early-stage tumors survived longer than those with late-stage tumors (**Figure 2** and **Figure 3**). Although tumor recurrence was rare (12 [13%] of 92 patients), it was associated with a high mortality rate (9 [75%] of 12 patients; $P=.02$). The average time to recurrence was 458 (range, 179-1195) days. The most frequent locations for tumor recurrence were in the lung and bone. Only 4 (33%) of 12 patients who developed tumor recurrence had recurrence in the transplanted liver. Recurrence data are summarized in **Table 2**.

PRE-LT THERAPY

Fifteen patients (16%) received some form of pre-LT therapy: 6 patients (7%) received RFA; 2 patients (2%) received PEI; 4 patients (4%) received TACE; 2 patients (2%) had tumors resected; and 1 patient (1%) received cryotherapy ablation. There was no significant difference in survival and recurrence rates or waiting time between patients who received pre-LT therapy and those who did not (Table 1). When the recent experience was analyzed, patients with stages I and II disease who received pre-LT therapies survived longer than those who received no treatment, but the difference was not significant (**Figure 4**).

EARLY VS LATE EXPERIENCE

In the last 5 years, improvements in staging and the application of the MELD have reduced the number of stage III and IV tumors from 39% (13/33) to 19% (11/59). During the same period, the 5-year survival rate increased to 69%. Kaplan-Meier analysis of survival demonstrated a significant difference between the initial (1983-1998) and the recent (1999-2003) experience with LT for HCC ($P=.03$; **Figure 5**).

COMMENT

In the last 20 years, the use of LT in patients with HCC has evolved. Early enthusiasm for the procedure waned because of initially poor results.[5,6] However, evidence showed that LT improved survival for select patients with HCC.[5-10] The Milan criteria[9] demonstrated that patients with early-stage HCC could undergo LT and have survival rates equal to those of patients who underwent LT for benign disease. Once there was consensus that LT offered superior results to surgical resection, LT became the primary therapy for early-stage HCC.[5,6] However, the relative shortage of donor organs has limited the number of patients who can be treated.[6]

In our study, 92 patients underwent LT for HCC in a 20-year period. During this time, the overall 5-year survival rate was 50% (46 patients). We were able to demonstrate a long-term survival with 29 (32%) alive at 10 years and 25 (27%) alive at 15 years. Based on the most

Table 1. Treatment vs No Treatment Prior to Liver Transplantation in 92 Patients With Hepatocellular Carcinoma

	No. (%) of Patients		
	Tumor Recurrence	1-Year Survival	Tumor in Explant
Treatment (n = 15)	2 (13)	13 (86)	13 (86)
No treatment (n = 77)	10 (14)	60 (78)	77 (100)

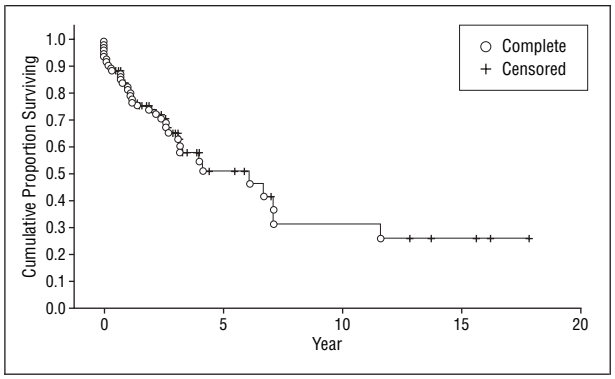


Figure 1. Kaplan-Meier analysis of survival in patients who underwent liver transplantation for hepatocellular carcinoma from 1983 to 2003.

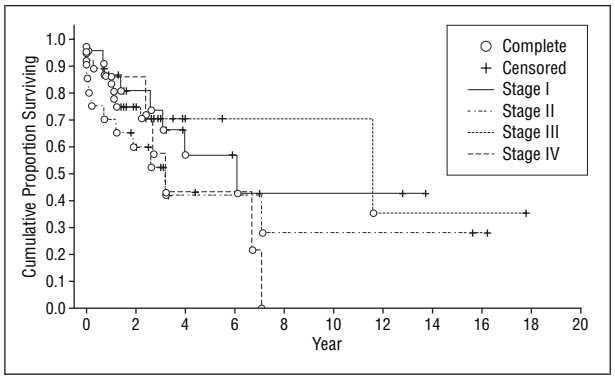


Figure 2. Kaplan-Meier analysis of survival by tumor stage in patients who underwent liver transplantation for hepatocellular carcinoma.

