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LIVER TRANSPLANTATION IN A RANDOMIZED CONTROLLED TRIAL OF EMERGENCY TREATMENT OF ACUTELY BLEEDING ESOPHAGEAL VARICES IN CIRRHOSIS

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Abstract

Background—Bleeding esophageal varices (BEV) in cirrhosis has been considered an indication for liver transplantation (LT). This issue was examined in a randomized controlled trial (RCT) of unselected, consecutive patients with advanced cirrhosis and BEV that compared endoscopic sclerotherapy (EST) (n=106) to emergency direct portacaval shunt (EPCS) (n=105).

Methods—Diagnostic workup and treatment were initiated within 8 hours. Patients were evaluated for LT on admission and repeatedly thereafter. 96% underwent over 10 years of regular follow-up. The analysis was supplemented by 1300 unrandomized cirrhotic patients who previously underwent portacaval shunt (PCS) with 100% follow-up.

Results—In the RCT, long-term bleeding control was 100% following EPCS, only 20% following EST. 3, 5, 10, and 15-year survival rates were 75%, 73%, 46%, and 46% following EPCS, compared to 44%, 21%, 9%, and 9% following EST (p<0.001). Only 13 RCT patients (6%) were ultimately referred for LT mainly because of progressive liver failure; only 7 (3%) were approved for LT and only 4 (2%) underwent LT. 1- and 5-year LT survival rates were 0.68% and 0, compared to 81% and 73% after EPCS. In the 1300 unrandomized PCS patients. 50 (3.8%) were referred and 19 (1.5%) underwent LT. Five-year survival rate was 53% compared to 72% for all 1300 patients.

Conclusions—If bleeding is permanently controlled, as occurred invariably following EPCS, cirrhotic patients with BEV seldom require LT. PCS is effective first-line and long-term treatment. Should LT be required in patients with PCS, although technically more demanding, numerous

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studies have shown that PCS does not increase mortality or complications. EST is not effective emergency or long-term therapy.

Keywords

Portacaval shunt; endoscopic sclerotherapy; liver transplantation; survival

INTRODUCTION

Bleeding esophageal varices (BEV) in patients with cirrhosis of the liver are common and highly lethal [1]. Extensive data have shown that the period surrounding the episode of acute bleeding accounts for much of the mortality rate associated with BEV [1–10]. Emergency treatment of BEV, therefore, is of singular importance in the care of patients with cirrhosis. Nevertheless, few randomized trials of emergency treatment, including surgical therapy have been reported.

Liver transplantation (LT) is the only curative treatment of cirrhosis. Some transplant centers have considered BEV in cirrhosis to be an indication for LT. It has been proposed that LT be considered the treatment of choice for “patients with advanced liver disease after failure of sclerotherapy” [11,12] and for “all patients with end-stage liver disease (group C) and variceal bleeding... in the absence of any contraindications” [11–13]. Regrettably, there have been no randomized controlled trials of LT following any of the emergency modalities of therapy for BEV to support or contradict these proposals. All reported data on LT in patients with BEV have been based on retrospective reviews of medical records. Furthermore, recommendations regarding LT in patients with BEV generally have not taken into account the well known limitations, particularly insufficient donor organs.

From April 8, 1988, to December 31, 2005, we conducted a randomized controlled trial (RCT) in 211 unselected, consecutive patients with cirrhosis and acute BEV in whom emergency and long-term endoscopic sclerotherapy (EST) was compared to emergency direct portacaval shunt (EPCS). The trial was a community-wide endeavor and was known as the San Diego Bleeding Esophageal Varices Study. In two recent publications, we described the study in detail and reported the outcomes first with regard to control of bleeding and survival [14], and second with regard to development of portal-systemic encephalopathy (PSE) [15]. This report examines the question of the need for LT after the life-threatening problem of BEV has been addressed. In addition, the effect of EST or EPCS on the conduct and outcome of LT is examined.

As a supplement to the RCT data, we have analyzed our results regarding LT in 1300 unrandomized patients in whom we performed portacaval shunt (PCS) beginning in 1978, 600 as an emergency PCS and 700 electively.

