1431

LIVER TRANSPLANTATION AS A TREATMENT OF HEPATOCELLULAR CARCINOMA

D.H. Van Thiel, M.D., B. I. Carr, M.D., Ph.D.,
I. Yokoyama, M.D., S. Iwatsuki, M.D.
and T.E. Starzl, M.D., Ph.D.

From the Department of Surgery
University of Pittsburgh School of Medicine
Pittsburgh, PA 15213

This work was supported in part by grants NIDDK AM32556 and NIAAA AA06601

Address reprint requests to:

David H. Van Thiel, M.D.
3601 Fifth Avenue
Falk Clinic 5C
Pittsburgh, PA 15213
TEL:412-624-0129
FAX:412-624-0192

ABSTRACT

The experience with liver transplantation at the University of Pittsburgh for hepatic cancer is presented. The results for "usual" and "incidental" tumors are compared. Based upon this experience, a revision of current recommendations for transplantation consideration is suggested. Finally, the concept of a team approach to this problem and its implementation at the University of Pittsburgh is described.

Hepatic cancer is an unusual tumor in the United States. However, it is a common cause of death in the more populous area of the world such as southeast Asia and southern Africa. In such areas, it is the most common cause of death among young adult working males between the ages of 30 and 50 years (1).

In the United States, primary hepatic cancer has an estimated annual incidence of 13,600 cases (Table 1). Because hepatic cancer is not responsive to current modes of systemic cancer chemotherapy, because it is not particularly radiosensitive, and because most of all it often presents late in its natural history or in individuals, who are either not operable or who are unresectable, its annual prevalence and its annual incidence are almost the same.

Currently, surgical excision of hepatic cancer is the only therapy capable of curing the disease (2). Surgical procedures that have been utilized to accomplish such cures range from subsegmental resections of small lesions to major hepatic resections such as right and left trisegmentectomy (3-6). The larger of these procedures may have an operative mortality as high as 40%. Unfortunately, most individuals with primary hepatic cancer are either not operable or if operable, are not resectable at the time of initial presentation because of the presence of associated cirrhosis or local nodal or even more distant metastasis (7-12). Thus, currently less than 35% of explored cases are

resectable and less than 20% of explored cases are resected "totally" at the time of their initial surgical procedure.

An extension of the surgical approach to hepatic cancer is the application of orthotopic liver transplantation to the treatment of this difficult disease (7-12). The resection in such cases is typically extended beyond that of a "simple" liver transplant to include resection of the gastro-hepatic and gastro-duodenal ligaments, skeletalization of all of the vascular structures leading to the liver as well as the common bile duct and resection of the bile duct as it crosses behind the duodenum with the creation of a roux-en-Y choledochojejunostomy. Despite such extensive surgery, the results with liver transplantation for hepatocellular carcinoma have been rather poor. Pichlmayr, who utilized the data available in the European Liver Transplant Registry, reported a 30% survival at 2 years for patients transplanted for hepatocellular carcinoma. A more recent series from Pittsburgh reports 1, 3 and 5 year survival rates for liver transplantation performed for hepatocellular carcinoma of 64%, 37% and 37% respectively (14). Thus, despite careful selection of patients and the application of more extensive surgical resections both in Europe and the United States, only a third of the patients operated upon for hepatocellular cancer are cured (survive > 5 years).

The situation is quite different, however, in cases of incidental hepatocellular carcinoma (2,15,16). Such cases consist of tumors that are recognized incidentally as a consequence of a workup directed toward some other goal; such as determining the candidacy for liver transplantation of an individual with liver disease. These incidental tumors are detected as a consequence of a computerized tomography scan or ultrasound examination or as a result of a regular quarterly or semiannual monitoring of a cirrhotic patient for the development of a hepatocellular carcinoma. In contrast to what is seen for cases transplanted for clinically evident hepatic cancer, the experience with liver transplantation for incidental lesions has been excellent with 2 and 5 year survival rates of 90% (2).

In general such tumors are small, less than 5 cm in diameter, have a capsule or at least a pseudocapsule of surrounding non-neoplastic hepatocytes; importantly, such tumors usually lack either nodal involvement or vascular invasion.

These characteristics stand in contrast to the current generally accepted parameters that are used to identify cases for possible liver transplantation for hepatocellular carcinoma which are the following:

1) the presence of cirrhosis;
2) multifocal disease;
3) a central location of the tumor near or involving the porta; and

4) extensive disease involving more than one lobe.

The factors currently recognized as identifying good and poor risk patients for a surgical cure are summarized in Table 2.

