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A randomized controlled trial of emergency treatment of bleeding esophageal varices in cirrhosis for hepatocellular carcinoma

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Abstract

BACKGROUND: Ninety percent of patients with hepatocellular carcinoma (HCC) have cirrhosis. Bleeding esophageal varices (BEV) is a frequent complication of cirrhosis. Detection of HCC in cirrhotic patients with BEV has not been studied.

METHODS: Two hundred eleven unselected patients with cirrhosis and BEV were randomized to endoscopic sclerotherapy (n = 106) or emergency portacaval shunt (n = 105). Diagnostic workup and treatment were initiated within 8 hours. Ninety-six percent had >10 years of follow-up. HCC screening involved serum α -fetoprotein (AFP) every 3 months, ultrasonography every 6 months, and selective computed tomography (CT).

RESULTS: HCC occurred in 15 patients, all incurable, a mean of 2.94 years after entry. They died a mean 1.33 years after discovery. Serial AFP and ultrasound examinations were unrevealing over a mean of 2.3 years. The mean model of end-stage liver disease score was 12.7 at entry and 17.4 at HCC diagnosis.

CONCLUSIONS: Long-term screening by AFP and ultrasound plus selective CT failed to detect HCC at a curable stage. The detection of HCC in cirrhotic patients with BEV remains a serious, unsolved problem. The use of CT for routine screening warrants consideration despite increased costs.

Keywords

Cirrhosis; Bleeding esophageal varices; Emergency portacaval shunt; Endoscopic sclerotherapy; Hepatocellular carcinoma (HCC); Screening for HCC

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Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the fastest growing cause of cancer-related deaths in the United States.^{1,2} The incidence of HCC is increasing in the United States^{3,4} and in northern Europe.⁵ Cirrhosis of the liver is present in approximately 90% of patients with HCC,^{6,7} and HCC is a frequent cause of death in patients with cirrhosis.^{8–10}

Bleeding esophageal varices (BEV) in patients with cirrhosis is common and life threatening and demands emergency treatment. Once bleeding is controlled, long-term follow-up directed at maintaining hemostasis and improving liver function is essential. Such follow-up must include screening for the development of HCC. Unfortunately, there are no reports of studies aimed at detecting and treating HCC in cirrhotic patients following emergency treatment of BEV. The question is, Are the incidence, detection, and behavior of HCC in cirrhotic patients following one or more bouts of BEV different from those in nonbleeding cirrhotic patients?

From April 8, 1988, to December 31, 2005, we conducted a randomized controlled trial in 211 unselected, consecutive patients with cirrhosis and acute BEV in whom emergency and long-term endoscopic sclerotherapy (EST) was compared with direct emergency portacaval shunt (EPCS). An integral part of the trial was a long-term program of regular screening for HCC. In 2 recent publications, we described the study in detail and reported the outcomes first with regard to control of bleeding and survival¹¹ and second with regard to development of portal-systemic encephalopathy (PSE).¹² This report focuses on the incidence, detection, course, and treatment of HCC.

Methods

Design of randomized controlled trial

The objectives of this study were to compare, in unselected consecutive patients who entered the University of California, San Diego (UCSD), Medical Center with cirrhosis and acute BEV, the influence on survival rate, control of bleeding, quality of life, and economic costs of (1) EST and (2) EPCS. Our 2 recent publications,^{11,12} which described the trial and provided full information on the protocols and methods, should be consulted for details. The study protocol and consent forms were approved before the start of the study and at regular intervals thereafter by the UCSD Human Subjects Committee (Institutional Review Board). Figure 1 is a CONSORT flow diagram that shows the overall design and conduct of the trial.^{13,14}