PATIENTS AND METHODS

Design of Randomized Controlled Trial

Our two recent publications [14,15] described our RCT and provided full information on the protocols and methods. These include (1) design of study; (2) patient eligibility; (3) definitions (bleeding esophageal varices (BEV), unselected patients (“all comers”), emergency endoscopic sclerotherapy (EST), long-term endoscopic sclerotherapy (EST), emergency portacaval shunt (EPCS), failure of emergency primary therapy, failure of long-term therapy, rescue therapy, informed consent; (4) randomization; (5) diagnostic work-up; (6) quantitative Child’s classification; (7) initial emergency therapy during workup; (8) endoscopic sclerotherapy; (9) emergency portacaval shunt; (10) posttreatment therapy; (11)

lifelong follow-up; (12) quantitation of portal-systemic encephalopathy (PSE); (13) data collection. 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 RCT [16,17].

Liver Transplantation in the Randomized Controlled Trial

Patients were evaluated by the UCSD liver transplantation program during the index hospital admission and intermittently during follow-up. They underwent extensive evaluation for liver transplantation if and when they exhibited progressive liver failure. 13 survivors of emergency treatment of BEV developed progressive liver failure and underwent complete LT evaluation, 7 from the EST group and 6 from the EPCS group.

Unrandomized Portacaval Shunt Patients

Beginning in 1978 when LT became available to us, we performed portacaval shunt (PCS) for BEV in 1300 cirrhotic patients at UCSD Medical Center Hospitals and the San Diego Veterans Administration Hospital. Patients were studied prospectively according to a well-defined protocol with on-line data collection to determine the indications for subsequent LT. The diagnostic work-up was identical in the unrandomized patients and the RCT patients. From 1978 until the start of our RCT in 1988, EPCS was performed for acute variceal bleeding within 8 hours of initial contact in 600 unselected patients, all comers included. Elective PCS was done over a period of 20 years in 700 selected patients referred to us only after recovery from one or more bouts of BEV elsewhere. Follow-up rate was 100% at 5 years and 97% at 10 years.

Statistical Analysis

The survival rates in the EST and EPCS groups, and in the subgroups determined by the Child's risk class were calculated and plotted using the Kaplan-Meier method, and compared using the log-rank test. Statistical comparisons between the EST and EPCS groups in the RCT were performed as follows: The proportion of subjects referred for LT evaluation, the proportion approved for LT, and the diagnosis of the LT candidates, were compared using Fisher's exact test (FET). The time after entry in the RCT to LT evaluation and the duration of survival after evaluation and since entry were compared using the log-rank test. The MELD at time of LT was evaluated using the Wilcoxon rank test, and the Child's risk class at LT evaluation using Fisher's exact test. Statistical significance was considered at the 0.05 level.

RESULTS

Outcome Data in Randomized Controlled Trial

The clinical characteristics of the 211 patients involved in the RCT were described in our recent publications, including 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 and data on quality of life [14,15]. There were no significant differences between the EST and EPCS groups in any important characteristics of cirrhosis. Child's risk classes on study entry in the EST and EPCS groups, respectively, were 30% and 25% in A, 43% and 47% in B, and 26% and 29% in C. Overall Child's quantitative point scores in the two groups were essentially identical. Three-fourths of the patients had advanced liver disease on admission, often categorized as "end-stage". Histologic proof of cirrhosis was obtained in all patients. Mean and median times from onset of bleeding to start of EST and EPCS were less than 24 hr. Excluding indeterminate deaths within 14 days from causes

other than bleeding, EST achieved permanent long-term control of bleeding in only 20% of patients. In contrast, EPCS promptly and permanently controlled bleeding in every patient. Patients in the EST group required significantly more units of packed red blood cells than those in the EPCS group because of continued or recurrent BEV.

Survival in the Randomized Controlled Trial

Figure 2 shows 15-yr Kaplan-Meier estimated survival plots for the EST and EPCS groups. There were highly significant differences in the survival rates of the two study groups at all time intervals ($p < 0.001$). As expected, the survival rate was related to the severity of hepatic disease at the time of entry in the study, as expressed by Child's risk classes. Survival rates at all time intervals and in all Child's classes were significantly higher after EPCS than after EST. Moreover, EPCS resulted in substantial long-term survival of patients in Child's risk class C who had the most advanced cirrhosis of the liver. Persistent or recurrent BEV was the main cause of death in 44% of the EST patients, but in none of the patients treated by EPCS. Hepatic failure was responsible for 28% of the deaths in the EST group and 33% of the much smaller number of deaths in the EPCS group.

