American Journal of Transplantation 2004; 4: 782–787
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2004.00413.x

Hepatic Artery Chemoembolization for Hepatocellular Carcinoma in Patients Listed for Liver Transplantation

Paul H. Hayashi[a,d,*], Michael Ludkowski[b], Lisa M. Forman[a], Michael Osgood[a], Stephen Johnson[b], Marcelo Kugelmas[a], James F. Trotter[a], Thomas Bak[c], Michael Wachs[c], Igal Kam[c], Janette Durham[b] and Gregory T. Everson[a]

Divisons of [a] Gastroenterology and [b] Interventional Radiology, and [c] Department of Transplant Surgery, University of Colorado Health Sciences Center, Denver, CO, USA
**Corresponding author: Paul H. Hayashi, hayaship@slu.edu*

We retrospectively analyzed all listed patients having hepatic artery chemoembolization (HACE) for hepatocellular carcinoma (HCC) stage T2 or less. Outcomes were transplantation, waiting list removal, death, and HCC recurrence. Twenty patients (mean age 55.7 years; 15 males) were identified. Twelve (60%) were transplanted, seven (35%) were removed from the list and one (5%) remains listed. Fourteen (70%) are alive. All 12 transplanted patients are alive (mean 2.94 years); one of seven removed from the list is alive (mean 1.45 years). Survival was significantly higher for those transplanted or listed vs. removed from the list (100% vs. 14.3%, p = 0.0002). No HCC's recurred. Three patients (15%) were removed from the list after prolonged waiting times before MELD. Hepatic artery chemoembolization induced deterioration and removal from the list of one (5%) patient. Survival for those transplanted was excellent(100%), but overall survival was significantly lower (61.3%) at a mean 5.48 years. Hepatic artery chemoembolization for listed patients with ≤ T2 stage HCC is beneficial, but must be weighed against decreased waiting times and risk of HACE-induced deterioration. This balance is influenced greatly by the MELD system's determination of waiting times for HCC patients.

Key words: Chemoembolization, liver transplantation

Received 27 August 2003, revised and accepted for publication 5 January 2004

Introduction

Liver transplantation remains the best option for long-term cure of hepatocellular carcinoma (HCC) in the setting of cirrhosis. The proportion of transplanted patients diagnosed with HCC increased threefold since the implementation of the model for end-stage liver disease (MELD)-based allocation system (1). However recent changes in MELD points allocated for HCC will likely lead to fewer transplants and longer waiting times. The best management of HCC patients on the waiting list remains unclear.

Local ablative therapy such as hepatic artery chemoembolization (HACE) or radiofrequency ablation (RFA) is often performed in listed patients with HCC. Several studies indicate histopathologic response to such treatments pretransplantation, but improvement in survival has been less apparent (2–4). Moreover, many studies include only those patients ultimately having a transplantation. Analysis of all patients intended for transplantation is important because both HACE and RFA carry measurable morbidity and mortality. If waiting times remain significantly shortened by the MELD system, then ablative therapies may be unnecessary and even harmful. On the other hand, if the MELD score adjustments for HCC diagnosis increase the waiting time, then the benefit of HACE may outweigh the risks. Because of these unresolved issues, we performed a retrospective analysis on all listed patients receiving HACE.

Methods

Patients

Our Colorado Multiple Institution Review Board (COMIRB) approved this study. We searched the interventional radiology database for all cases of chemoembolization between January 1, 1995 and April 30, 2003. Patients identified by these queries were cross-referenced with all patients listed for liver transplantation during the same time period. All matches were investigated further by review of the medical records to confirm (a) hepatocellular cancer clinical diagnosis, and (b) HACE therapy while listed. Only patients with TMN stage T2 or less based on pretransplant imaging studies were included in this study. Only patients who had started HACE therapy at the time of listing or later were included.

