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ORIGINAL ARTICLE

The optimal timing of liver transplantation in patients with chronic cholestatic liver disease

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Summary

The current opinion is that liver transplantation for chronic cholestatic liver disease should be done before the terminal, high-risk stage. However, most studies do not take waiting list mortality into account. We analysed 113 consecutive patients with chronic cholestatic liver disease, stratified according to estimated survival. Overall and post-transplantation survival was calculated using the Kaplan–Meier method. Including patients who died awaiting transplantation lowered the 1-year survival by 19% in the high-risk category. In this group survival at 4 years was 45%, with an estimated survival benefit of 45%. For the intermediate- and low-risk groups these numbers were 56% and 36% vs. 81% and 7%. Including the waiting list period in the analysis of the benefits of liver transplantation strengthens the case for early transplantation. Our study confirms that liver transplantation should be considered before the high-risk stage of chronic cholestatic liver disease is reached.

Introduction

For patients with chronic liver disease and a poor prognosis or a low quality of life, liver transplantation is the treatment of choice. A patient-centred approach leads to priority for the sickest patients on the transplantation waiting lists. There are, however, more ways to determine the optimal timing of transplantation for patients with chronic liver disease. When viewed from the perspective of the donor, the aim should be a maximal survival after transplantation. Yet another goal is a maximal survival benefit, calculated as the difference between estimated survival without transplantation and estimated or actual survival with transplantation. Each of these approaches requires estimation of the risk of dying without transplantation, which can be done for groups but is unreliable for individual patients. Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are chronic cholestatic liver diseases that are routinely treated with ursodeoxycholic acid but, nevertheless, usually are progressive. PBC and PSC can serve as prototypes to study the effect of liver transplantation, as survival models are available for both [1,2].

The current opinion in the United States as well as in Europe is that in patients with chronic cholestatic liver disease transplantation should be carried out before they reach the terminal, high-risk stage of their disease, as the larger number of life-years gained by transplantation in the high-risk category is offset by a lower survival after transplantation [3,4]. However, only one study on this issue has included patients who died on the waiting list for transplantation [5]. Patients that die awaiting liver transplantation could have an important impact on survival estimates, and including them might strengthen the

case for early transplantation. We therefore studied the survival in our series of 113 patients with cholestatic liver disease enlisted for liver transplantation. We calculated the 1-, 2-, 3- and 4-year survival for all patients and for transplanted patients only in three different risk categories. We also compared the estimated and the actual survival of all patients at 1, 2, 3 and 4 years for the different risk categories.

Methods

Study design and study population

We included all consecutive patients with cholestatic liver disease who were accepted as candidates for liver transplantation from October, 1986, through September, 2004. Indications for liver transplantation were end-stage liver disease as evidenced by a score >8 points in the Child-Pugh classification [6]. Patients in earlier stages of their disease were also enlisted because of life threatening complications like spontaneous bacterial peritonitis, recurrent bacterial cholangitis and recurrent oesophageal variceal bleeding, or a severely diminished quality of life because of pruritus or fatigue. Persistent extrahepatic infectious foci, extrahepatic malignancy including cholangiocarcinoma and other diseases that directly influence the prognosis with or without liver transplantation were considered as absolute contra-indications.

The time of entry for this study was defined as the date of enlistment for liver transplantation. Patient characteristics and the most recent clinical and laboratory data available at the moment of inclusion needed to apply the Mayo models for survival of PBC and PSC patients were extracted from the patient files. The moment of liver transplantation was defined as the time and date of reperfusion of the transplanted organ. The follow-up of all 73 surviving patients is complete until 30 September 2004, the closing date of this study.

Statistics

The Mayo risk score at entry in the study was calculated for all PBC patients $\{[0.871 \times \ln(\text{bilirubin in mg/dl})] - [2.53 \times \ln(\text{albumin in g/dl})] + [0.039 \times (\text{age in years})] + [2.38 \times \ln(\text{prothrombin time in s})] + [0.859 \times (\text{oedema score})]\}$ and for all PSC patients $\{[0.03 \times (\text{age in years})] + [0.54 \times \ln(\text{bilirubin in mg/dl})] + [0.54 \times \ln(\text{AST in U/l})] + [1.24 \times (\text{variceal bleeding Y} = 1/\text{N} = 0)] - [0.84 \times (\text{albumin in g/dl})]\}$.