Liver Transplantation in the Randomized Controlled Trial

Table 1 summarizes data on the 13 patients who were ultimately referred for LT in our RCT. They constituted only 6% of the total patients entered into the RCT. 7 patients were approved for LT, but only 4 patients, all in the EST group, underwent LT. 6 patients were denied LT because of continued alcoholism or substance abuse, or non-USA resident status. All patients referred for LT evaluation had advanced cirrhosis in Child's class C or B, with a mean MELD score of 21.

Figure 2 shows Kaplan-Meier survival plots of the patients who underwent LT and the patients who were evaluated for but did not undergo LT, and compares their survival curves with the Kaplan-Meier curves showing the overall survival of patients who received EST or EPCS in the RCT. As was true of the overall survival of patients in the EPCS group, patients from this group who were evaluated for LT lived more than 8 years, even though they did not undergo LT. In contrast, as was true of the EST group in general, patients from this group who were evaluated for or underwent LT had a mean survival of 1.5 years or less.

Liver Transplantation in the Unrandomized Portacaval Shunt Patients

All 1300 unrandomized patients had cirrhosis proven by biopsy and bleeding varices proven by endoscopy. The cause of cirrhosis in 85% of the patients was chronic alcoholism without or with serologically proven chronic viral hepatitis. Quantitative Child's risk classes were A, 11%; B, 50%; and C, 39%. Serious risk factors on admission or past history were ascites in 64%, jaundice in 58%, PSE in 36% and severe muscle wasting in 49%. 90% of the patients had end-stage cirrhosis. Indications for LT after PCS were declining liver function in the presence of end-stage cirrhosis. Only patients who had been abstinent for 6 or more months were accepted as candidates for LT.

Only 50 of the 1300 patients (3.8%) were referred for LT. 19 of the 1300 (1.5%), all in Child's class B (26%) or C (74%), underwent LT. 12 were EPCS patients and 7 were elective PCS patients. The remaining 31 patients were rejected for LT because of resumption of alcoholism, substance abuse, infection, and various other serious comorbidity.

The 30-day, 5-year, and 10-year survival rates, respectively, were 83%, 67%, and 67% after emergency PCS, and 98%, 76%, and 71% after elective PCS. Following LT, the 30-day and 5-year survival rates were 89% and 53%, respectively. The 5-year survival rate of the 31 patients who were proposed but rejected for LT was only 7%. PCS did not increase the

mortality rate or complications of subsequent LT compared with the reports in the literature of that time period and with a large group of unshunted cirrhotic patients who underwent LT. Figure 4 compares 5-year Kaplan-Meier survival plots of the 1300 PCS patients with both the PCS patients who underwent LT and the PCS patients who were rejected for LT.

Regular follow-up was achieved in 100% of the patients for 5 years and 97% for 10 years. During those time periods, all but 2 of the 1300 patients remained free of recurrent BEV and the PCS remained permanently patent in all but 2 patients (99.8%). Recurrent PSE was observed in 10% of the patients. Liver function improved in 76% of the patients and, after 5 years, only 6% of the patients were in Child's class C, compared to 39% on admission.

