? T-O. Data } Tumors
(2) to Klitmalm
(3) -Conf- 3F+4F survivs

MAR 2, 2000

Backup\cltsg\constat.98

CANADIAN TRANSPLANTATION SOCIETY (CTS)/
CANADIAN LIVER TRANSPLANTATION STUDY GROUP (CLTSG)

CONSENSUS STATEMENTS ON ~~CONTROVERSIAL~~ SPECIFIC INDICATIONS FOR LIVER TRANSPLANTATION

Third Revision February 24, 1995
Fourth Revision February, 1997
Canadian Liver Transplant Study Group/Canadian Transplantation Society

Preamble: Liver transplantation has become the treatment of choice for many patients with end-stage liver disease. Controversy remains, however, for a subgroup of disease processes resulting in liver failure or threatening life and treatable by liver transplantation (tumors and certain inborn errors of metabolism). A series of annual meetings including representatives of active liver transplant programs in Canada has resulted in the following consensus based on experience in Canada and ongoing review of the pertinent literature.

The Canadian Liver Transplantation Study Group, with membership and input form all active liver transplant programs in Canada, has prepared the following guidelines for candidacy for liver transplantation in Canada. These guidelines are intended to address equity and fairness in access to donor organs and transplantation as a therapy for end-stage liver disease and to optimize survival and full rehabilitation of patients with end-stage liver disease, in areas where the indications for transplantation remain controversial. The criteria for transplantation for these 5 indications should be formalized and written into the selection protocols of all active transplant centres. In view of a national sharing policy of a limited donor resource, regular review of these criteria on a local, regional, and national level should be carried out, both with respect to Canadian outcomes and results in the published literature.

1. Hepatitis B
2. Hepatic Tumors
3. Fulminant Liver Failure
4. Alcohol Associated Cirrhosis
5. Transplantation of Foreign Nationals
6. Retransplantation

SECTION I: HEPATITIS B LIVER DISEASE

Transplantation for hepatitis B virus induced liver disease has historically been associated with unacceptably high rates of recurrent disease post-transplantation. Data are becoming available which allow a rational approach to selection of suitable patient subgroups for transplantation. In addition, promising therapeutic approaches for the prevention of hepatitis B reinfection post-transplant are becoming available in the context of clinical trials. This consensus statement from the Canadian Liver Transplant Study Group consolidates published results and ongoing clinical experience into recommendations for patient selection and appropriate therapy of end-stage liver disease due to hepatitis B.

HEPATITIS B: (Update with references to San Fran & Virginia report of HBIg. Edm, London, Miami lamivudine)

1) Patients with fulminant hepatic failure as a result of hepatitis B are considered to be suitable candidates for liver transplantation.

2) Patients with chronic liver disease who are HBsAg positive and who have no serologic evidence of active viral replication/infectivity (HBV DNA ~~negative~~ and HBeAg negative), *may be* considered to be suitable candidates for liver transplantation.*

3) Patients with chronic liver disease who are HBsAg positive and who have evidence of co-infection with the δ agent (anti-δ positive), *may be* considered to be suitable candidates for liver transplantation due to a diminished incidence of recurrence post-transplant.*

4) Patients with chronic liver disease who are HBsAg positive and who have serologic evidence of active viral replication/infectivity (HBV DNA positive and/or HBeAg positive), *are not*, presently considered to be suitable candidates for liver transplantation outside of the setting of ~~controlled~~ clinical trials due to the high incidence of recurrent disease post-transplant.

5) All other patients with chronic liver disease and evidence of hepatitis B infection should be transplanted only in the context of investigational protocols.

6) Retransplantation for recurrence of hepatitis B disease should only be carried out in the context of ~~controlled~~ clinical trials.

* Candidates in categories 2 and 3 warrant careful consideration for long-term immunoprophylaxis with HBIg and/or inclusion in clinical trials of antiviral therapy.