Screening for HCC

Screening for HCC involved serial abdominal ultrasonography at study entry and every 6 months and serial measurements of serum α -fetoprotein (AFP) at study entry and monthly for the first year and every 3 months thereafter. Ultrasonography was performed under the direction of a senior radiologist with long experience in the detection of liver lesions. Selected technicians who had received training in the detection of liver tumors were assigned to perform ultrasonography of the patients enrolled in the trial. None of the patients had morbid obesity. Computed tomography (CT) was performed during the index admission

and subsequently when a questionable or suspicious abnormality was found on ultrasonography. In addition, ultrasonography was performed and AFP measured during every hospital readmission. In the 50 EST patients who underwent rescue portacaval shunt, the liver was thoroughly examined and a second liver biopsy was obtained during operation. Patients were evaluated by the UCSD liver transplantation program during or shortly after the index hospital admission and intermittently thereafter.

Statistical analysis

Comparison between HCC and no HCC within each treatment arm used Fisher's exact test for binary and categorical outcomes and baseline characteristics and Wilcoxon's rank-sum test for continuous outcomes. Overall comparison between HCC and no-HCC groups combined the comparisons within each treatment arm, stratified for treatment, using Mantel-Haenszel tests for binary and categorical variables and stratified Wilcoxon's tests for continuous outcomes. Survival was computed using Kaplan-Meier analysis and compared between groups using the Gehan-Wilcoxon rank test, stratified by treatment. The cause of recurrent PSE was compared using Pearson's χ^2 tests. *P* values were not adjusted for multiple comparisons.

Results

Overall outcome data of EST versus EPCS

Our recent publications should be consulted for data on the clinical characteristics of the 211 patients, findings on upper endoscopy and liver biopsy, results of laboratory blood tests, data on rapidity of therapy, data on control of bleeding, operative and endoscopic data, data on PSE, and data on survival.^{11,12} The 2 groups were similar in every aspect of cirrhosis and BEV. Histologic proof of cirrhosis was ultimately obtained in all patients. Mean and median times from the onset of bleeding to entry in the study were <20 hours in both groups of patients, and times from the onset of bleeding to the start of EST and EPCS were <24 hours. EST achieved permanent long-term control of bleeding in only 20% of patients. In contrast, EPCS promptly and permanently controlled bleeding in every patient. Survival rates were significantly higher after EPCS than after EST (*P* < .001). The incidence of recurrent PSE following EST was 35%, which was more than twice the 15% incidence following EPCS (*P* < .001).

Results in patients with HCC

Clinical characteristics.—HCC developed in 10 of the 106 patients randomized to EST and 5 of the 105 patients randomized to EPCS. Table 1 presents the clinical characteristics on admission of the 15 patients who developed HCC and compares these with the data on the 196 patients who did not develop HCC. Generally, there were no significant and meaningful differences that distinguished the patients who subsequently developed HCC from those who remained free of HCC. In 12 of the 15 patients (80%) who developed HCC, cirrhosis was due to hepatitis C, alone or with alcoholism, an incidence that was significantly higher than the 35% incidence of hepatitis in the 196 patients without HCC (*P* = .003). However, hepatitis cannot be considered a telltale sign of future development of HCC, because hepatitis played a causative role in cirrhosis in 68 patients who remained free

of HCC. Chronic alcoholism was involved in the etiology of cirrhosis in 163 of the 196 patients (83%) who remained free of HCC and in 11 of the 15 patients (73%) who developed HCC, a difference that was not significant. There were somewhat fewer patients in Child's risk class C (13%) and more patients in Child's class A (40%) among the HCC patients than among the non-HCC patients, but again, the differences were not significant. Median times from the onset of bleeding to entry in the study were <20 hours in both non-HCC and HCC patients, and median times from the onset of bleeding to the start of EST or EPCS were <24 hours.

Control of bleeding.—Table 2 shows data on control of bleeding and requirement for blood transfusions in the EST and EPCS groups without and with HCC. Excluding indeterminate deaths within 14 days unrelated to bleeding, EST achieved control of bleeding for >30 days in only 21% of the entire group and in only 22% of the subgroup with HCC. In contrast, EPCS promptly and permanently controlled bleeding in every patient. In patients with EPCS, HCC had no influence on the invariably successful control of bleeding. Patients in the EST group and the subgroup with HCC required significantly more units of packed red blood cell transfusions than those in the EPCS group.

