Transpl Int (2003) 16: 270–275
DOI 10.1007/s00147-002-0539-1

ORIGINAL ARTICLE

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Applicability of liver transplantation in Catalonia at the end of the millennium. A prospective study of adult patient selection for liver transplantation

Received: 25 January 2002
Revised: 12 July 2002
Accepted: 23 August 2002
Published online: 21 February 2003

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Abstract We prospectively studied the global applicability of liver transplantation in Catalonia, a region with a high rate of organ donation. We followed 232 adult patients assessed as possible candidates for liver transplantation over 12 months in the three hospitals that perform the procedure in this region. The liver disease leading to patient assessment was cirrhosis in most cases, alone (159 patients) or associated with hepatocellular carcinoma (57 patients). After being assessed, 150 patients (65%) were accepted for transplantation and included on the waiting list, and 82 (32%) were excluded. Death during the period of assessment, advanced tumoral disease, early stage of liver disease, and extrahepatic co-morbidities were the most important reasons for exclusion. The median time of assessment of patients accepted for transplantation was 40 days. Of the 150 patients included on the waiting list, 131 (87%) received transplants, 17 (11%) were removed from the list, and two were still waiting for transplantation at the end of the follow-up period. Death and tumor progression were the most important reasons for patients' removal from the waiting list. The median time on the waiting list was 59 days. In conclusion, among liver-transplant candidates the overall applicability of this therapy in Catalonia was relatively low (131 out of 232 transplant candidates finally underwent transplantation, 56%), and inadequate liver-transplant indications and death or tumor progression during the period of assessment or while the patient was on the waiting list were the most frequent reasons why liver transplantations did not proceed.

Keywords Waiting list · Liver transplantation · Selection · Candidates

Introduction

Since the 1980s, liver transplantation has been an accepted treatment for liver diseases when no alternative medical or surgical treatment is possible [9]. In spite of improvements in survival and better management of liver-transplant patients, donor scarcity is a very important problem in connection with this technique. For this reason, not all patients acceptable for this treatment can receive a transplant, and selection of candidates is required. Although we accurately know from liver-transplant registries the number of patients included on the waiting lists and the rate of patients that undergo transplantation, there are few data on the patients considered by their physicians to be potentially suitable for liver transplantation and the rate of those finally undergoing transplantation. Moreover, the vast majority of these studies were made in the initial days of liver

transplantation [2, 5, 6, 12, 15], without reassessment in recent years.

In this paper we have prospectively studied the applicability of liver transplantation in Catalonia, a region in Spain with 6 million inhabitants, a health-care coverage of 100%, and a high rate of organ donation, ranging from 34.1 to 40.6 per million people during the past 5 years [1, 10]. We prospectively followed the assessment and selection of 232 adult candidates for a first liver transplant, who were consecutively studied over 12 months in the three hospitals that perform liver transplantation in the region.

Materials and methods

In this study we included all adult patients consecutively assessed as being possible candidates for liver transplantation during the year from March 1997 to February 1998 in the three centers performing this procedure in Catalonia: Hospital Clinic, Ciutat Sanitària i Universitaria de Bellvitge, and Hospital Vall d'Hebron.