LIVER TRANSPLANTATION FOR HEPATITIS B

PRETRANSPLANT	RECURRENCE OF HBV		RECOMMENDATION
Status	No Therapy	HBIg (long-term)	
HBV DNA (+) or HBeAg (+)	85-95%[1][X6]	50[2]-96%[3]	controlled clinical trials of new therapeutic approaches only
HBV DNA (-) and HBeAg (-)	50-60%[1]	10[4][X2]-30%[3]	long-term HBIg or controlled clinical trials
HDV	30[3]-50%[5]	+13[3]-17%	long-term HBIg or controlled clinical trials
fulminant HBV	15-20%[3]	0%[3]	transplant suitable candidates consider immunoprophylaxis

SECTION II: LIVER TRANSPLANTATION FOR HEPATIC TUMORS (Clarify cholangio ca categories with Klintmalm)

Liver transplantation (OLT) for hepatic cancers was performed frequently during its developmental years but it was realized rapidly that the results were very poor in the majority of tumors. Among the primary liver tumors that were treated by OLT, some are now clearly excluded such as hemangiosarcomas where no patient survived for more than 28 months.[7] On the other hand, tumors like hepatoblastoma[8] and epitheloid hemangioendothelioma[7] are well accepted indications for OLT with a 5 year survival of 45-50%.

Cholangiocarcinomas should be divided in three distinct categories: those complicating primary sclerosing cholangitis (PSC), cholangiocellular carcinoma (peripheral or intrahepatic) and large bile duct cholangiocarcinoma (Klatskin tumor). The median survival post OLT for cholangiocarcinoma complicating PSC is 14 months when diagnosed preoperatively and 23 months if diagnosed after the surgery, with 2-year survival of 28.6% and 54.6% respectively.[9] Early diagnosis may be obtained by CA 19-9 assay.[10] This complication of PSC should be considered as a contraindication to OLT. Cholangiocellular carcinomas are also associated with ~~dismal~~ poor results. In a collective review of 42 cases, no patient survived for more than one year. Again, those patients should not be offered OLT.[11] The consensus has not been fully reached for large bile duct cholangiocarcinoma (Klatskin tumor). Even though the results are quite poor after OLT (3-year survival: 20%, 5-year survival: 15%), some centres still consider those patients for OLT.[12,13] The only potentially justifiable indication would be a non-resectable tumor with clear margins and negative lymph nodes (0% survival at 1-year if positive lymph nodes). This situation occurs very rarely and OLT should be considered only inside an experimental protocol.

The major area of discussion and controversy in regard to hepatic tumors and OLT concerns hepatocellular carcinoma (HCC). The first aspect of the problem is to determine whether a patient should have a liver resection or should be offered an OLT. Only a few centres reported better survival with less recurrences after OLT compared with resection.[14,15] Most series report a comparable survival of 40/45% at 3-years.[12,16] Immunosuppression after OLT increases the tumor growth rate by decreasing the tumor doubling time from 273.8±79.1 days (post liver resection) to 37.6±8.9 days (post OLT).[17] Based on these facts and in consideration of ongoing organ shortage, liver resection should be performed when feasible and OLT considered only ~~central~~ for unresectable location.[12,18]

Secondly, is OLT appropriate for every tumor? It was previously described that a tumor larger than 5 cm in diameter, multiple nodules and vascular invasion were all negative prognostic factors. The International Union Against Cancer (UICC) has subdivided the HCC into a 4 stage classification (T.N.M. cf. Fig. 1.[19]. Stage I is equivalent to the incidental finding and has a near normal prognosis post-OLT. The stage II patient may correspond to a coincidental findings where a tumor is diagnosed during the pre OLT evaluation but does not constitute the primary indication for transplantation. Stage III and IVa patents are usually considered for OLT primarily because of the tumor. Stage IVb patient have known metastasis pre OLT.[18] The survival for stage III-IV is very poor. (cf. Table I). Based on these results, we believe only stage I and II patients should be offered OLT. Different adjuvant therapy modalities are under investigation including arterial embolization, chemoembolization, intra-arterial chemotherapy, systemic chemotherapy, interferon and radiotherapy given perioperatively.[18] These approaches have been applied mainly to stage III-IVa patients with encouraging results (64% 3-year survival) in the limited experience published thus far.[20] Patients with stage III and IVa HCC should be considered for transplantation on a very selective basis and only under experimental protocol with adjuvant therapy.