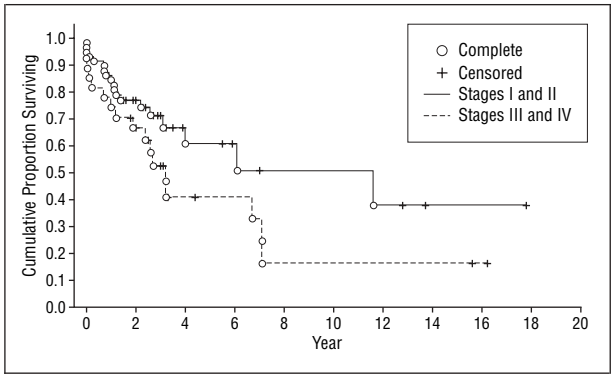


Figure 3. Kaplan-Meier analysis of survival in patients with early-stage (I and II) and late-stage (III and IV) disease.

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Table 2. Tumor Recurrence Data

Patient No.	Tumor Size, cm	Unifocal/Multifocal	Time to Recurrence, d	Survival, y	Location of Recurrence
1	12.0	Multifocal	436	6.7	Liver
2	2.5	Unifocal	309	1.1	Liver, lung
3	12.0	Multifocal	179	1.0	Bone, lung
4	5.0	Multifocal	651	3.2	Bone, skin
5	3.7	Unifocal	1195	7.1	Lung
6*	5.0	Unifocal	750	3.5	Bone
7	2.0	Multifocal	229	1.2	Liver
8	4.0	Unifocal	210	1.1	Lung
9	3.0	Multifocal	752	2.3	Liver, bone
10	11.0	Multifocal	152	2.4	Bone, lung
11*	3.5	Multifocal	248	1.5	Lung
12*	2.5	Unifocal	381	1.3	Lung

*The patient was alive at the time of data analysis.

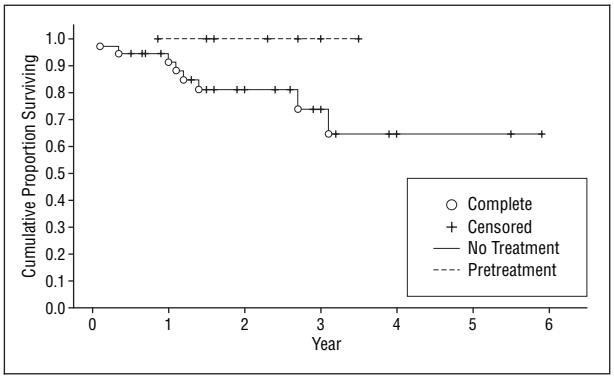


Figure 4. Kaplan-Meier analysis of survival in patients with early-stage disease who received pretreatment compared with those who received no treatment from 1988 to 2003. The difference was not statistically significant using log-rank analysis (*P*=.10).

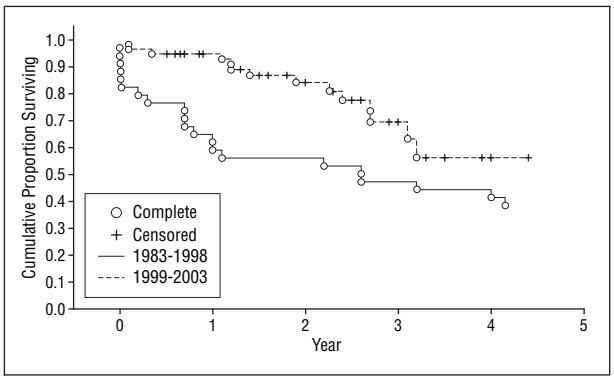


Figure 5. Kaplan-Meier analysis of survival in patients who underwent liver transplantation for hepatocellular carcinoma in the early period (1983-1998) vs the recent period (1999-2003). Log-rank analysis demonstrated that there is a statically significant difference between the 2 groups (*P*=.03).

recent experience, the 5-year estimated survival rate increased to 69% based on the Kaplan-Meier analysis. These results compare favorably with those of other recent studies of LT for HCC that reported 5-year survival rates of 57% to 75%.[6,8] Kaplan-Meier analysis demonstrated a significant difference in survival between the initial and recent experience with LT for HCC. The improvement in survival is likely the result of improved selection and staging of patients with HCC. However, despite the ability to stage patients using radiography prior to LT, 11 (19%) of the 59 patients who underwent LT had stage III and IV tumors in the last 5 years. Given the deleterious effect of advanced tumor stage, further improvements in our ability to assess tumors prior to LT will increase the success of this procedure.

