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ORIGINAL ARTICLE

Routine use of livers from deceased donors older than 70: is it justified?*

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Summary

Since 1998, our institution has routinely accepted livers from deceased donors older than 70 years for transplantation. The aim of this study was to determine whether these older donor livers should be used in a routine manner. Twenty-five patients received livers from older donors between 1998 and 2002. Older donor liver recipients' actuarial survival was 95.4% at 1 year and 89.8% at 3 years. Graft survivals were 82.7% at 1 year and 71.7% at 3 years. Five older donor liver recipients with hepatitis C had worse patient survival (80% at 1 year and 40% at 3 years) and graft survival (80% at 1 year and 20% at 3 years). In conclusion, use of livers from deceased older donors affords excellent patient and graft survival, comparable with results achieved with younger donor organs. However, use of older donor livers for patient with hepatitis C may result in worse outcome.

Introduction

Liver transplantation is an accepted treatment for patients suffering from complications of end-stage liver disease (ESLD) with excellent results. The success of liver transplantation has led to an increase in the number of patients being listed for liver transplantation [1]. However, the number of livers transplanted from deceased donors in the United States has remained static during the same time period [1] and has resulted in a donor organ crisis.

Livers from older deceased donors are a potential source for expanding the donor organ pool. Many transplant centers are hesitant to routinely use donor organs from old people. Older donor livers are considered by many centers to be marginal organs with higher risks for poor graft function and graft failure [2,3]. Older donors are also considered high-risk donors because of the possibility of transmitting occult malignancies [4,5]. Furthermore, the long-term outcome with use of older donor livers is unknown. Several series have shown that selective use of such livers is possible with patient and graft survivals comparable with results achieved with more conventional donors [6–8]. Despite these reports, use of older donor livers has not increased [1]. Since 1998, our institution routinely accepted livers from deceased donors older than 70 years old for transplantation. The aim of this study was to determine whether results achieved with older donor livers warrant routine use of these organs for transplantation.

Materials and methods

We reviewed all liver transplants performed at the Mayo Clinic, Rochester, Minnesota between July 1998 and June 2002. During this time, livers from donors older than 70 years were accepted for transplantation, usually for older patients and other patients considered to be at a disadvantage on the waiting list (e.g. severe disease with little

waiting time). Recipients undergoing re-transplantation and with fulminant hepatic failure were included in this study. Immunosuppression was similar for all recipients (tacrolimus, mycophenolate mofetil, and steroids), regardless of primary liver disease and donor and recipient ages.

Donor liver acceptance was in accord with our standard clinical, biochemical, anatomical, and histological criteria. These criteria were the same for all donors, regardless of age. We collected donor information, including procuring region, age, gender and cause of death. All donor organs were preserved with a commercially available modified University of Wisconsin solution (Viaspan® Barr Laboratories Inc., Pomona, NY). Liver biopsies were routinely performed at the time of procurement but only processed before implantation when the donor liver appeared abnormal.

We had a uniform method of performing multi-organ procurements, using *in vivo* dissection prior to aortic and portal venous perfusion with Viaspan®. We used identical techniques for older and younger donors. We dissected out the common hepatic artery to the celiac artery prior to perfusion, preserving any accessory or replaced vessels. The aorta was perfused with 3–4 l of Viaspan® and the portal vein was separately perfused with 2 l of Viaspan®. Older donor iliac arteries were frequently calcified and unusable. If we needed an arterial graft, we used other ABO compatible donor vessels preserved in UW less than 2 weeks.

We analyzed recipient characteristics including primary liver disease, United Network for Organ Sharing (UNOS) status [prior to the implementation of the Model for End-Stage Liver Disease (MELD) system], age, and gender. We compared preservation times (defined as the time of cross-clamp to the time of reperfusion) and the incidence of primary nonfunction and initial poor function between recipients of older and younger donor livers.

We compared the results achieved with older donor livers with other recipients of deceased donor livers. We separately analyzed our results with older donor livers for recipients with hepatitis C. Statistical analyses were performed using the statistical software package, JMP, Version 4.0.4 (SAS Institute, Inc., Cary, NC, USA). Chi-square analyses or ANOVA were used to compare groups as appropriate. Kaplan–Meier analysis was used to estimate patient and graft survival, and statistical significance was determined using the log-rank test. The study protocol was approved by the Mayo Foundation Institutional Review Board, Rochester, Minnesota.