The protocols for assessment of liver-transplant candidates were similar in the three centers, with only minor differences. Protocols of assessment included medical history, physical examination, blood group, blood cell test, coagulation test, urine and serum biochemical test, viral serologies (HBV, HCV, herpes virus, Epstein–Barr virus, cytomegalovirus, HIV), chest radiography, pulmonary-function test, echocardiography, abdominal ultrasound or CT scan of abdomen, and gastroscopy. In selected cases other tests were also performed (e.g., colonoscopy). In patients with hepatocellular carcinoma we also performed helical CT scan of the abdomen and thorax (sometimes applying additional imaging techniques such as magnetic resonance and angiography), cranial CT scan, and bone scintigraphy. Patients were assessed either as outpatients or after hospital admission. Criteria for acceptance of candidates for liver transplantation were essentially the same in all centers. For patients with non-cholestatic cirrhosis, a minimum of 7 points on the Child–Pugh score with the existence of at least one sign of clinical decompensation was required. These signs were: intractable ascites, an episode of spontaneous bacterial peritonitis, variceal bleeding refractory to pharmacological or endoscopic treatment, and one episode of hepatic encephalopathy. Minimum criteria for acceptance of patients with chronic cholestatic disease were serum bilirubin higher than 7 mg/dl and/or one or more signs of clinical decompensation (criteria similar to those in non-cholestatic patients). For patients with hepatocellular carcinoma, the maximum tumoral extension permitted was a uninodular tumor of less than 5 cm or 2–3 nodules of less than 3 cm each, without invasion of the great hepatic veins or extrahepatic disease. The diagnosis of hepatocellular carcinoma was confirmed by fine-needle biopsy in all cases except for coincidental hepatocellular carcinoma. In these patients, the diagnosis was based on the unequivocal results of at least two imaging techniques. For patients with acute liver failure, two centers used King's College criteria, and in the third, the criteria were hepatic encephalopathy grades III or IV or progression of encephalopathy following a transient improvement [3]. In patients with other liver diseases, individual appraisal for acceptance or exclusion was performed. Absolute contra-indications for liver transplantation were also very similar in the three centers: severe extrahepatic disease (e.g., heart failure, respiratory insufficiency, severe arteriopathy), anti-HIV-positive, active alcoholism or other drug addiction within the 6 months prior to evaluation, and HBV infection with HBV-DNA positivity by molecular hybridization. Advanced age was also considered to be a contra-indication in the three centers, but there was no uniformity regarding the highest age limit (65 years in two centers and 70 in the other).

In all centers, members of the liver-transplant teams who performed candidate assessment prospectively collected the following data: the reviewing hospital, the center referring the patient, gender, age, diagnosis and clinical signs of liver disease, main reason for potential liver transplant indication, and acceptance for or exclusion from transplantation. In accepted patients, the time lapse between the beginning of assessment and inclusion on the waiting list was also recorded. In patients rejected from transplantation, the reason for exclusion was registered.

Organs were first allocated to the centers and not to individual patients. At the centers, organs were allocated in chronological order to patients, except for those entered into urgency code. In this situation, a patient has absolute priority and receives the first organ available in Spain. The urgency code was used for patients with fulminant hepatic failure or those with primary non-function after liver transplantation.

Patients accepted for transplantation and included on the waiting list were followed up until 1 year after the assessment of the last patient (February 1999). The interval between inclusion and liver transplantation or removal from the list was registered. In patients who were removed from the waiting list the reason for removal was recorded. Results are expressed as median (and range).

Results

A total of 232 patients was assessed. There were 130 men and 102 women. The median age of these patients was 57 (range: 15–70) years. Of the patients initially appraised, 132 (59%) had been controlled in the appraising hospital itself, while 100 were referred from other hospitals. Fifteen patients (6%) were referred by Spanish hospitals outside Catalonia.

The disease which led to the patient's being assessed was cirrhosis in 159 cases, hepatocellular carcinoma in 57 cases, liver metastasis in six (five from neuro-endocrine tumors and one from colon cancer), fulminant hepatitis in three cases, and other causes in seven cases (four familial amyloid polyneuropathy, two congenital hepatic fibrosis, and one chronic Budd–Chiari syndrome) (Table 1). All 57 patients assessed for hepatocellular carcinoma also had cirrhosis (41 HCV-related and three HBV-related). Among the 159 patients appraised for cirrhosis, ascites was the main reason leading to assessment in 81 cases (in 19 patients ascites was associated with present or recent history of spontaneous bacterial peritonitis, and in two patients, with hepatorenal syndrome), hepatic encephalopathy in 41 cases, jaundice in nine cases, refractory gastrointestinal bleeding in three cases, a combination of clinical signs of liver disease in 22 cases (without any specific predominating sign), and other reasons in three cases (recurrent bacterial cholangitis in one patient and isolated but marked alteration of liver-function tests in two). After being assessed, 82 (35%) candidates were rejected from liver transplantation and 150 (65%) were accepted for

Table 1 Diagnosis of the 232 patients assessed for liver transplantation and the 103 patients accepted for this therapeutic procedure and included on the waiting list

Diagnosis	Patients assessed (*n*)	Patients accepted *n* (%)
Liver cirrhosis	159	103 (65)
HCV cirrhosis	71	48 (68)
Alcohol-induced cirrhosis	54	35 (65)
HBVcirrhosis	11	6 (55)
Primary biliary cirrhosis	7	4 (57)
Autoimmune cirrhosis	5	3 (60)
Secondary biliary cirrhosis	2	1 (50)
Primary sclerosing cholangitis	2	2 (100)
Hemochromatosis	1	1 (100)
Cirrhosis and mucoviscidosis	1	0 (0)
Cryptogenic cirrhosis	5	3 (60)
Hepatocellular carcinoma[a]	57	39 (68)
Metastatic tumor[b]	6	3 (50)
Fulminant hepatitis	3	1 (34)
Congenital hepatic fibrosis	2	1 (50)
Chronic Budd–Chiari syndrome	1	0 (0)
Familial amyloid polyneuropathy	4	3 (75)
Total	232	150 (65)