The fibrolamellar hepatocarcinoma is a special type of tumor usually arising in a normal liver and characterized by slow growth and late metastasis. It has been an accepted indication for OLT because of the encouraging

results reported after liver transplantation for unresectable tumors with a 2-year survival of 60%.[18,21]

Liver transplantation has been performed for metastatic tumors but with extremely poor results. As such, these patients should no longer be considered for OLT. An occasional exception is the neuroendocrine tumor for which a 2-year survival of 50-81% can be attained. OLT may be indicated for patients with minimal extrahepatic disease, who are symptomatic despite optimal medical treatment, presenting with a slow growing tumor and having metastasis comprising more than 70% of the liver.[23-26]

Table 2: Survival post-liver transplantation for hepatocarcinoma

origin?

T.N.M. STAGE	II	III	IVa	IVb
5-year survival (%)	60-75%	48%	0	0
Median Survival (months)	120	11.9	8.8	1

SECTION III: FULMINANT HEPATIC FAILURE

Reported short and long-term survival rates after liver transplantation for fulminant hepatic failure (FHF) continue to be below that seen for liver transplantation in general. In view of the limited donor resource, the results of transplantation for FHF should be subject to ongoing audit and review.

1. Definition

The development of severe impairment of hepatocellular function in an individual with no evidence of previous liver disease.

2. Classification

A. **Hyperacute:** Onset of illness less than 48 to 72 hrs after onset of symptoms.

B. **Acute:** Onset of illness less than 8 weeks from onset of symptoms.

C. **Subacute:** Onset of liver failure within 8-28 weeks from onset of symptoms.

3. Mortality

>80% with Grade III-IV hepatic encephalopathy

The Canadian Liver Transplant Study Group consensus holds that criteria for transplantation for fulminant liver failure including meeting the guidelines from King's College Hospital (O'Grady et al, Gastroenterology, 1989;97:439-45). These criteria indicate a high mortality without transplantation and also attempt to minimize transplantation in those who may recover without transplant. The King's College Criteria for liver transplantation in fulminant hepatic failure vary according to the cause of liver failure:

Acetaminophen induced:

pH <7.30 (irrespective of grade of encephalopathy)
or
Prothrombin time >100 s (INR >6.5) *and* serum creatinine >300 μmol/L
in patients with grade III or grade IV encephalopathy

Non-acetaminophen induced

Prothrombin time >100 s (INR >6.5) (irrespective of grade of encephalopathy)
or
Any 3 of the following variables (irrespective of grade of encephalopathy):

- Age <10 or >40 years
- Etiology non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions
- Duration of jaundice before onset of encephalopathy >7 days
- Prothrombin time >50 s (INR >3.5)
- Serum bilirubin >300 μmol/L

SECTION IV: ALCOHOL ASSOCIATED LIVER DISEASE: (Louis Pagliaro 492-2856 (Anne-Marie)

1) Patients with chronic liver disease for which alcohol is considered to be a dominant etiologic factor may be acceptable candidates for liver transplant. Individual program criteria for accepting such individuals should be formalized and written into the protocols of the transplant centre. (Can we standardize these?)

2) In addition to meeting the physical criteria for admittance into the transplant program, prospective recipients must indicate a willingness to comply with medical advice and demonstrate an ability to do so. This is particularly important in patients who have a history of substance abuse, regardless of type. Demonstration of an ability to comply shall include at minimum a six month period of abstinence.