Tumor recurrence was relatively rare (13%). However, tumor recurrence was associated with a high mortality rate (75%). The well-described factors associated with tumor recurrence include tumor size, tumor grade, vascular invasion, and serum α-fetoprotein.[5,6,10,11,22] Of the patients whose disease recurred (8 [67%] of 12), the tumor was in the lung and bone and not in the liver. It has previously been suggested that removal of the entire liver with LT is beneficial to patients with HCC.[6] Total hepatectomy should reduce intrahepatic tumor recurrence and prevent the formation of primary HCC a second time. The rarity of tumor recurrence in our study seems to support this theory.

One of the primary limitations of the use of LT for patients with HCC has been the limited availability of transplant organs.[6] Living-donor adult liver transplantation has been proposed as a way to increase the number of transplanted organs.[7,12,13] Our results demonstrate that LDALT is an acceptable alternative to cadaveric transplantation for patients with HCC. These findings are consistent with other reports of LDALT in this population.[7,12,13] With the use of the MELD in 2002, patients with early-stage HCC began to receive priority in organ allocation.[23] Our results did not show a reduction in waiting time for patients with HCC after the implementation of the MELD. However, our data measured the time from listing to LT. A more accurate analysis of the effect of the MELD should consider when the patient was diagnosed as having HCC and when the patient was listed for LT. Although patients with early-stage HCC receive priority in the MELD, we have continued to use LDALT for select patients with HCC. Living-donor adult liver transplantation allows the surgical team to control the timing of the surgical procedure and has the same survival rate as cadaveric transplantation.

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During the last several years there has been increasing interest in the use of pre-LT therapies for tumor control in patients with HCC. Previous reports[16-20] have advocated the use of such therapies as RFA, PEI, TACE, and surgical resection while patients wait for donor organs. While preliminary results have been promising, few data exist on the overall effectiveness of these therapies in this setting.[16-20] In our study, these therapies were particularly effective in patients with early-stage disease. Our results demonstrated improved survival rates in patients who received pre-LT therapies, but the results were not statistically significant because of the small number of patients. An interesting finding was that 13 (86%) of the 15 patients who had some form of pre-LT therapy still had viable tumor present in the liver explants. As primary tumor treatment, the individual therapies have a generally poor success rate.[22,24,25] However, it is possible that by simply limiting tumor progression, these therapies may confer a survival advantage for patients before LT. The role of these therapies prior to LT merits further study.

A number of recent studies have addressed the utility of the Milan criteria[9] for selecting patients for LT. While the Milan criteria have been validated as a useful predictor of survival, many authors[11,12,26,27] have suggested that the criteria are too restrictive. It has been suggested that strict application of the Milan criteria denies LT to patients who could still have long-term survival.[11,12] At the University of California, San Francisco (UCSF), Yao et al[28] have described more liberal guidelines that would allow more patients to receive LT while limiting the number of patients who are likely to experience early recurrence. The UCSF criteria have subsequently been validated as an acceptable predictor of outcome.[29,30] We did not have a sufficient number of patients to accurately compare the Milan and UCSF criteria, but we were able to demonstrate long-term survival in some patients who underwent LT but whose disease did not meet the Milan criteria. This finding suggests that the Milan criteria may be too restrictive. Further study is needed to determine if more liberal guidelines, such as the UCSF criteria, would improve the selection of patients who should undergo LT for HCC.

During the last 5 years LT has become the primary therapy for patients with early-stage HCC.[5,6] Patients who undergo LT have a survival rate that is equal to that in patients who undergo LT for benign disease,and this survival rate is higher than the survival rate after surgical resection.[6,8-10] Our results indicate that long-term survival is possible after LT for HCC. The results of LT for HCC can be further improved with better patient selection using improved pre-LT disease staging. Reducing the number of patients with stages III and IV disease who receive LT should increase post-LT survival rates and improve the effectiveness of LT for HCC.