Hepatic artery chemoembolization

Our center used only hepatic artery chemoembolization (HACE) for HCC during this time period. Hepatic artery chemoembolization was performed via femoral artery access in all cases. Diagnostic hepatic angiography confirmed tumor blush in all cases before chemotherapy delivery and embolization. Diagnostic angiography was performed to document portal vein patency before embolization. A mixture of adriamycin (50 mg), mitomycin (10 mg), cisplatin (40 mg) and lipiodol (total volume 17 mL) was used for locally delivered chemotherapy. Polyvinyl alcohol (PVA) particles of 300–500 μm in size were used for embolization to stasis after administration of the chemo-lipiodol combination. Chemoembolization was performed on the entire

affected lobe unless hepatic dysfunction was severe, in which case subselective embolization was performed. Contraindications to HACE included: (1) platelet count less than 50 000/mL despite platelet transfusions, (2) serum creatinine greater than 2.0 mg/dL, (3) severe or poorly controlled hepatic encephalopathy, (4) total bilirubin greater than or equal to 3.0 mg/dL, or (5) INR >2.0 despite fresh-frozen plasma infusion. Exceptions to these cut-offs were made on a case-by-case basis. Hepatic artery chemoembolization was repeated until the tumor was devascularized by angiography. No other modalities such as radiofrequency ablation or percutaneous alcohol were used on this study cohort. One patient had one HACE treatment at an outside hospital. The protocol for this patient was identical to our facility using the same chemoembolic agents and dosages. Dual phase CT or magnetic resonance imaging of the liver was obtained 4–6 weeks after HACE to determine residual tumor and provide a baseline for follow-up studies.

Radiographic data

The date and criteria for the initial HCC diagnosis were obtained from a review of medical records. Radiology reports were analyzed for HCC stage and response to HACE. Number and dates of HACE treatments were recorded from the hospital record.

Histology

Pre-transplant HCC histology was recorded if available, and explant histology reports were reviewed and recorded.

Clinical data

Demographics including patient ages, gender and primary liver disease were obtained from the medical record. All patient outcomes were investigated using hospital computer record, medical record, liver transplant database, physician interview, hepatology clinic and liver transplant clinic records. Outcomes of either the time of patient death or the censor date of May 26, 2003 were evaluated and recorded.

Statistical analysis

Unadjusted patient survival was estimated using the Kaplan-Meier method with log-rank testing for comparison between those transplanted or listed vs. those removed from the list. We also compared the survival of those managed before (pre-MELD) and after (post-MELD) February 27, 2002. Logistic regression analysis was used to identify factors independently associated with patient survival. Student's *t*-test was used in the statistical comparison of mean waiting times to transplantation before and after MELD implementation. Patients receiving living donor liver transplantation were excluded from the pre-MELD vs. post-MELD analysis. Logistic regression was performed using SPSS for Windows software, version 11.5.0 (SPSS Inc. 2002, Chicago, IL). Kaplan-Meier and log-rank analysis was performed using Stata Statistical Software, release 7.0 (StataCorp 2001, College Station, TX).

Results

Patients

The study cohort consisted of 20 listed patients who underwent HACE for HCC (median: 2.0 treatments, range 1–6). Mean age was 55.7 years at the time of HCC diagnosis and 75% (15 of 20) were male. All had biopsy-proven or clinical diagnosis of cirrhosis. The etiologies of cirrhosis, demographics, median MELD scores, and mean lab values at the time of HCC diagnosis are listed in Table 1. Hepatocellular carcinoma was diagnosed before or within 1 month of listing in 12 (60%) patients. Pre-HACE diagnosis of hepatocellular carcinoma was made by imaging studies alone in 13 (65%) and imaging with biopsy in seven (35%) patients. Diagnosis was confirmed by hepatic arteriogram before HACE treatment in all cases. One patient had HACE carried out at a referring facility, which used a HACE protocol identical to ours. The distribution of Child's Pugh Class, CLIP Score and Okuda Stage based on laboratory testing and clinical evaluation at the time of HCC diagnosis are shown in Figure 1. Overall mean and median times on the waiting list with a HCC diagnosis were 333.2 (± 302.3) and 206 (range 55–1030) days, respectively.

Table 1: Patient characteristics

Gender	Gender and age 15 (75%) male; 5 (25%) female
Mean age (years)	55.7 ± 8.29
Underlying liver disease	
HCV	8 (40%)
HCV and alcohol	4 (20%)
Alcohol	2 (10%)
NASH	2 (10%)
Hemochromatosis	1 (5%)
HBV	1 (5%)
PSC	1 (5%)
Shistosomiasis	1 (5%)
Laboratory values	
Mean bilirubin (mg/dL) (n = 19)	1.82 ± 1.01
Mean creatinine (mg/dL) (n = 18)	0.83 ± 0.23
Mean INR (n = 19)	1.31 ± 0.23
Mean albumin (g/dL) (n = 19)	3.31 ± 0.47
Median alpha-fetoprotein (ng/mL) (n = 18)	107.3 (4.80–5800.3)
MELD[a] (median) (n = 18)	11 (6–17)

HCV = hepatitis C virus; NASH = non-alcoholic steatohepatitis; HBV = hepatitis B virus; PSC = primary sclerosing cholangitis; MELD = model for end-stage liver disease.