3) Because of the need to demonstrate compliance, which will include absolute abstinence from alcohol and illicit drug use for a minimum of six months patients with fulminant hepatic failure attributed to alcoholic hepatitis are generally not considered to be suitable candidates for liver transplantation, as it is not possible to complete the prerequisite determination of ability to comply in this setting. In addition, potential reversibility of acute alcoholic hepatitis with supportive medical care should make liver transplantation for a first episode of alcoholic hepatitis an extremely rare event.

SECTION V: LIVER TRANSPLANTATION FOR FOREIGN NATIONALS:

The delivery of health care varies widely around the world. This is especially true for transplantation. Liver transplantation is a life-saving procedure generally employed only when all alternative therapies have been exhausted. Liver transplantation requires a high level of expertise, a large expenditure of resources and most importantly a reliable source of organs for transplantation. Along with economic constraints, religious, ethnic, and national laws regarding death and organ donation severely curtail transplant activity in many areas throughout the world.

During the developmental era of liver transplantation, many programs encouraged foreign transplant recipients on moral grounds but also to promote liver transplantation as a recognized treatment for end-stage liver disease. In 1982 liver transplantation became a recognized treatment modality for patients with end-stage liver disease following a consensus conference held by the National Institutes of Health.() A rapid proliferation of transplant centres and procedures began to tax donor resources. In order to ensure fair distribution of these resources a national and regional organization (UNOS) was established in the USA in the mid 1980's. One of the UNOS rules was to limit the number of foreign nationals to 10% in all programs. This allotment was reduced to 5% in 1996. The cost of those transplants was to be paid by the patient or the centre.

Canada does not have a national governmental policy for transplantation of foreign nationals, however, there are several political forces which influence this activity such as immigration, visa's, and residency status, provincial health insurance coverage, and delivery committees associated with hospitals and transplant programs. The following statement represents the unanimous agreement of all liver transplant programs in Canada.

FOREIGN NATIONALS

1) Due to the scarcity of the donor organ resource, allocation priority must be given to Canadian citizens and landed immigrants ~~in the majority of circumstances~~.

2) Transplantation may be offered to foreign nationals who develop fulminant hepatic failure or manifest severe liver disease while temporarily visiting Canada and for which liver transplantation is considered to be the only treatment. Such patients will have equal access to the donor organ resource on the basis of priority listing as for Canadian citizens and landed immigrants.

3) Elective liver transplantation may be offered on a compassionate/goodwill basis to foreign nationals from countries that do not have liver transplantation programs provided the resources for the procedure are from sources outside the government funded Canadian health care system. Once accepted, such patients will have equal access to the donor organ resource on the basis of priority listing as for Canadian citizens and landed immigrants. However, it is understood and agreed that foreign nationals shall comprise less than 5% of those individuals awaiting liver transplantation at any centre.

4) The utilization of the Canadian donor resource to provide liver transplantation at a cost advantage to foreign nationals from countries that do have liver transplantation programs or to their insurance carriers is not acceptable.

REFERENCES

1. Samuel D, Muller R, Alexander G, et al. Liver transplantation in European patients with the hepatitis B surface antigen. N.Eng. J. Med. 1993; 329:1842-1847.

2. Neuhaus P, Blumhardt G, Bechstein W, et al. Liver transplantation in HBsAg - patients with short and long-term immunoprophylaxis (abstr.) Hepatology, 1993:58A.

3. Samuel D, Bismuth A, Mathieu D, et al. Passive immunoprophylaxis after liver transplantation in HBsAg-positive patients. Lancet 1991; 337:813-815.

4. Ouzan D, Gugenheim J, Crafa F, et al. Long-term passive immuno-prophylaxis of B virus recurrence after liver transplantation in HBs antigen-positive patients (abstr.) Hepatology 1992; 16:287A.

5. Ottobrelli A, Marzano A, Smedile A, et al. Patterns of hepatitis delta virus reinfection and disease in liver transplantation. Gastroenterology 1991; 101:1649-1655.