[a]All hepatocellular carcinomas were associated with cirrhosis
[b]Five were metastasis of neuro-endocrine tumors and one was a metastasis of colon adeno carcinoma

transplantation and included on the waiting list. The median time from the beginning of the assessment to inclusion on the waiting list in the 150 patients accepted for transplantation was 40 (range: 1–463) days.

Reasons for exclusion of the 82 candidates were: early stage of liver disease in 15 patients, improvement during the period of assessment due to alcohol abstinence in two, death during assessment due to complications related to liver disease in 17, very advanced liver disease in 18 (14 with highly extensive hepatocellular carcinoma, three with hepatic metastasis, and one with terminal stage of cirrhosis), concomitant extrahepatic disease in nine (six with cardio-respiratory problems, one with alcohol-induced dementia, one with multiple myeloma, and one with pulmonary tuberculosis), active alcoholism in seven, HBV-DNA-positive in four, possibility of effective alternative therapy in three, advanced age in one, and miscellaneous in six (three refused to undergo transplantation, two received transplants in other centers outside Catalonia before the assessment had been finished, and one did not complete the assessment and was lost to follow-up). Table 2 shows the causes of exclusion from liver transplantation in relation to the disease that led patients to be considered as liver-transplant candidates.

Of the 150 patients accepted for transplantation and included on the waiting list, 131 (87%) received transplants, 17 (11%) were removed from the waiting list before transplantation, and two patients were still on the list at the end of follow-up. The median time on the waiting list was 59 days (interval: 1–547 days). Overall, in 131 (56%) of the 232 patients, liver transplantation was performed. The reasons for being withdrawn from the waiting list for the 17 patients who were removed were: death (ten cases; 6.7% of the whole number of patients on the waiting list), excessive tumor growth (two cases), improvement of liver disease (two cases), intestinal tuberculosis (one case), extrahepatic tumoral disease seen at laparotomy before transplantation in a patient with neuro-endocrine tumor (one case), and mesenteric and portal thrombosis that contra-indicated transplantation (one case). In the two cases with excessive tumor growth, the latter was seen by imaging techniques at 74 and 114 days after the patients had been included on the waiting list. Table 3 shows the reasons for patient removal from the waiting list according to the primary liver disease indicating transplantation. Figure 1 summarizes the course followed by the 232 patients assessed as being liver-transplant candidates.

Table 2 Reasons for exclusion during evaluation for liver transplantation

	Cirrhosis	Hepato-cellular carcinoma	Fulminant hepatitis	Metas-tasis	Congenital hepatic fibrosis	Familial amyloidotic polyneuropathy	Budd–Chiari syndrome	Total *n* (%)
Early stage of disease or improvement	15		1				1	17(20.7)
Alcoholism	7							7(8.5)
Severe extrahepatic disease	6	2			1			9(11.0)
HBV-DNA positive	3	1						4(4.9)
Advanced age	1							1(1.2)
Advanced disease	1	11		3				15(18.3)
Advanced hepatocellular carcinoma[a]	3							3(3.7)
Effective alternative therapy	2	1						3(3.7)
Death	13	3	1					17(20.7)
Other	5					1		6(7.3)
Total	56	18	2	3	1	1	1	82(100)

[a]Unknown at the time of patient referral

Table 3 Liver disease and reasons for removal from the waiting list for 17 patients

Patient no.	Liver disease	Reason for removal
1	Alcohol-induced cirrhosis	Intestinal tuberculosis
2	Alcohol-induced cirrhosis	Death
3	Hepatocellular carcinoma	Tumor overgrowth
4	Hepatocellular carcinoma	Tumor overgrowth
5	HCV cirrhosis	Death
6	HCV cirrhosis	Death
7	HCV cirrhosis (+alcohol)	Improvement
8	Alcohol-induced cirrhosis	Death
9	HCV cirrhosis (+alcohol)	Death
10	Alcohol-induced cirrhosis	Death
11	HCV cirrhosis	Death
12	HCV cirrhosis	Death
13	Alcohol-induced cirrhosis	Death
14	HCV cirrhosis	Mesenteric and portal thrombosis
15	HCV cirrhosis	Death
16	Metastatic liver (neuro-endocrine)	Extra hepatic tumoral disease
17	HCV cirrhosis	Improvement