DISCUSSION

Comment is warranted about two widely used emergency measures that were not included in our RCT, namely endoscopic variceal ligation (EVL) and transjugular intrahepatic portosystemic shunt (TIPS). In 1988 when the San Diego BEV Study was initiated, EST was a mainstay of therapy of BEV and the sole form of endoscopic therapy in use. More recently, elective therapy with endoscopic variceal ligation (EVL) has replaced EST in some centers as a result of several studies showing more rapid eradication of varices, lower rates of recurrent bleeding, and fewer complications [22]. However, replacement of EST by EVL increasingly has been questioned [22–25]. In a 2003 survey of 93 gastroenterologists who treated 725 patients in various centers, EST was used more frequently than EVL for control of variceal bleeding, and as frequently as EVL for initial control of acute bleeding [23]. Several recent trials have reported a significantly higher failure rate with band ligation of actively bleeding varices, and an overall higher recurrence rate of varices treated by EVL [22,25]. Moreover, EST has been reported to be more cost-effective if active variceal hemorrhage is present at the index endoscopy procedure [24]. It is noteworthy that none of 9 randomized controlled trials observed a statistically significant difference in survival rate between EVL and EST [22]. In a recent meta-analysis of emergency EST in 40 trials involving 4031 patients reported by Triantos and colleagues in 2006, there was no statistically significant difference in survival rate between EVL and EST [25]. The authors concluded that “the conclusive evidence for substituting banding ligation or the combination of vasoconstrictors with sclerotherapy as better therapeutic approaches has not been provided in randomized trials. Sclerotherapy can remain a gold standard in variceal bleeding...”. At the time when EVL was introduced at our institution, we were well into our RCT and made the decision not to change from EST to EVL.

With regard to TIPS, our RCT was initiated well before clinical use of TIPS was introduced. Moreover, as we and others have pointed out previously, TIPS has a high rate of stenosis and occlusion, a resultant high incidence of portal-systemic encephalopathy (PSE), and limited durability. The TIPS occlusion rate has been reduced by the recent introduction of the polytetrafluorethylene-coated stent, but the rates of occlusion and PSE are still much higher than the incidences of these serious complications following portacaval shunt in all of our studies.

One purpose of the San Diego BEV Study that involved 211 randomized patients, and the supplementary analysis of the 1300 unrandomized cirrhotic patients who underwent PCS for BEV was to answer several questions about the role of emergency treatment of BEV in subsequent LT. In so doing it is important to recognize that to date no RCTs have been reported in which the relationship of BEV to LT has been examined prospectively. Since our RCT involved a comparison of EST and EPCS, the first question is: what is the role of endoscopic therapy of BEV in patients who might subsequently need LT? Several experienced workers at liver transplantation centers have proposed that EST or endoscopic

variceal ligation (EVL) is the first line of treatment for BEV, and that “there are ample data in the literature to support long-term sclerotherapy as the treatment of first choice for bleeding esophageal varices” [11,12,26]. The results of our RCT contradict this proposal. EST achieved permanent long-term control of bleeding in only 20% of unselected consecutive patients. The 5-year survival rate of patients treated by EST was only 21%, and median survival was less than 3 years, even with rescue PCS. The reasons why LT was not considered in more patients in the EST group are that death from recurrent bleeding in 44% of patients, frequent PSE often due to non-compliance as well as to recurrent bleeding, and social issues such as continued alcoholism, drug abuse and non-USE residence status obviated considerations of LT.

The second question is: how often following an episode of acute BEV in patients with advanced cirrhosis is LT required? The results of our study indicate that LT is seldom required following control of bleeding by PCS. In our RCT, only 6% of the patients were referred for LT, only 3% were approved for LT, and only 4 patients (2%) underwent LT. Of our 1300 unrandomized patients with PCS, only 3.8% of the patients were referred for LT, and only 19 patients (1.5%) underwent LT. Furthermore and most important, if recurrent BEV is prevented, as was true in 100% of the PCS patients, both randomized and unrandomized, prolonged survival occurs, equal to or better than survival following LT. 30-day and 5-year survival rates were 87% and 73%, respectively, following EPCS in 105 patients in the RCT, 83% and 67%, respectively, following EPCS in 600 unrandomized patients, and 98% and 71%, respectively, following elective PCS in 700 unrandomized patients. Survival rates following LT during the period 1988 to 2001 in 46,940 patients reported by the United Network for Organ Sharing (UNOS), were 74.5% at 1 year, 67.4% at 3 years and 62.7% at 5 years [27]. Clearly, the 5-year survival rate following PCS (73%, 67% and 71%) was higher than that of the UNOS LT survival rate (62.7%). It is noteworthy that close to one-half of the patients in the RCT (46%) were alive 15 years after EPCS.