Results

During the 4-year period, our local organ procurement organization was involved in the allocation of 577 livers for transplantation. Thirty-one of these livers, or 5.4%, were from donors older than 70 years. Twenty-five of these older donors' livers were transplanted into recipients at our institution while the other six were transplanted elsewhere. During this 4-year period, 329 recipients were transplanted with 343 livers; and, 25 of these patients received livers from donors older than 70 years.

Donor and recipient characteristics are given in Tables 1 and 2. Twenty-two of the 25 (88%) recipients of older donor livers underwent primary transplantation for chronic liver diseases – hepatitis C ($n = 6$), alcoholic cirrhosis ($n = 8$), nonalcoholic steatohepatitis ($n = 5$), cholestatic liver diseases ($n = 4$), autoimmune hepatitis ($n = 2$), and alpha-1 antitrypsin deficiency ($n = 1$). One patient underwent emergency primary liver transplantation for acute fulminant hepatic failure from acetaminophen overdose. Three recipients (12%) of older donor livers were re-transplantation for recurrent hepatitis C ($n = 1$), ductopenic rejection ($n = 1$) and cryptogenic cirrhosis ($n = 1$).

Table 1. Recipient characteristics.

Age (mean ± SD)	49.1 ± 12.7 years
Male:female	14:11 (56:44)
Primary transplants	22 (88)
Hepatitis C	6 (24)
Alcoholic cirrhosis	8 (32)
NASH	5 (25)
Cholestatic diseases	4 (16)
Autoimmune disease	2 (8)
Alpha-1-antitrypsin deficiency	1 (4)
Acetaminophen overdose	1 (4)
Re-transplants	3 (12)
Recurrent hepatitis C	1 (4)
Cryptogenic cirrhosis	1 (4)
Ductopenic rejection	1 (4)
UNOS status	
Status 2B	20 (80)
Status 2A	4 (16)
Status 1	1 (4)

Percentage values are given in parentheses.

Table 2. Donor characteristics.

Age (median)	74 years (range 70–80 years)
Male:female	13:12 (52:48)
Race	
White people	24 (96)
Others	1 (4)
Cause of death	
Cerebrovascular accident	22 (88)
Trauma	3 (12)
Source of donor liver	
Local organ procurement organization	22 (88)
Import	3 (12)

Percentage values are given in parentheses.

Upon review of the histology of the 25 livers from donors older than 70 years, there were only three with steatosis between 10% and 15%. There were no liver biopsies that had greater than 15% steatosis (Table 3). The other biopsies were otherwise normal or showed mild portal inflammation. It should be noted that all biopsies were wedge biopsies; thus, nonspecific portal inflammation/fibrosis would be expected. Histology findings with the older donors were essentially no different from the younger donors, with the possible exception of less steatosis.

There were no differences in preservation times between the older and younger donors. The preservation time for the older donors was (mean ± SD) 526 ± 97 min compared with 510 ± 123 min (P = NS; chi-square) for donors <70 years old.

Actuarial patient and graft survival results are shown in Figs 1 and 2. There were no statistically significant differences in patient survival between recipients of livers from deceased donors ≥70 years old and all other recipients: 95% vs. 92% at 1 year and 89% vs. 89% at 3 years. Likewise, there were no significant differences in graft survival between older donor livers and younger donor livers: 83% vs. 85% at 1 year, and 72% vs. 79% at 3 years.

The causes of the seven graft losses for the older donor livers included primary nonfunction (re-transplantation on day 1), prolonged poor function (re-transplantation at 6 weeks), hepatic artery thrombosis (re-transplantation at 8 weeks), recurrent hepatitis C (death at 13 and 18 months), and death with functioning graft [recurrent hepatocellular carcinoma (HCC) at 8 months and re-transplantation for donor malignancy at 1.5 years]. Other complications included biliary leaks ($n = 4$), early hepatic artery thrombosis with successful revascularization ($n = 1$), chylous ascites ($n = 1$), and early acute cellular rejection ($n = 5$).