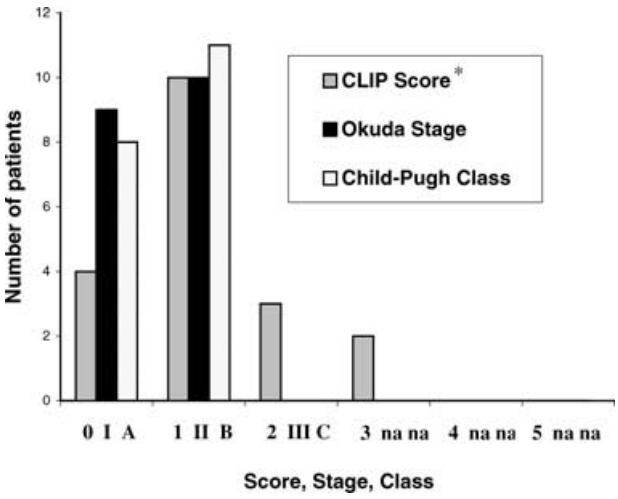

Figure 1: Distribution of CLIP Scores, Okuda Stages and Childs-Pugh Classes. Sufficient clinical information was available for 19 of 20 patients. *Cancer of the Liver Italian Program Score, NA = not applicable.

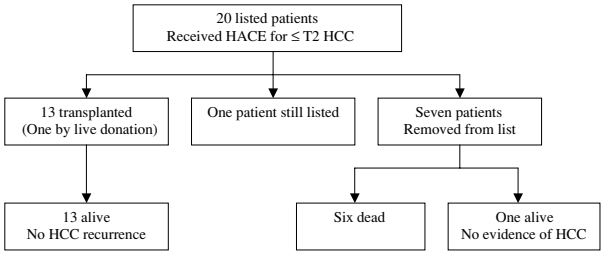

Figure 2: Outcomes of 20 listed patients with Stage T2 or less hepatocellular carcinoma (HCC) receiving hepatic arterial chemoembolization.

Transplantation

Twelve (60%) were successfully transplanted; one by live donation. One patient (5%) remained listed for transplantation as of the censor date, May 23, 2003 (Figure 2). Mean waiting time to transplant with the diagnosis of HCC was 343 (± 293.5) days, excluding the one patient transplanted by live donation.

HACE response in transplanted or listed patients

Pre-HACE tumor size and number were compared with explant histology findings for those transplanted. Six of the 12 transplanted had a decrease in tumor size and/or number. Five had increase in tumor size or number with two increasing their stage to T3 on explant examination. One patient who had shown no change in tumor size based on imaging studies pretransplant visited another country for his transplant, and we were unable to obtain explant histology. Hepatic artery chemoembolization responses for those patients removed from the list are shown in Table 2. The one patient still awaiting transplant was awaiting a follow-up CT scan after his second HACE at the time of censor.

HACE response in patients removed from list

Seven (35%) were removed from the waiting list (Table 2). Of the four who had a complete response (no radiographic evidence of tumor) to HACE, two went on to develop more tumors leading to removal and two were removed for other reasons (advanced age, sepsis). Of the two with partial responses (<50% shrinkage of tumor), one was removed for HACE related decompensation and one was removed for increased tumor burden. One patient had a poor response (no change or growth of tumor) to HACE and was removed for increased tumor burden.

Survival

Overall, 14 (70%) of 20 are alive for a cumulative survival of 61.3% at a mean of 5.48 years post-HCC diagnosis (95% CI: 3.76–7.20 years) (Figure 3A). Of the 13 transplanted or currently listed patients, all are alive for cumulative survival of 100% at a mean of 2.76 years (Figure 3B). Cumulative survival for those removed from the list was significantly lower (14.3%, $p = 0.0002$), with only one of seven patients alive at 1.45 years (95% CI: 0.61–2.28 years).

HCC recurrence

None of the 12 patients transplanted had developed HCC recurrence at a mean of 2.94 ± 2.22 years.