PSE.—The 35% incidence of recurrent PSE following EST was more than twice the 15% incidence following EPCS ($P < .001$). Within the EST and EPCS groups, there were no significant differences between patients with and without HCC in incidence of recurrent PSE, episodes of PSE per patient and per year of follow-up, hospital readmissions for PSE per patient and per year, and proportion of patients with a high PSE index.

Survival.—Detailed data on survival of the EST and EPCS groups were reported in our recent publications.^{11,12} Survival rates at all time intervals and in all Child's classes were significantly higher after EPCS than after EST ($P < .001$). Median survival of patients who developed HCC was 1.46 years in the EST group and 5.15 years in the EPCS group. The difference in length of survival occurred whether or not the patients developed HCC and was due to success in controlling BEV, which generally failed in response to EST and was invariably successful following EPCS. Median survival after discovery of HCC was short in both groups, lasting only .02 years in the EST patients and .18 years in the EPCS patients. Only 5 of the 15 patients with HCC survived >1 year. Because of the low overall survival rate of the EST group because of failure to control BEV, there was no significant difference between patients free of HCC and those who developed HCC. In contrast, in the EPCS group, development of HCC shortened life significantly.

HCC screening program.—All patients underwent regular screening for HCC, described previously. Follow-up was 100% and lasted 10 years or until death in 96%. Table 3 summarizes the courses of the 15 patients who developed HCC and the results of screening tests.

On admission, in all 211 patients, the results of serum AFP measurements were normal, which was <11 ng/mL in the UCSD clinical laboratory, and the results of both ultrasonography and CT were negative. The mean time lapse from entry in the trial to diagnosis of HCC was between 2.4 and 3.0 years. Only 1 patient was found to have HCC

within 1 month of entry in the trial, and he had negative screening results on admission. The frequency of success in controlling bleeding in the 15 patients with HCC was identical to the success in the 211 patients randomized to EST and EPCS, specifically, 22% in the EST patients and 100% in the EPCS patients. As a result, 6 patients in the EST group underwent rescue portacaval shunt early in their course. Discovery of HCC during rescue portacaval shunt by inspection of the liver and liver biopsy occurred in only 1 of these 6 patients.

Serial AFP determinations were normal for a mean of 2.3 to 2.8 years before detecting HCC, and the results of serial ultrasonography were negative for a mean of 2.17 to 2.6 years. This amounted to a substantial number of negative screening results, specifically, a mean of 11.9 to 14.0 AFP measurements and a mean of 6.5 to 8.0 ultrasound procedures. One patient had 35 normal AFP determinations and 18 ultrasound examinations with negative results. After the index hospitalization, CT was performed in 12 patients, always following abnormal results on ultrasonography and as a prelude to making the diagnosis of HCC. CT performed in all patients during the index admission did not suggest the presence of HCC. The mean time interval between negative screening results and positive results indicating HCC was 5.5 months.

HCC was discovered by screening tests and subsequent needle liver biopsy in 7 of the 10 patients in the EST group and all 5 patients in the EPCS group. In 2 patients in the EST group, HCC was discovered at autopsy, and in 1 patient, HCC was discovered at rescue portacaval shunt surgery. The mean survival after discovery of HCC ranged from 1.53 to 1.74 years. Of the 13 patients in whom HCC was discovered during life, 9 (69%) died within 6 months. Those patients were evaluated for liver transplantation, but unfortunately, curative treatment in the form of resection or liver transplantation was not an option when HCC was detected. All patients died of HCC.

The mean model of end-stage liver disease scores at the time of entry in the trial in patients who developed HCC were 13.4 in the EST group and 10.4 in the EPCS group. At the time of discovery of HCC, the mean model of end-stage liver disease scores were 17.9 and 18.4, respectively, in the EST and EPCS patients. Liver function, determined by quantitative Child's class, did not decline between entry in the trial and diagnosis of HCC.