The third question is: should transplant surgeons avoid portacaval shunts or surgical decompressive procedures that involve the hepatic hilum in potential LT candidates? There are numerous statements in the transplantation literature urging avoidance of PCS and strong recommendations to that effect from some recognized transplantation centers [11,12, 23,28–30]. However, there are no valid, representative data from prospective studies, randomized or unrandomized, that support such a proposal. Our studies indicate that PCS is the most effective treatment of BEV, invariably prevents recurrence of bleeding, and achieves long-term survival so that the vast majority of patients do not require LT.

The fourth question is: do portosystemic shunts and, particularly, portacaval shunt, affect the outcome of LT? Our RCT in which only 4 of the 211 patients underwent LT does not provide sufficient data to answer this question. However, the survival rate of the 19 unrandomized patients who underwent LT was 89% after 30 days and 53% after 5 years, which was not significantly different from the survival rates for LT reported by UNOS. PCS did not increase the mortality rate or complications of subsequent LT. Added to the data from our study are at least 10 reports of retrospective studies in the literature that concluded that portosystemic shunts do not affect the results of subsequent LT [11–13,29–36]. That conclusion has not been contradicted by reported studies.

Liver transplantation plays a central role in the treatment of cirrhosis of the liver. Nevertheless, there are a number of limitations on the use of this important therapeutic measure as a cure for cirrhosis [37]. The most important limitation is unavailability of donor livers. In year 2008 there were 17,167 candidates on the waiting list for LT at the beginning of the year and 16,538 on the waiting list at the end of the year (based on OPTN data as of 5/31/09). 6,319 candidates or 37% received LT. 2,456 patients died or deteriorated while

awaiting LT. The median waiting time for LT in 2002 was 974 days and, although the wait was shorter in 2005, it was still 321 days [27]. Furthermore, numerous patients referred for LT have been disqualified for various reasons. Of the patients referred for LT evaluation, 46% in the RCT and 62% in the unrandomized series were turned down for valid reasons including continued alcoholism, drug abuse, and non-USA resident status. Additionally, the costs of LT are substantial. Direct costs of care, as reflected by charges for patients who underwent EPCS in our RCT including costs of lifelong follow-up, averaged a total of \$150,400 or \$39,400 per year. In contrast, the mean cost of LT for cirrhosis in adult patients in 2008, including 180 days of post-transplant care, averaged \$523,400., which is more than 3 times the lifelong average cost of EPCS [27]. Finally, third-party insurance coverage for emergency treatment of BEV such as EPCS has been readily obtainable, while coverage for LT is sometimes difficult to obtain. At one of our institutions, of 182 patients referred for LT from January through July, 2009, 11% were denied LT because of insurance issues.

The results of EPCS in our RCT are generally superior to the results of other reported studies of emergency treatment, all of which have been retrospective and unrandomized. We believe there are several reasons for the difference in outcome. Firstly, our RCT was an organized, community-wide endeavor in which physicians rapidly referred patients from hospitals in 4 neighboring counties to UCSD Medical Center for treatment. Secondly, the diagnostic workup was simplified by eliminating time-consuming, often invasive and unnecessary studies so that the entire diagnostic work-up was completed at the bedside within a mean 3.1 to 4.4 hours of initial contact. Third, with a few minor exceptions, definitive therapy was initiated within 8 hours of initial contact. Fourth, EPCS was performed under the direction of one or the other of two senior faculty surgeons who had extensive operative experience with EPCS. Fifth, concerted efforts were made, with the regular help of dietitians and nurses, to control dietary protein intake and to achieve permanent abstinence from alcohol. Sixth, regular follow-up was 100% and was for 9.4 to more than 10 years until death. Seventh, the direct side-to-side PCS remained permanently patent and functioning in 98% of patients, a rate that is consistent with our past experience with more than 2500 side-to-side PCS, with a failure rate of 2%, substantially lower than reported shunt occlusion rates of 12% to 29% for conventional portal-systemic shunts, 14% to 23% for distal splenorenal shunts [38], 24% to 53% for mesocaval interposition shunts [39–41], and greater than 50% for transjugular intrahepatic portosystemic shunts (TIPS) [42–47].