Affect of MELD implementation

We found no significant difference in survival between the pre-MELD and post-MELD groups (50% vs. 64%, $p = 0.35$). However, there were only 15 patients (eight pre-MELD, seven post-MELD) in this analysis after excluding the patient receiving live-donor liver transplantation and those with waiting times spanning February 27, 2002 (date of MELD implementation). While the mean waiting time to transplant for the pre-MELD group was longer than that of the post-MELD group, the difference did not reach statistical significance in this small subgroup (327.8 vs. 177.5 days, $p = 0.37$). There were only five patients transplanted pre-MELD and four post-MELD, when patients with waiting times spanning across February 27, 2002 were excluded.

Table 2: Patients removed from waiting list

HCC number : size	Response to HACE	Reason for removal	Time on list with HCC diagnosis (days)
1: 2 cm	Complete ablation[a]	Advanced age (70 years), comorbidities	1030
2: both <2 cm	Complete ablation	Sepsis unrelated to HACE	662
3: all <2 cm	Complete ablation	Two new tumors found in follow-up surveillance	105
1: 3.8 × 3.2 cm	Complete ablation	Three new lesions (one >3 cm) found in follow-up surveillance.	355
1: 4 × 3.4 cm	Partial response[b]	Hepatic decompensation after second HACE	91
1: 3 × 5 cm	Partial response[b]	Additional 2-cm lesion found	148
1: 4.2 × 3.2 cm	Poor response[c]	Tumor growth to 5 × 6 cm and new 2-cm lesion, 1 month after HACE	60

[a]No evidence of vascular tumor.
[b]<50% shrinkage.
[c]No shrinkage or growth seen on follow up.
HACE = hepatic artery chemoembolization, HCC = hepatocellular carcinoma.

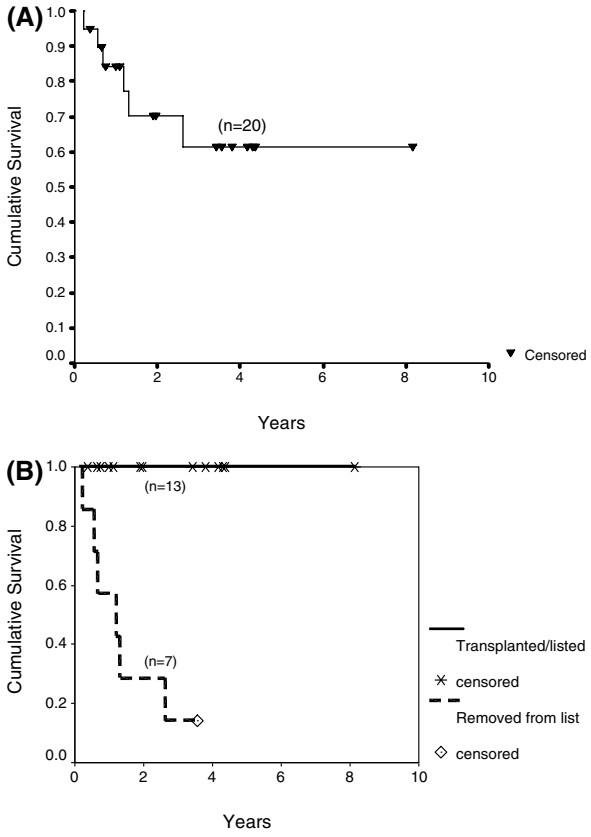

Figure 3: Kaplan-Meier survival curves. (A) Overall group of 20 patients, and (B) transplanted and still listed vs. those removed from the list.

Factors associated with removal from the list and survival

We examined CLIP score, Okuda Stage, Childs-Pugh class, age, gender, alpha-fetoprotein and TMN stage (greater than T2 vs. T2 or less) by logistic regression. None of these was statistically associated with overall survival or removal from the list. The patient with HACE-related decompensation was 58 years old with a CLIP Score of 2, Childs-Pugh Class B, Okuda 2 and MELD of 17 (bilirubin of 2.6 mg/dL, INR of 1.85 and creatinine of 1.0).