Comments

HCC is an important complication of cirrhosis of the liver. Approximately 90% of patients with HCC have cirrhosis.^{6,7} The mean annual incidence of HCC in cirrhotic patients in the West has been reported to be 3% to 4%.^{8-10,15,16} It is clearly important to detect HCC in cirrhotic patients early in its course, when there is a possibility of curing the cancer by resection or liver transplantation.

BEV is a frequent and life-threatening complication of cirrhosis and presents a special problem. Emergency and lifelong control of bleeding have priority over other considerations. However, once bleeding has been controlled, attention must include the long-term detection of HCC. Regrettably, there are no reports of the development, diagnosis, and treatment of HCC in cirrhotic patients who have recovered from BEV. The literature contains 3 retrospective reports of patients with HCC who simultaneously presented with

esophageal varices.^{17–19} None of these reports dealt with the problem of screening for HCC or the development of HCC in the large population of cirrhotic patients who present with acute variceal bleeding.

The literature contains a substantial amount of data regarding screening for HCC in cirrhotic patients. In studies of the value of AFP in screening, when the threshold AFP level was set at 10.3 ng/mL, the sensitivity of AFP ranged between 56% and 77%, and the specificity ranged from 76% to 94%.²⁰ When the threshold was raised only slightly to 20 ng/mL, sensitivity dropped to 25% to 65%.^{2,21–23} When the AFP threshold was set at 200 ng/mL, sensitivity declined to 22%.²¹ The many studies of AFP indicate clearly that AFP alone is not an adequate screening test for detecting HCC.²⁴

The radiologic test used most widely for HCC surveillance is ultrasonography, which has been reported to have sensitivity of between 65% and 80% and specificity >90% when used as a screening test.^{16,21,25,26} Major drawbacks of ultrasonography for HCC surveillance are that it is very operator dependent and may be inaccurate in obese patients. Our trial benefitted from having specifically trained technicians who were supervised by an experienced senior radiologist. Also, none of our patients were morbidly obese. Combined use of AFP and ultrasonography has been shown to increase detection rates of HCC, and most screening programs now use this combination.^{2,21}

Other serologic tests that have been used in HCC screening include des- γ -carboxy prothrombin, lectin-bound AFP, α -fucosidase, and glypican 3. None of these have improved the sensitivity of AFP in detecting HCC.^{2,20,21}

CT is a more accurate imaging modality than ultrasonography for detecting HCC. Patients in our trial underwent CT during the index admission and selectively thereafter when a questionable or suspicious abnormality was found on ultrasonography. Some reports have suggested using CT as a routine screening test for HCC.^{21,25,27–30} In a study of HCC screening in patients awaiting liver transplantation, Saab et al³¹ observed that screening with CT was associated with the greatest gain in life expectancy but also the greatest costs. Moreover, it has been suggested that the use of CT as a screening test subjects patients to significant radiation exposure. Higher cost and dangers of radiation have deterred the use of CT in routine screening.^{20–22,28,31} At the same time, most investigators have concluded that screening for HCC in cirrhosis by AFP and ultrasonography is unsatisfactory.^{21,23,26,28,31–34} Of the 211 patients enrolled in our trial, 184 survived 30 days and were discharged from the hospital. Fifteen of the 184 (8%) subsequently developed HCC and died. If the addition of CT to the repetitive screening program were to facilitate the identification and treatment of HCC in 8% of the patients, it would seem that CT is a useful screening modality.