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REFERENCES

1. Okuda K, Tabor E, eds. *Liver Cancer*. New York, NY: Churchill Livingstone; 1997.
2. Taylor-Robinson SD, Foster GR, Arora S, Hargreaves S, Thomas HC. Increase in primary liver cancer in the UK, 1979-94. *Lancet*. 1997;350:1142-1143.
3. Deuffic S, Poynard T, Buffat L, Valleron AJ. Trends in primary liver cancer. *Lancet*. 1998;351:214-215.
4. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med*. 1999;340:745-750.
5. Kashef E, Roberts JP. Transplantation for hepatocellular carcinoma. *Semin Oncol*. 2001;28:497-502.
6. Hemming AW, Cattral MS, Reed AI, Van der Werf WJ, Greig PD, Howard RJ. Liver transplantation for hepatocellular carcinoma. *Ann Surg*. 2001;233:652-659.
7. Roberts JP. Role of adult living liver donation in patients with hepatocellular cancer. *Liver Transpl*. 2003;9(10, suppl 2):s60-s63.
8. Shetty K, Timmins K, Brensinger C, et al. Liver transplantation for hepatocellular carcinoma validation of present selection criteria in predicting outcome. *Liver Transpl*. 2004;10:911-918.
9. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996; 334:693-699.
10. Figueras J, Ibanez L, Ramos E, et al. Selection criteria for liver transplantation in early stage hepatocellular carcinoma with cirrhosis: results of a multicenter study. *Liver Transpl*. 2001;7:877-883.
11. Cillo U, Vitale A, Bassanello M, et al. Liver transplantation for the treatment of moderately or well-differentiated hepatocellular carcinoma. *Ann Surg*. 2004; 239:150-159.
12. Gondolesi GE, Roayaie S, Munoz L, et al. Adult living donor transplantation for patients with hepatocellular carcinoma extending UNOS priority criteria. *Ann Surg*. 2004;239:142-149.
13. Todo S, Furukawa H. Living donor transplantation for adult patients with hepatocellular carcinoma: experience in Japan. *Ann Surg*. 2004;240:451-461.
14. Trotter JF, Wachs M, Everson GT, Kam I. Adult-to-adult transplantation of right hepatic lobe from a living donor. *N Engl J Med*. 2002;346:1074-1082.
15. Strong RW. Whither living donor liver transplantation? *Liver Transpl Surg*. 1999; 5:536-538.
16. Belghiti J, Cortes A, Abdalla EK, et al. Resection prior to liver transplantation for hepatocellular carcinoma. *Ann Surg*. 2003;238:885-892.
17. Adam R, Azoulay D, Castaing D, et al. Liver resection as a bridge to transplantation for hepatocellular carcinoma. *Ann Surg*. 2003;238:508-519.
18. Graziadei IW, Sandmueller H, Waldenberger P, et al. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. *Liver Transpl*. 2003;9:557-563.
19. Fontana RJ, Hamidullah H, Nghiem H, et al. Percutaneous radiofrequency thermal ablation of hepatocellular carcinoma: a safe and effective bridge to liver transplantation. *Liver Transpl*. 2002;8:1165-1174.
20. Llovet JM, Mas X, Aponte J, et al. Cost effectiveness of adjuvant therapy for hepatocellular carcinoma during the waiting list for liver transplantation. *Gut*. 2002; 50:123-128.
21. Rode A, Bancel B, Douek P, et al. Small nodule detection in cirrhotic livers: evaluation with US, spiral CT, and MRI and correlation with pathologic examination of explanted liver. *J Comput Assist Tomogr*. 2001;25:327-336.
22. Lau WY. Management of hepatocellular carcinoma. *J R Coll Surg Edinb*. 2002;47: 389-399.
23. United Network for Organ Sharing. Policy 3.6.4.4: Liver Transplant Candidates with Hepatocellular Carcinoma (HCC). Available at: http://www.unos.org/PoliciesandBylaws/policies/pdfs/policy_8.pdf. Accessed June 28, 2002.
24. Harrison LE, Koneru B, Baramipour P, et al. Locoregional recurrences are frequent after radiofrequency ablation for hepatocellular carcinoma. *J Am Coll Surg*. 2003;197:759-764.
25. Vivarelli M, Gugliemi A, Ruzzenente A, et al. Surgical resection versus percutaneous radiofrequency ablation in the treatment of hepatocellular carcinoma. *Ann Surg*. 2004;240:102-107.
26. Llovet JM, Bruix J, Fuster J, et al. Liver transplantation for small hepatocellular carcinoma: the tumor-node-metastasis classification does not have prognostic power. *Hepatology*. 1998;27:1572-1577.
27. Figueras J, Jaurrieta E, Valls C, et al. Survival after liver transplantation in cirrhotic patients with and without hepatocellular carcinoma: a comparative study. *Hepatology*. 1997;25:1485-1489.