Patients were classified as high risk with an estimated median survival of up to 1 year when they scored more than 8.2 points in the Mayo PBC formula or more than 3.9 points in the Mayo PSC formula. The intermediate risk category with an estimated median survival of 1–3 years was formed by patients with a score of 6.8–8.2 in the Mayo PBC model or 2.6–3.9 points in the Mayo PSC model. The low risk group with an estimated median survival >3 years comprised the remaining patients.

The survival probabilities without transplantation for each individual patient at 1, 2, 3 and 4 years were estimated from the risk score using the appropriate model. The 1, 2, 3 and 4 year survival for the total group and for the transplanted patients only was estimated using the Kaplan–Meier method.

Results

Included were 113 patients, 48 males and 65 females, with a median age of 49 years (range 15–67 years). Over two-thirds of the patients were enlisted in the second half of the study period, and <10% in the period before 1990. The liver disease was PBC in 46 patients and PSC in 67 patients. Liver transplantation was performed in 85 patients. At least one retransplantation was necessary in 14 patients. There were two peroperative deaths and 27 postoperative deaths in this series. Of the PBC patients 18 fell in the high-risk category, 16 in the intermediate risk category and 12 in the low risk category against 4, 22 and 41 of the PSC patients, respectively. At the closing date of the study 14 patients were still on the waiting list, three were removed from the waiting list because of extrahepatic malignancies, and 11 died while waiting. The median waiting time for transplantation was 23 days (range 2–104 days) in the high-risk group, 40 days (3–593 days) in the intermediate-risk group, and 166 days (7–459 days) in the low-risk group (Table 1). The median follow up of the 73 survivors was 1810 days (range 18–5499 days).

The 1-year survival calculated according to the intention-to-treat principle was 45% in the high-risk group, 69% in the intermediate risk category and 94% in the low risk category. When only transplanted patients are considered the 1-year survival rises from 45% to 64% in the high-risk category, with no major changes in the other two groups (Table 2). In the high-risk group the survival at 2, 3 and 4 years remains 45%. The survival at 2, 3 and 4 years was 63%, 63% and 56% in the intermediate-risk group, vs. 84%, 84% and 81% in the low-risk group, respectively. The largest survival benefit of transplantation is found in the high risk category, here the difference between estimated survival without liver transplantation and actual survival is 18% at 1 year, 38% at 2 years and 45% at 3 and 4 years. These figures are −3%, 14%, 32% and 36% in the intermediate risk group, and 0%, −3%, 4% and 7% in the low risk group, respectively (Table 3).

Table 1. Waiting times and outcomes in the different risk categories.

Risk category	High	Intermediate	Low
Estimated median survival	<1 year	1–3 years	>3 years
Total	22	38	53
PBC	18	16	12
PSC	4	22	41
Still waiting or removed (*n*)	1	4	12
Waiting time in days [median (range)]	375	113 (18–246)	320 (44–949)
Deaths on the waiting list (*n*)	7	2	2
Waiting time in days [median (range)]	30 (6–89)	129, 390	212, 446
Transplanted (*n*)	14	32	39
Waiting time in days [median (range)]	23 (2–104)	40 (3–593)	166 (7–459)
Per- and postoperative deaths (*n*)	6	15	8
All deaths (*n*)	13	17	10

Table 2. Effect of patient selection on survival in the different risk categories.

Risk category	High	Intermediate	Low
All candidates (*n*)	22	38	53
Actual 1-year survival [% (95% confidence interval)]	45 (24–64)	69 (51–82)	94 (82–98)
Transplanted patients (*n*)	14	32	39
Survival 1 year post OLT [% (95% confidence interval)]	64 (34–83)	69 (49–82)	89 (74–96)

Note: The actual 1-year survival percentages were calculated using the Kaplan–Meier method.