One objective of our trial was to determine if there were any warning signs indicating the future development of HCC in patients with cirrhosis who presented with BEV. Unfortunately, despite intensive, 100% long-term follow-up with routine examinations every 3 months, we did not discover any features that distinguished the 15 patients who subsequently developed HCC from the 196 patients who remained free of HCC. There were no findings at the time of entry in the trial that indicated the presence of HCC or the

likelihood of subsequent development of liver cancer. Control of bleeding and development of PSE were similar in the HCC patients and the non-HCC patients. Liver function determined by quantitative Child's class estimates was similar at the time of trial entry and at the time when HCC was detected. The screening program of serial AFP determinations and ultrasound examinations was ineffective. The mean time between entry in the trial and diagnosis of HCC was between 2.4 and 3.0 years. By the time HCC was discovered by abnormal screening results, the neoplasm obviously had been present for a considerable time, and there was no possibility of curative treatment. Screening for HCC by ultrasonography every 6 months was done according to the consensus recommendation of the American Association for the Study of Liver disease²¹ and the European Association for the Study of the Liver.³⁵ The screening for HCC by AFP determinations monthly for the first postentry year and every 3 months thereafter was more frequent than that recommended by consensus. Regrettably, there are no reports in the literature that describe a more effective surveillance program for detecting HCC in cirrhotic patients with BEV.

It is possible, indeed likely, that HCC could have been prevented in some patients if they had undergone liver transplantation soon after control of acute BEV. We examined the issue of liver transplantation as part of our trial of emergency treatment of BEV, and in addition, we analyzed our results regarding liver transplantation in 1300 nonrandomized patients in whom we previously performed portacaval shunt beginning in 1978.³⁵ The results of our study indicate that liver transplantation is seldom required following control of bleeding by portacaval shunt. If recurrent BEV is prevented, as was true in 100% of the portacaval shunt patients, both randomized and nonrandomized, prolonged survival occurs, equal to or better than survival following liver transplantation.³⁶ Furthermore, there are a number of limitations on the use of liver transplantation as a cure for cirrhosis, specifically the scarcity of donor livers, long waiting times, and high costs. Liver transplantation is clearly not the answer to preventing HCC in patients with BEV due to cirrhosis.

As a final note, explanatory comments are indicated about 2 aspects of our trial, (1) the use of EST rather than endoscopic variceal ligation (EVL) as the emergency endoscopic treatment of BEV and (2) absence of transjugular intrahepatic portosystemic shunt (TIPS). We discussed the justification for our use of EST in our recent publications.^{11,12} Our use of EST has received strong support from studies published in 2003, 2005, and 2006 that have questioned replacement of EST by EVL.³⁷⁻⁴⁰ Furthermore, it is noteworthy that currently, in our 4-county community of 8.5 million people, gastroenterologists with whom we have had regular and frequent contact use EST more frequently than EVL. At the time when EVL was introduced at our institution, we were well into our trial and made the decision not to change from EST to EVL.

With regard to TIPS, which was popularized long after our trial was initiated, it has become the most widely used procedure of choice when it is believed that portal decompression is indicated. However, as we have pointed out previously, TIPS has a high rate of stenosis and occlusion, a resultant high incidence of PSE, and limited durability. The TIPS occlusion rate has been reduced by the recent introduction of the polytetrafluoroethylene-coated stent, but the rates of occlusion and PSE are still much higher than the incidences of these serious

complications following portacaval shunt observed in all of our studies. Recently, we completed a trial comparing TIPS and EPCS and are analyzing the data for publication.

In conclusion, in this randomized controlled trial of 211 cirrhotic patients with BEV in which 15 developed incurable HCC, there were no clinical features at study entry that suggested the likely development of HCC. Moreover, regular long-term screening by routine AFP and ultrasonography plus selective CT failed to identify HCC at a stage when curative treatment by resection or liver transplantation was possible. The detection of HCC in cirrhotic patients following control of BEV remains a serious, unsolved problem. If the detection of HCC is to be improved, the use of CT as a routine screening procedure warrants consideration, despite the increased costs.