Table 3. Liver biopsies of donor livers.

Donor	Histology
1	Normal
2	Focal coagulative necrosis, no steatosis
3	<5% steatosis
4	Normal
5	Normal
6	Minimal inflammation
7	Normal
8	Normal
9	Normal
10	15% steatosis
11	Normal
12	Abundant lipofuscin, no steatosis or inflammation
13	Normal
14	Mild subcapsular portal fibrosis
15	Mild zone 3 steatosis (15%), mixed micro/macrovesicular steatosis
16	10% macrovesicular steatosis, focal periductal and portal fibrosis
17	Normal
18	Focal subcapsular infarct, von Meyenberg complex
19	<5% steatosis
20	Mild nonspecific portal inflammation
21	No biopsy
22	Mild nonspecific portal inflammation
23	Normal
24	Minimal portal lymphocytic infiltrate
25	Mild zone 3 sinusoidal dilatation

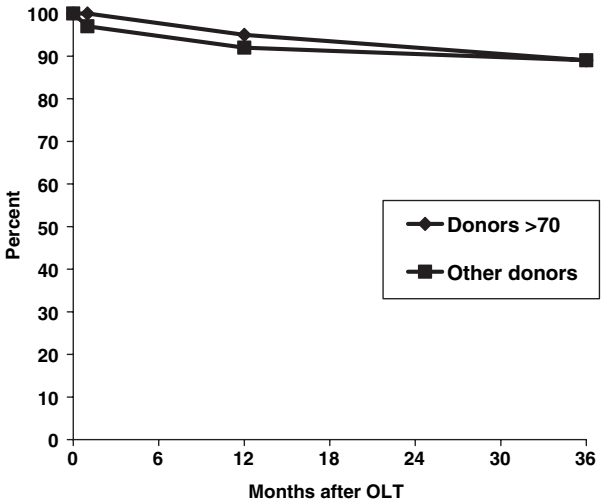

Figure 1 Actuarial patient survival curves are not significantly different between those who received livers from donors older than 70 years versus those who received livers from donors younger than 70 years.

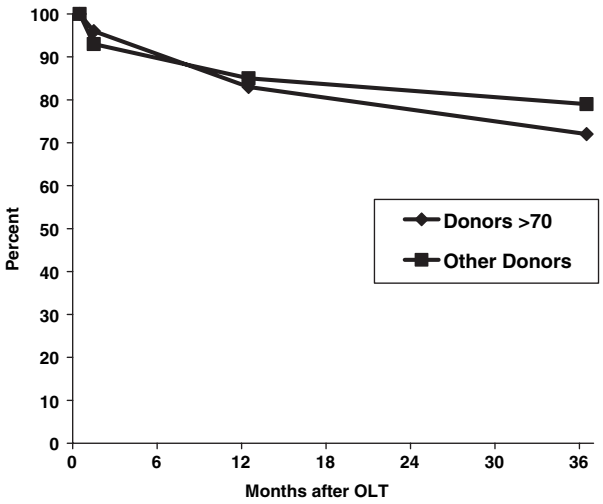

Figure 2 Actuarial allograft survival curves, like the actuarial patient survival curves, are not significantly different between those recipients who received older liver versus those who received livers from donors younger than 70 years.

Four of the 25 recipients died 247 days to 3.5 years after transplantation. The causes of death were recurrent hepatitis C (13 and 18 months), recurrent HCC (8 months), and metastatic pancreatic cancer of donor origin 1.5 years after primary transplantation with an older donor liver. This patient received a liver from 72-year-old man whose cause of death was a cerebrovascular accident. Routine ultrasound 9 months after transplantation detected a 1-cm lesion in the donor liver. Percutaneous biopsy of the lesion demonstrated metastatic adenocarcinoma, presumably of pancreatic origin. Donor origin was confirmed by microsatellite studies. The patient underwent re-transplantation at 13 months but eventually died from metastatic disease 3.5 years after primary transplantation with the older donor liver harboring the occult metastasis.