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28. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limit does not adversely impact survival. *Hepatology*. 2001;33:1394-1403.
29. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: comparison of the proposed UCSF criteria with the Milan criteria and the Pittsburgh modified TNM criteria. *Liver Transpl*. 2002;8:765-774.
30. Leung JY, Zhu AX, Gordon FD, et al. Liver transplantation outcomes for early-stage hepatocellular carcinoma: results of a multicenter study. *Liver Transpl*. 2004; 10:1343-1354.

DISCUSSION

Thomas Colacchio, MD, Lebanon, NH: . . . in those patients who had pretreatment vs those who were untreated?

Dr Island: The number of patients who received pretreatment was actually too small to demonstrate a difference in recurrence.

Thomas Tracy, MD, Providence, RI: Could you comment on the patients with stage III and stage IV disease, especially the stage IV patients, and how do you accept those patients for transplantation? What are the minimum criteria? We have had some experience with younger patients with metastatic disease and certain requirements by different transplant centers for PET [positron emission tomographic] scanning or CT [computed tomographic] scanning in terms of clearance of metastases following chemotherapy.

Dr Island: When you analyze the entire cohort, this includes our early experience with HCC in which we were not necessarily limiting transplantation to patients with stage I and stage II disease. However, it is a little disturbing when you look at our latest 5-year experience, and we see that 19% of the patients came to transplant with stage III and stage IV disease. All these patients were screened prior to transplant with a combination of ultrasound and multiphasic CT scan, and, based on these results, we considered them to have stage I or stage II disease. Therefore 19% of patients were understaged by these radiographic modalities. I think with improvements in staging we could demonstrate better results.

James Whiting, MD, Portland, Me: That is a very nice series, very nice long-term results, trying to meld a number of different areas.

I would like to go back to the issue of pretreatment. A number of other groups have also looked at the pretreatment issue and have actually developed algorithms on how to handle patients. You obviously still have significant ways for these patients despite the change in allocation rules. Do you have a specific algorithm, a specific modality that you like to take? When do you trigger in someone who is waiting on your list who has a tumor that is growing, when do you put them for, do you put them through radiofrequency or some other sort of pretreatment regimen while they are waiting and if their disease continues to progress vs even delisting them?

Dr Island: At this point, we do not have a specific algorithm. Patients are assigned to pretreatment at the discretion of the evaluating surgeon or hepatologist. It is interesting to note that with our more recent experience we are moving toward treating patients more with radiofrequency ablation as opposed to the other modalities. Fewer patients are being treated with surgical resection. Patients who are not candidates for living-donor transplant and are likely to have longer waiting times, those are the patients who undergo strong consideration for some sort of preoperative treatment, in particular radiofrequency ablation. However, there are some patients who, due to the characteristics of their tumor or its location within the liver, are not good candidates for this treatment.

Dr Whiting: Do you have patients you have delisted whose disease has progressed while they have been waiting?

Dr Island: Yes; actually it is not included in this series, but there is an incidence of patients being delisted, in particular patients who have not received any sort of pretransplant therapy.

Blake Cady, MD, Providence: I presume, to follow up on that, that the effectiveness of the pretreatment is that it selects out the patients who progress or get metastatic disease and that is why it does so well. So the real issue is what was your total pool of patients with pretreatment for the expectation of transplant who did not receive transplants? The other question is, at transplantation in the patients who originally had disease, in how many did you find no tumor in the removed liver after pretreatment?

Dr Island: The number of patients who received pretreatment who are subsequently removed from the transplant list is actually relatively low when you look at the other patients, but there have been a few patients and particularly some patients who underwent resection and 1 or 2 patients who underwent radiofrequency ablation who did have to be removed due to tumor progression.

Regarding your next question, in terms of overstaging tumors or listing people with HCC and finding no tumor in the specimen, we actually have a very low incidence of that. This particular analysis was limited to patients whose explants demonstrated tumor. However, the incidence of patients undergoing liver transplantation for HCC, and subsequently not finding HCC in the explant, is very low.

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