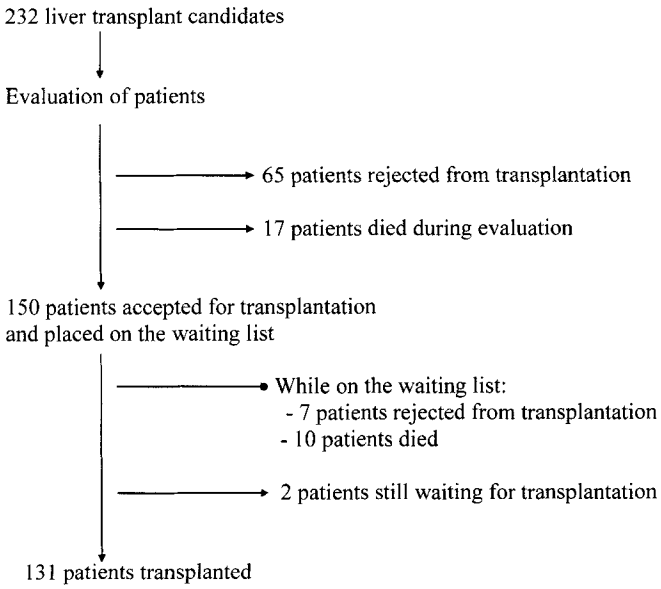

Fig. 1 Outcome of 232 patients referred as candidates for liver transplantation

Discussion

This prospective study included patients referred for liver-transplant assessment, over the course of 1 year, to the three hospitals that perform this procedure in Catalonia. The main objective was to assess the applicability of liver transplantation in a region with a high rate of organ donation, such as Catalonia [1, 10]. The discussion of the results of the study is mainly focused on patients with advanced chronic liver disease, especially cirrhosis with or without hepatocellular carcinoma, because the number of patients with other diseases included in our study was very small. The topics discussed are: referral for liver transplantation in relation to the needs of this procedure in our region, the results of the assessment of transplant candidates, and the outcome of patients accepted for transplantation and placed on the waiting list.

During recent years, there have been approximately 1,000 deaths yearly due to cirrhosis among adults in Catalonia [1]. The age of most of these patients was within the range of acceptance for liver transplantation in Catalonia. However, during the 1-year period of our study only 232 patients (most with cirrhosis, alone or associated with hepatocellular carcinoma) were referred as liver-transplant candidates, representing around 25% of the patients dying of cirrhosis. This low rate of referral could be due to different reasons. It is likely that liver transplantation was not considered to be adequate by referring physicians in a number of patients because of obvious technical contra-indications for this procedure, such as, for example, active alcoholism, terminal or premortem stage of the disease, or severe extrahepatic comorbidities. Furthermore, as reported by other authors [13], non-technical reasons could also have accounted for the low percentage of referrals (for example, patient refusal, or low confidence of patients or their physicians in the results of liver transplantation). Nevertheless, it is important to remark that if more cirrhotic patients had been referred as potential liver-transplant candidates, the number of liver donors would have been very much lower than that theoretically needed: in Catalonia there are around 180–190 liver donors versus approximately 1,000 deaths from cirrhosis per year [1, 10].

In addition to the initial selection made before patient referral to transplant centers, it should be noted that not all patients considered by their physicians to be potential liver-transplant candidates, and consequently referred to transplant centers for a more accurate assessment, reach transplantation. In our study, when patients referred to our centers and established as liver-transplant candidates were prospectively followed up, we observed that approximately one-third of the patients were rejected for transplantation and, among patients accepted for transplantation and placed on the waiting list, 87% finally underwent transplantation. The global applicability of liver transplantation in the current investigation was modest: only 56% of the patients referred for assessment received liver transplantation.