6. O'Grady JG, Smith HM, Davies SE, et al. Hepatitis B virus reinfection after orthotopic liver transplantation. Serological and clinical implications. J. Hepatol. 1992; 14:104-111.

7. Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. Surgery 1991; 110:726-773.

8. Liver Transplantation for Hepatoblastoma. Koneru B, Flye MW, Busuttil RW, Shaw BW, Lorber MI, Emond JC, Kalayoglu M, Freese DK, Starzl TE.

9. Cholangiocarcinoma and Sclerosing Cholangitis: Clinical Characteristics and Effect on Survival After Liver Transplantation. Abu-Elmagd KM, Selby R, Iwatsuki S, Fung J, Tzakis A, Todo S, Demetris AJ, Baddour N, Irish W, Van Thiel DH, Starzl TE.

10. Ramage JK, Farrant JM, Forns R et al: Serum tumor markers for diagnosis of cholangiocarcinoma in patients with primary sclerosing cholangitis. Gut 1992 33:515.

11. Ismail T, Angrisani L, Gunson BK, Hübscher SG, Buckels JAC, Neuberger JM, Elias E, et al. Primary hepatic malignancy: the role of liver transplantation. Br J Surg 1990;77:983-987.

12. Indications for Liver Transplantation in Hepatobiliary Malignancy. Pichlmayr R, Weimann A, Ringe B.

13. Yokoyama I, Todo S, Iwatsuki S. Starzl TE. Liver transplantation in the treatment of primary liver cancer. Hepato-Gastroenterology 1990;37:188-193.

14. Iwatsuki S Starzl TW, Sheahan DG. Yokoyama I, Demetris AJ, Todo S, Tzakis AG, et al. Hepatic resection versus transplantation for hepatocellular carcinoma. Ann Surg 1991; 214:221-229.

15. Bismuth H, Chiche L, Adam R, Castaing D, Diamond T, Dennison A. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. Ann Surg 1993; 218:145-151.

16. Bronowicki JP, Nisand G, Altieri M, Wenger JJ, Uhl G, Jaeck D, Boissel P, et al. Compared results of

resection (RX), orthotopic liver transplantation (OLT) and transcatheter oily chemoembolization (TOCE) in the treatment of Okuda's stage I hepatocellular carcinoma (HCC) (Abstract). Gastroenterology 1993; 104(suppl):A881.

17. Yokoyama I, Carr B, Satisu H, et al: Accelerated growth rates of recurrent hepatocellular carcinoma after liver transplantation. Cancer 1991; 68:2095.

18. Liver Transplantation for Malignant Disease. Gores GJ.

19. Hermanek P, Sobin LH, eds. TNM classification of malignant tumors. 4th ed 2nd revision. Berlin: Springer-Verlag, 1992.

20. Multimodal Adjuvant Treatment and Liver Transplantation for Advanced Hepatocellular Carcinoma. Cherqui D, Piedbois P, Pierga JY, et al.

21. Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. Surgery 1991; 110:;726.

22. Pichlmayr R. Is there a place for liver grafting for malignancy? Transplant Proc 1988; 20:478.

23. Makowka L, Tzakis AG, Mazzaferro V, Teperman L, Demetris J, Iwatsuki S, Starzl TE. Transplantation of the liver for metastatic endocrine tumors of the intestine and pancreas. Surg Gynecol Obstet 1989; 168:107-111.

24. Alsina AE, Barus S, Hull D, et al. Liver transplant for metastatic neuroendocrine tumor. J Clin Gastroenterol 1990; 12:533.

25. Ringe B, Wittekind C, Bechstein WO, et al. The role of liver transplantation in hepatobiliary malignancy. Ann Surg 1989; 209:88.

26. Arnold JC, O'Grady JG, Bird GL, et al. Liver transplantation for primary and secondary hepatic apudoma. Br J Surg 1989; 76:248.