Discussion

Recent studies suggest that HACE increases survival in unresectable HCC (5–7). However, the role of HACE as an adjuvant to surgery remains less clear. Histologic examination of tumors treated with HACE indicates necrosis in >50% of cases and increased survival in certain patient groups (8–10). The only randomized, controlled trial using HACE before resection did not improve cancer-free survival (11). There have been no randomized controlled trials to date of HACE before transplantation, and nonrandomized data are conflicting (2–4,12). Also, there are very few studies that include all patients intended for transplant and receiving HACE. The latter analysis is important, as the current MELD-based allocation system has significantly increased the chance for HCC patients to be transplanted (1). We therefore examined outcomes in all patients listed for transplant who received HACE therapy for HCC.

We were able to transplant the majority of our patients with excellent post-transplant survival. Twelve (60%) of our listed 20 patients receiving HACE were successfully transplanted and one (5%) is still listed in stable condition. Cumulative survival for all 20 patients was 61.3% at 5.48 years, but survival among those transplanted or still listed was much higher (100% at 2.76 years mean follow up).

One group reported their experience with pretransplantation HACE in patients with HCC greater than 5 cm (3). Forty-nine percent of their patients were transplanted and the overall 5-year survival rate was 44%. The lower rates in their study compared with ours was related to more advanced stage of HCC. Another center reported that 26 (78%) of 33 HCC patients were successfully transplanted, while 15% were removed from the list (13). Their pretransplant adjuvant therapy differed from ours. Patients were given either radiofrequency ablation or HACE depending on clinical judgment. Overall survival was 84.8% at 3 years.

Graziadei et al. from Austria, successfully transplanted 41 of 48 HCC patients receiving pretransplant chemoembolization (14). All 48 had HCC stage T2 or less, similar to our study, but none of their patients fell off the list; seven were still waiting. Their patients were similar to ours in terms of Childs-Pugh Class, age and underlying liver disease. However, their mean waiting time was only 178 days compared with 343 days in our study. While our study was too small to detect statistically significant differences between survival and waiting times, pre and post-MELD, three of our seven patients were removed from the list after more than 350 days on the waiting list (Table 2). All three were in the pre-MELD era.

One (5%) of our patients had significant decompensation attributable to HACE. Hepatic decompensation is a well-known risk of HACE. Our patient was removed from the list for rapid deterioration and eventually died. Significant post-HACE decompensation can occur in 2.5–15% of patients (3,12,15). While the study by Graziadei et al. had no patients removed from the list for HACE-related complications, one patient did develop a hepatic abscess requiring surgical drainage (14). Complications such as hepatic artery thrombosis or arteritis are also reported (12) but do not appear to occur at a higher rate than background (16).

Such complications have gained more significance since the implementation of MELD. If the MELD-based system shortens the waiting time for a HCC patient to less than 4–5 months, then HACE may be unnecessary

and even detrimental. Recent data suggest that listed HCC patients have a relatively low predicted risk of list drop-out in the first 6 months (7.2–11%) using the MELD-based system that was implemented on February 27, 2002 (15). These rates are similar to the above-mentioned HACE-related complication rates. The majority of HCC patients with MELD score upgrades were, in fact, transplanted within 3 months during the first 12 months under the MELD system (1). In addition, patients undergoing HACE are more stable with preserved hepatic and renal function (Figure 1). Presumably they will be less likely to drop off the list for cirrhosis progression. Conversely, if the newly lowered MELD scores for HCC (implemented April 2003; 17) increase the waiting times well over 6 months, then pretransplant HACE is certainly more justified.

Unfortunately, our study was too small to identify risk factors for HACE-related decompensation. Our one patient's Childs-Pugh Class, Okuda Stage, and CLIP score were unremarkable (B, II and 2, respectively), but her MELD score of 17 was the highest in this cohort. Perhaps larger studies will identify a particular MELD score or other factors such as Karnofsky score, tumor location and vascular supply as predictive of HACE-related complications. Our study had no control group and relied on retrospective data collection. However, we took significant measures to find all listed patients receiving HACE and followed them all to death or censor date. For these reasons, our study reflects clinical practice and provides insight into the success, failure and complication rates of HACE as a pretransplantation therapy. We conclude that a balance between waiting time and the risk of HACE must be struck. Pre-transplantation HACE leads to excellent outcomes for those making it to transplantation, but long waiting times will decrease survival when all patients intended for transplant are analyzed. When waiting time is short, as in the study from Austria (14) and during the first year of MELD in the USA, the necessity of pretransplant HACE becomes debatable and may be outweighed by procedural risk.