The rate of transplantation and the rate of dropout from the waiting list in liver-transplant candidates are periodically reported by different transplant- and organ-procurement organizations, but almost all reports are related only to the patients included on the waiting lists and not to the patients referred for assessment as potential transplant candidates. Therefore, with the

exception of some data on acute liver failure [3], few reports have taken into consideration the applicability of the procedure from the beginning of the process leading to liver transplantation, and even fewer have addressed this issue prospectively. In one prospective report, Van der Putten et al. [15] published the following results obtained from 362 patients established as liver-transplant candidates between 1977 and 1985: 27% of the patients were accepted for transplantation and placed on the waiting list, 56% were rejected, and a final decision had not been made for the remaining 17%. Among patients placed on the waiting list, 45% received a liver transplant (12% of the total number of patients assessed), 42% remained on the waiting list at the time of calculation of results, and 12% were definitively removed from the waiting list. When compared with the Van der Putten study, our investigation, performed more than 10 years later when liver transplantation had become a common therapeutic procedure, showed a higher rate of acceptance for transplantation (65% of the patients assessed in our study vs 27% in the Van der Putten study) and a higher transplant applicability (56% in our study vs 12% in the Van der Putten study). One reason for these differences could be the better knowledge that physicians presently have of the indications and contra-indications for liver transplantation. Another reason could lie in the progressively liberal criteria for acceptance of liver-transplant candidates, especially those concerning absolute and relative contra-indications for the procedure [11]. For example, 11 patients from the study by Van der Putten et al. were rejected from transplantation because of previous portal surgery [15], whereas at present, these patients would probably have been accepted.

Other studies published at least a decade ago, all retrospective, also reported a rate of acceptance of candidates for liver transplantation (ranging between 34 and 57%) lower than that in the present study [2, 6, 8, 12]. Despite the relatively high rate of acceptance for transplantation in our study, a significant number of potential candidates were rejected. Although in some patients the reasons for rejection were evident contra-indications for the procedure, death during the period of assessment occurred in 17 (21%) of the 82 patients who were excluded from transplantation. With the exception of one patient with fulminant hepatitis, the remaining 16 deaths were related to end-stage chronic liver disease. A similar finding was reported in a study by Samuel et al., published in 1987, in which nine out of 130 candidates died during the assessment period [12]. Another major reason for candidate rejection was highly extensive hepatocellular carcinoma, accounting for 14 (17%) of our patients not being accepted for transplantation. Finally, the third important reason was early stage of liver disease or improvement during assessment (17 patients; 21%). These data indicate that referral of patients for liver transplantation 'too early or too late' still occurs at present, with subsequent impact on transplant applicability, and that careful assessment of liver-transplant candidates is still necessary. Probably the degree of confidence of referring doctors is low, and this could be due to lack of a close relationship between transplant centers and referring doctors. This led us to improve our policy through the organization of regional conferences and more frequent contact among transplant centers and referring doctors.

At the time of the study, four patients had not been accepted for transplantation because they were HBV-DNA-positive. At present, these patients would have been treated with lamivudine with probable transplant acceptance in cases in which HBV-DNA became negative [4].

The 7% mortality rate while on the waiting list found in our study on Catalonia is almost identical to that reported by other authors or registries. Thus, in the US, it was 7.2% in 1998 [14]. The reason why Catalonia and the US have a similar mortality rate for patients on the waiting list in spite of their quite different rates of organ donation (higher in Catalonia than in the US) and different times on the waiting list (much shorter in Catalonia than in the US) cannot be ascertained from the results of our study. However, it can be speculated that this feature could be due to a higher severity of patients placed on the liver transplant waiting list in Catalonia than in the US, although no comparative data are available.

Another aspect, not always specified in the official registries of transplant organizations, is patient dropout from the waiting list for reasons other than death. One of these reasons is excessive tumor growth in patients with hepatocellular carcinoma, whose importance has been recently stressed by Llovet et al. in an investigation performed in our geographical area [7].

In summary, only a little more than half of the patients referred to transplant centers as potential liver-transplant candidates in Catalonia finally receive transplants. Inadequate indications and death or tumor progression during assessment or while on the waiting list are the most frequent reasons why liver transplantations did not proceed. Since a tendency towards an increase in number of candidates for liver transplantation has been observed in our region in recent years, without a proportional rise in organ donation, a progressively worse rate of transplantation can be anticipated. Only measures increasing the donation rate or innovative techniques making maximum use of the organs offered for transplantation (such as splitting livers, the use of 'marginal organs', and living-donor liver transplantation) can improve the transplantation rate.

Acknowledgements This study was supported by a grant from Agencia d'Avaluació de Tecnologia Mèdica, Departament de Sanitat i Seguretat Social, Generalitat de Catalunya, 1997.

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