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Figure 1.
CONSORT flow diagram showing the overall design and conduct of the prospective randomized controlled trial.^{13,14}

Table 1

Clinical characteristics in patients with cirrhosis and BEV randomized to EST or EPCS

Variable	EST		EPCS		P	HCC (n = 5)	P (Overall HCC vs no HCC)
	No HCC (n = 96)	HCC (n = 10)	No HCC (n = 100)	HCC (n = 100)			
History					.028 *		.024 *
Age (y)	47.1/44	55.3/58	49.6/47	55.4/60	.23		
Men	73 (76%)	8 (80%)	76 (77%)	5 (100%)	.58		.53
Cause of cirrhosis					.059		.023 *
Alcoholism alone	55 (57%)	3 (30%)	54 (54%)	0 (0%)			
Hepatitis B or C alone	7 (7%)	3 (30%)	7 (7%)	1 (20%)			
Alcoholism and hepatitis	25 (26%)	4 (40%)	29 (29%)	4 (80%)			
Hepatitis with or without alcoholism	32 (33%)	7 (70%)	36 (36%)	5 (100%)	.008 *		.001 *
Other	9 (9%)	0 (0%)	10 (10%)	0 (0%)			
Physical examination							
Jaundice	41 (43%)	4 (40%)	37 (37%)	1 (20%)	.65		.76
Ascites	59 (61%)	6 (60%)	52 (52%)	2 (40%)	.67		.91
PSE	17 (18%)	2 (20%)	17 (17%)	2 (40%)	.22		.58
Severe muscle wasting	47 (49%)	3 (30%)	63 (63%)	4 (80%)	.65		.81
Child's risk class					.27		.18
A (5–8 points)	28 (29%)	4 (40%)	24 (24%)	2 (40%)			
B (9–11 points)	41 (43%)	5 (50%)	47 (47%)	2 (40%)			
C (12–15 points)	27 (28%)	1 (10%)	29 (29%)	1 (20%)			
Child's risk class points	10.2/10	9.1/9	10.1/10	9.2/9	.36		.09
Rapidity of therapy (h)							
Onset bleeding to study entry	12/20.1 (0–144)	9/17.1 (1–64)	16/18.8 (0–72)	22/31.6 (5–95)	.50		.64
Onset bleeding to primary therapy	15/23.1 (3–147)	13/25.3 (5–66)	19/23.4 (2.6–75)	27/36.0 (8.5–100)	.86		.61
Study entry to primary therapy	2.5/3.1 (.8–8)	2.7/2.9 (1.5–5.2)	3.4/4.4 (1.4–24)	5/4.4 (2.4–5.8)	.84		.58
>8 h	0 (0%)	0 (0%)	3 (3%)	0 (0%)	1.0		.70

Data are expressed as mean/median (range) or as number (percentage).

* Statistically significant difference.