In conclusion, in this RCT of emergency treatment of acute BEV in 211 patients with cirrhosis, supplemented by analyses of 1300 unrandomized patients treated by portacaval shunt, prospective data indicate clearly that BEV by itself should not be considered an indication for LT. Moreover, the data show that PCS should be considered a first line treatment for BEV since it promptly and permanently stopped variceal bleeding, was accomplished with a relatively low (15%) incidence of subsequent PSE, and produced long-term survival rates equal or superior to those produced by LT. Furthermore, PCS did not increase the mortality rate or complications in the small number of patients who ultimately required LT, a finding that was confirmed by at least 10 retrospective studies reported in the literature. The importance of these results is underscored by the severe shortage of donor organs, the much higher cost of LT compared to PCS, and the substantial difficulties in obtaining insurance coverage for LT in some patients in the population that develops BEV due to cirrhosis.

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ABBREVIATIONS

BEV	bleeding esophageal varices
LT	liver transplantation
RCT	randomized clinical trial
EST	endoscopic sclerotherapy
EPCS	emergency portacaval shunt
PSE	portal-systemic encephalopathy
PCS	portacaval shunt
UGI	upper gastrointestinal
ICU	intensive care unit
MELD	Model for End-stage Liver Disease
EVL	endoscopic variceal ligation
TIPS	transjugular intrahepatic portosystemic shunt

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Figure 1.
The overall design and conduct of the prospective randomized controlled trial is shown in a
Consort Flow Diagram [18,19].

Figure 2. Kaplan-Meier estimates of survival of patients in the RCT who were evaluated for and did or did not undergo liver transplantation. The overall survival of patients in the EST and EPCS groups is shown for comparison.

Figure 3. Kaplan-Meier estimates of survival of 1300 unrandomized PCS patients including survival of patients who underwent LT and patients who were rejected for LT.

Table 1

Liver transplantation (LT) in randomized controlled trial of EST versus EPCS for BEV in cirrhosis

	EST (n=106)	EPCS (n=105)	TOTAL (n=211)	P Value
Referred for LT Evaluation – n (%)	7 (6.6%)	6 (5.7%)	13(6.2%)	1.0
Diagnosis of LT Candidates – n (%)				0.17
Alcoholism	3 (2.8%)	1 (1.0%)	4(1.9%)	
Hepatitis	2(1.9%)	0	2 (0.9%)	
Alcoholism and hepatitis	0	3 (2.9%)	3 (1.4%)	
Cryptogenic	1 (0.9%)	2(1.9%)	3 (1.4%)	
Autoimmune	1 (0.9%)	0	1 (0.5%)	
Results of LT Evaluation				
LT performed	4	0	4	
LT approved but not done	2	1	3	
LT denied	1	5	6	
Reasons for denial:	0			
Continued alcoholism	0	3	3	
Continued drug abuse	0	1	1	
Non-US resident	1	0	1	
Continued drug abuse + Non-US resident	0	1	1	
Time after entry in RCT to final LT evaluation: Mean (range), in years:	1.00 (n=7) (0.04–2.35)	2.70 (n=6) (0.02–6.74)	1.47 (0.02–6.74)	0.23
Approved for LT – n (%)	6 (5.6%)	1 (1.0%)	7 (3.3%)	0.050*
Time on waiting list: Mean (range), in years	0.162 (n=6) (0.00–0.59)	8.96 (n=1)		
Died on waiting list + time	0	0		
Survival after LT (n=4) Mean (range), yrs	0.204 (0.001–0.805)	NA	0.204 (0.001–0.805)	NA
Survival after evaluation, no LT Mean (range), years (n=9)	n=3 0.237 (0.047–0.586)	n=6 6.027 (0.017–12.73)	n=9 4.097 (0.017–12.73)	0.040*
Survival since entry: Mean (range), yrs (n=9)	1.266 (0.088–2.357)	8.720 (0.033–13.140)	4.706 (0.033–13.140)	0.008*
MELD at time of LT evaluation: Mean (range)	n=7 21.3(7–39)	n=6 20.2 (7–36)	n=13 20.8 (7–39)	0.89
MELD at evaluation in 4 LT patients Mean (range)	n=4 20.8 (17–27)	n=0	n=4 20.8 (17–27)	NA

	EST (n=106)	EPCS (n=105)	TOTAL (n=211)	P Value
Child's Class at LT evaluation (n=13)	A=0 B=1 C=6	A=0 B=4 C=2	A=0 B=5 C 8	0.10