All four of the patients who died had hepatitis C, and two of the deaths were the result of recurrent hepatitis C. Actuarial patient survival was 20% for the hepatitis C recipients versus 100% for the other recipients at 3 years ($P = 0.01$). Graft survival was also lower in the hepatitis C group, 20% vs. 77% at 3 years, but the difference did not reach statistical significance.

Discussion

Due to the success of liver transplantation, more patients with complications of ESLD are being listed for transplantation. Despite innovative methods to expand the donor liver pool including split, domino, and living donor liver transplantation, the number of liver transplants performed in the United States has not increased enough over the past several years to meet the demand. Marginal donors, including donors older than 70 years, may be an underutilized source of donor livers.

In the past, the maximal deceased donor age was considered to be 50 years [9]. Despite several retrospective studies reporting acceptable short-term patient and graft survival results [6–8], livers from donors older than 70 years are still not routinely considered for transplantation because of the perception that their use is associated with higher incidences of initial poor function and primary nonfunction.

Since 1998, our center has routinely considered livers from donors older than 70 years. It has been our program's philosophy that these donors are no different than younger donors given similar clinical presentation and biochemical findings. Donors older than 70 years made 7.3% of our productive liver donors during this time period. Our local organ procurement organization was involved in the allocation of 31 livers from donors older than 70 years during the 4-year study period and 25 (81%) of these older donors were used at our institution. Results with these 25 older donor livers compared favorably with our overall experience during the same time period with excellent 1 and 3-year patient and graft survival results.

There are potential risks of using livers from older donors. The recipient who had primary nonfunction was a 22-year-old female in need of emergency transplantation for acute fulminant liver failure. She received an imported liver from a 74-year-old female donor with prolonged preservation time (11.5 h). The recipient underwent emergency re-transplantation the next day with a 69-year old female donor liver and was alive and well 2 years later. Another risk of using an older donor liver is the risk of transmission of an occult malignancy. One of our recipients who received a liver from a 72-year-old male donor was found to have metastatic pancreatic adenocarcinoma in the liver 1 year after transplantation. Although the risk of transmitting a malignancy from a donor is low [10,11], the risk is presumably higher with an older donor who is more likely to harbor an occult malignancy. As with all donors, and especially older donors, thorough explorations of the donor chest and abdomen should be performed at the time of procurement.

It is worrisome that all of the deaths in our experience with older donor livers were with hepatitis C patients. Three of five recipients of older donor livers with hepatitis C died within 3 years and an additional patient died at 3.5 years. Two of these four deaths were the result of recurrent hepatitis C. The third death was caused by recurrent HCC, and the fourth death was because of metastatic pancreatic cancer of donor origin. Despite our small experience, actuarial patient survival was significantly worse in the hepatitis C patients. The finding that older donor livers are more susceptible to severe hepatitis C recurrence warrants further study. Nevertheless, we now avoid using older donor livers for recipients with hepatitis C.

It is known that older livers have impaired regenerative capacity compared with younger livers. Indeed, most centers active in living donor liver transplantation will not accept living liver donors older than 55 years because of this impaired regenerative capacity. SRTR (Scientific Registry of Transplant Recipients) data have shown a relationship between increasing donor age and earlier and more severe recurrence of hepatitis C after transplantation that is apparent even with 60-year-old donors [12]. Unfortunately, this information was not known when we began using livers from donors older than 70 years. As these older livers have impaired regeneration, we and others hypothesize that any damage caused by the hepatitis C virus to the donor liver may cause accelerated fibrosis and liver dysfunction, ultimately leading to graft loss. We do not believe it was a problem of treatment. The older

donor recipients did not have more acute cellular rejection episodes compared with the younger donor recipients. All recipients received similar immunosuppression; no attempt was made to wean off steroids or to discontinue mycophenolate mofetil more quickly for the older donor recipients.

In conclusion, use of livers from donors older than 70 years achieves patient and graft survival results comparable with results of younger donor livers. Therefore, we recommend routine consideration of older donor livers for transplantation. However, older donor livers may be more susceptible to severe recurrence of hepatitis C. Pending corroboration of these findings by additional studies, routine use of older donor livers should be avoided for hepatitis C recipients.

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