Table 2

Control of bleeding in patients with cirrhosis and BEV randomized to EST or EPCS

Variable	EST		EPCS		P	HCC (n = 5)	P	P (Overall HCC vs no HCC)
	No HCC (n = 96)	HCC (n = 10)	No HCC (n = 100)	HCC (n = 100)				
Control of bleeding								
Successful control by primary therapy excluding indeterminates for								
At least 14 d	18 (20%)	3 (30%)	.43	89 (100%)	5 (100%)	1.0	.73	
At least 30 d	18 (21%)	2 (22%)	1.0	85 (100%)	5 (100%)	1.0	.96	
>30 d	18 (21%)	2 (22%)	1.0	85 (100%)	5 (100%)	1.0	.94	
Declaration of primary therapy failure								
Required 6 U PRBC in first 7 d	13 (18%)	2 (29%)	.61	0 (0%)	0 (0%)	NA	.61	
Required 8 U PRBC in any 12 mo	42 (57%)	5 (71%)	.69	0 (0%)	0 (0%)	NA	.69	
Recurrent variceal bleeding after variceal obliteration was declared	27 (36%)	0 (0%)	.09	0 (0%)	0 (0%)	NA	.089	
>1 criterion for failure	8 (11%)	0 (0%)	1.0	0 (0%)	0 (0%)	NA	1.0	
PRBC transfusion (U)								
Index hospitalization								
Posttherapy bleeding								
Variceal	4.3/0 (0–37)	5.5/1 (0–20)	.40	0/0 (0–0)	0/0 (0–0)	1.0	.40	
Nonvariceal	.3/0 (0–11)	.5/0 (0–5)	.73	1.8/0 (0–29)	1.6/0 (0–8)	.80	.66	
Total PRBC	10.0/7 (2–44)	10.5/7 (2–23)	.92	15.3/10 (2–81)	8.6/8 (4–15)	.26	.55	
Readmission for bleeding								
Variceal	7.0/2 (0–60)	5.5/0 (0–23)	.61	.4/0 (0–26)	0/0 (0–0)	.75	.56	
Nonvariceal	3.8/0 (0–38)	3.5/0 (0–22)	.63	3.6/0 (0–33)	.4/0 (0–2)	.26	.27	
Total PRBC	10.8/7 (0–60)	9.0/2 (0–36)	.61	4.0/0 (0–33)	.4/0 (0–2)	.24	.27	
Grand total PRBC								
Variceal	15.8/14 (2–64)	15.5/15 (2–36)	.98	13.9/10 (2–73)	7/7 (4–10)	.12	.33	
Variceal and nonvariceal	19.5/17 (2–64)	19.5/15 (2–45)	.86	18.3/14 (2–81)	9/8 (4–17)	.10	.24	

Data are expressed as number (percentage) or as mean/median (range).

NA = not applicable; PRBC = packed red blood cells.

Table 3
Results of screening for HCC in patients with cirrhosis and BEV randomized to EST or EPCS

Variable	EST (n = 10)	EPCS (n = 5)
Trial entry to death (y)	4.01 (.07–13.67)	4.76 (.82–10.45)
Number of survivors	1	0
Trial entry to diagnosis of HCC (y)	2.41 (.011–8.17)	3.00 (.78–5.25)
Time from diagnosis of HCC to death (y)	1.53 (.0–11.67)	1.74 (.08–5.2)
HCC cause of death	100%	100%
Success in control of bleeding of EST or EPCS >30 d	2/9 (22%)	5/5 (100%)
Rescue PCS	6 (60%)	NA
Trial entry to rescue PCS (d)	19 (4–40)	NA
Normal AFP before diagnosis of HCC (y)	2.30 (.07–6.75)	2.80 (.5–5.0)
Negative ultrasound findings before diagnosis of HCC (y)	2.17 (.07–8.0)	2.60 (.5–5.0)
Number of normal screens before diagnosis of HCC		
AFP	11.9 (1–35)	14 (5–23)
Ultrasonography	6.5 (1–18)	8 (4–13)
How was diagnosis made?		
Screening tests, then liver biopsy	7 (70%)	5 (100%)
Autopsy	2 (20%)	0 (0%)
At rescue PCS	1 (10%)	0 (0%)
MELD score		
At trial entry	13.4 (8–24)	10.4 (7–16)
At time of HCC diagnosis	17.9 (12–35)	18.4 (15–25)
MELD score 20		
At trial entry	1 (10%)	0 (0%)
At time of HCC diagnosis	2 (20%)	1 (20%)
Child's class (mean points)		
A		
At trial entry	4 (7.5%)	2 (7.5%)
At time of HCC diagnosis	5 (7.2%)	1 (8.0%)
B		

Variable	EST (n = 10)	EPCS (n = 5)
At trial entry	5 (9.8%)	2 (9.5%)
At time of HCC diagnosis	3 (9.0%)	4 (10.0%)
C		
At trial entry	1 (12%)	1 (12%)
At time of HCC diagnosis	2 (12%)	0 (0%)
All classes		
At trial entry	10 (9.1%)	5 (9.2%)
At time of HCC diagnosis	10 (8.7%)	5 (9.6%)

Data are expressed as mean (range) or as number (percentage).
MELD = model of end-stage liver disease; NA = not applicable; PCS = portacaval shunt.