Until recently, it was not possible to use a nontreatment control arm because HACE improves survival in nonresectable HCC (5,6), and mortality of HCC patients on the waiting list was so high (18,19). However, the current MELD system has led to more transplants and presumably lower wait-list mortality for HCC patients. There are now data to suggest that list dropout is relatively low in the first 6 months of listing, and HACE may carry a similar risk of decompensation. If the current MELD system keeps the waiting time to less than 4 or 5 months, then a randomized, controlled trial may be feasible for cases with single tumors less than 3 cm (15). It would be best to perform such a trial under a stable MELD system. Certainly, such studies are necessary to clearly define the role of ablative therapies in the pretransplant setting. For now, our center continues to offer HACE in light of a respectable rate of transplantation, low complication rate and excellent post-transplant survival.

References

1. Sharma P, Balan V, Hernandez JL et al. Liver transplantation for hepatocellular carcinoma: the MELD impact. Liver Transpl 2004; 10: 36–41.
2. Majno PE, Adam R, Bismuth H et al. Influence of preoperative transarterial lipiodol chemoembolization on the resection and transplantation for hepatocellular carcinoma in patients with cirrhosis. Ann Surg 1997; 226: 688–703.
3. Roayaie S, Frisher JS, Emre SH et al. Long-term results with multimodal adjuvant therapy and liver transplantation for the treatment of hepatocellular carcinomas larger than 5 centimeters. Ann Surg 2002; 235: 533–539.
4. Oldhafer KJ, Chavan A, Fruhauf NR et al. Arterial chemoembolization before liver transplantation in patients with hepatocellular carcinoma: marked tumor necrosis, but no survival benefit? J Hep 1998; 29: 953–959.
5. Llovet JM, Real MI, Montana X et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. Lancet 2002; 359: 1734–1739.
6. Lo CM, Ngan H, Tso WK et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002; 35: 1164–1171.
7. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology 2003; 37: 429–442.
8. Zhang Z, Liu Q, He J, Yang J, Yang G, Wu M. The effect of preoperative transcatheter hepatic arterial chemoembolization on disease-free survival after hepatectomy for hepatocellular carcinoma. Cancer 2000; 89: 2606–2612.
9. Di Carlo V, Ferrari G, Castoldi R et al. Pre-operative chemoembolization of hepatocellular carcinoma in cirrhotic patients. Hepatogastroenterol 1998; 45: 1950–1954.
10. Lu CD, Peng SY, Jiang XC, Chiba Y. Preoperative transcatheter arterial chemoembolization and prognosis of patients with hepatocellular carcinomas. retrospective analysis of 120 cases. World J Surg 1999; 23: 293–300.
11. Yamasaki S, Hasegawa H, Kinoshita H et al. A prospective randomized trial of the preventive effect of pre-operative transcatheter arterial embolization against recurrence of hepatocellular carcinoma. Jpn J Cancer Res 1996; 87: 206–211.
12. Spreafico C, Marchiano A, Regalia E et al. Chemoembolization of hepatocellular carcinoma in patients who undergo liver transplantation. Radiology 1994; 192: 687–690.
13. Maluf DG, Fisher RA, Cotterell AH, Wolfe L, Shiffman ML, Posner MP. Non-resective ablation for hepatocellular carcinoma: effectiveness measured by intention-to-treat and dropout from liver waiting list [abstract]. Am J Transplant 2003; 3: 243.
14. 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.
15. Yao FY, Bass NM, Nikolai B et al. A follow-up analysis of the pattern and predictors of dropout from the waiting list for liver transplantation in patients with hepatocellular carcinoma: implications for the current organ allocation policy. Liver Transpl 2003; 9: 684–692.
16. Richard HM, Silberzweig JE, Mitty HA, Lou WY, Ahn J, Cooper JM. Hepatic arterial complications in liver transplant recipients treated with pretransplantation chemoembolization for hepatocellular carcinoma. Radiology 2000; 214: 775–779.

17. Liver Transplant Candidates with Hepatocellular Carcinoma. United Network for Organ Sharing OPTN/UNOS policy 3.6.4.4 2003 *http://www.unos.org/frame_default.asp*, accessed June 28.
18. Yao FY, Bass NM, Nikolai B et al. Liver transplantation for hepatocellular carcinoma: analysis of survival according to the intention-to-treat principle and dropout from the waiting list. Liver Transplant 2002; 8: 873–883.
19. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999; 30: 1434–1440.