Table 3. Comparison of the estimated survival without transplantation with the actual survival in the different risk categories.

Risk category	High	Intermediate	Low
All candidates (*n*)	22	38	53
Median estimated survival [% (range)]			
1 year	27 (0–49)	72 (50–83)	94 (86–100)
2 years	7 (0–24)	49 (22–69)	87 (70–100)
3 years	0 (0–6)	31 (7–49)	80 (57–100)
4 years	0 (0–2)	20 (2–39)	74 (44–100)
Actual survival [% (95% CI)]			
1 year	45 (24–64)	69 (51–82)	94 (82–98)
2 years	45 (24–64)	63 (45–77)	84 (69–92)
3 years	45 (24–64)	63 (45–77)	84 (69–92)
4 years	45 (24–64)	56 (37–71)	81 (65–90)
Median survival benefit (%)			
1 year	18	–3	0
2 years	38	14	–3
3 years	45	32	4
4 years	45	36	7

Note: The estimated survival probabilities were calculated using the Mayo-models for PBC and PSC. The actual survival was calculated using the Kaplan–Meier method.

Discussion

There were two questions that led to this study. The first one is about the effect of including the waiting list period in the analysis of the survival of liver transplantation candidates. Our data on patients with chronic cholestatic liver disease show a considerable difference between the total group and the transplanted patients in the category with the highest risk. In the patient group with an estimated survival of 1 year or less, the actual 1-year survival decreases by 19% when patients who die without transplantation are included. The magnitude of the effect of including the waiting period in the analysis of survival depends on the waiting time, which is relatively short in our high-risk patients. This effect probably will be larger when the waiting time increases. In the intermediate and the low risk categories, with an estimated median survival of 1 year or more, survival is not significantly influenced by the waiting list mortality. Here, too, a larger effect might well be found with longer waiting times.

The second question is what the overall outcome is for the different risk categories in terms of absolute survival and survival benefit. As expected, the highest absolute survival is found in our low-risk patients, but in this group there appears to be no meaningful survival benefit at a follow up of up to 4 years. In our study the effect of the waiting list mortality is negligible in the intermediate-risk group, but the postoperative mortality approaches that in the high-risk category. The largest survival benefit of liver transplantation is found in the group with the lowest estimated survival, even when patients who die without transplantation are included. This gain comes at the price of a 1-year mortality of 55% in our high-risk patients.

The final point is what the implications of our study are for the waiting list policy. It would be unfair to deny high-risk patients the chance of liver transplantation because of an increased postoperative mortality, and the largest survival benefit is found in this group. Although the current postoperative survival for high-risk patients may be higher than in our series, it is likely to remain worse than in the other groups. The effect of the waiting list mortality will not disappear, and can only become stronger with longer waiting times. When high-risk patients are informed about their prognosis, the waiting list mortality certainly should be included.

When a lower postoperative mortality than in our series can be attained, intermediate-risk patients are the most attractive candidates for liver transplantation. Both waiting list mortality and postoperative mortality will be lower than in high-risk patients, and there is a substantial survival benefit, certainly on the longer term. Thus two of the three goals mentioned in the introduction would be reached. For selected low-risk patients with a relatively good prognosis but a poor quality of life, liver transplantation also seems worthwhile, as it does not diminish survival on the short term and may well improve it on the longer term. In general, a policy of transplantation in an early disease stage would reduce the waiting list mortality and improve both overall and post-transplantation survival. Whenever possible, transplantation should not be postponed until the terminal, high-risk stage of chronic liver disease is reached.

Appendix

The Rotterdam Liver Transplantation Group is formed by HLA Janssen, RJ de Knegt, J Kwekkeboom, RA de Man, HJ Metselaar, S de Rave, SW Schalm, Department of Gastroenterology and Hepatology; CHJ van Eijck, G. Kazemier, HW Tilanus, JNM Ijzermans, Department of Surgery; ThN Groenland, L Visser, Department of Anaesthesiology; PE Zondervan, Department of Pathology; W Weimar, Department of Internal Medicine, Erasmus Medical Center Rotterdam, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

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