The failure of liver transplantation to yield long term survival when performed for hepatocellular carcinoma is a direct consequence of the failure of current diagnostic modalities to be able to identify micrometastasis beyond the confines of the extended hepatectomy performed as part of the transplant procedure performed for hepatocellular carcinoma. Because of this failure and because of the remarkable success experienced with liver transplantation for incidental tumors, one has to question the validity of current guidelines for considering liver transplantation in cases with hepatocellular carcinoma. Based upon the experience with incidental cancer, it is quite clear that the surgical goal of excising all neoplastic disease is predictably achievable only if the tumor is small and asymptomatic (i.e. incidental) (2). Therefore, the current practice of offering liver transplantation for large symptomatic tumors appears unsound, and attention might be better directed toward transplantation being offered for small tumors that are identified as incidental lesions during the routine followup of patients with cirrhosis.

Such an approach should result in a high cure rate for both the hepatic cancer and the underlying hepatic disease. Table 3 shows the range of underlying liver diseases for which non-fibrolamellar hepatic cancer has been the indication for liver transplantation at the University of Pittsburgh. Fifty-two percent

of the patients with hepatic cancer seen at this institution for possible transplantation have had chronic hepatitis B. An additional 22.5% have had either cryptogenic or putative NANB chronic hepatitis and cirrhosis. Seventeen and a half percent (17.5%) have had an underlying metabolic liver disease. Thus serial screening of patients with advanced hepatic disease as a result of chronic viral infection or metabolic disease would have identified 94% of the cases at an early state at which time their survival could have been improved from its current 37% at 5 years to 90%, nearly a three fold improvement. Thus it is quite clear that the responsibility of improving the current results resides with physicians rather than with the transplant surgeons. Surgeons have already proven their skill and can cure hepatic cancer if appropriate patients are referred to them. Early detection of HCC in an individual with advanced liver disease as a result of serial ultrasound and serologic investigations (e.g. α fetoprotein and descarboxyprothrombin) by specialist physicians in hepatology should markedly increase the identification of "incidental lesions" where the rate of failure to cure with liver transplantation approaches the reported operative mortality rate experienced with a major hepatic resection. With a more appropriate referral of early cases, even those greater than 5 cm but less than 10 cm in diameter, which are single lesions involving only 1 hepatic lobe, coupled with the utilization of adjuvant chemotherapy with or

without associated radiotherapy should result in improved results manifested as longer survivals and greater cure rates than heretofore have been possible.

With these concepts in mind, a combined transplantation oncology program has been developed at the University of Pittsburgh. This program consists of individuals with expertise in surgery, medical oncology, radiology, radiation therapy and hepatology. The experience of this group with hepatic cancer is still preliminary but appears quite promising as is shown in Table 4.

The experience with liver transplantation for cholangiolar carcinoma has been even poorer than that experienced with hepatocellular carcinoma. This is true whether or not such tumors are divided into those that are bile duct cancers (extrahepatic, large duct, central lesions) or cholangiocarcinomas (intrahepatic, small duct, peripheral lesions). The 1 year survival for such lesions is 25% and declines further to less than 20% at 2 years. These lesions occur frequently in individuals with primary sclerosing cholangitis (PSC). Statistically, one of every 10 individuals transplanted for PSC will be found to have a cholangiolar carcinoma. Despite the well recognized predilection of individuals with PSC to develop cholangiolar carcinoma, no good method for early detection of such cancers exists. These tumors are difficult to identify with current imaging techniques except when there is a high grade biliary obstruction which occurs late in their natural history. Moreover, it is frequently difficult,

if not impossible, to distinguish obstructing malignant from obstructing non-malignant lesions in PSC. Bile duct cytology has been utilized and found to be a specific but not a very sensitive means of distinguishing between the two. In addition to being more difficult to identify, once identified, most cases have nodal involvement which prohibits any chance of a surgical cure. Worse yet, because this tumor is neither radiosensitive nor responsive to available chemotherapy regimens; adjuvant methods have not enhanced the outcome experienced with surgical resection alone.

Despite such grim facts, the oncology program within the transplant service at the University of Pittsburgh has developed therapeutic protocols for these patients. The early experience with cholangiolar carcinoma by this group is shown in Table 5.

In summary, hepatic cancer is most likely to be an increasing indication for liver transplantation as a consequence of better survival as a result of earlier detection and referral for transplantation by physicians adjuvant chemotherapy.

REFERENCES

1. Cancer Statistics 1986 CA 36:9-25.

2. D.H. Van Thiel, V. Dindzans, J.S. Gavaler, L. Makowka, and T.E. Starzl, Liver transplantation for hepatocellular carcinoma. In *Liver Cell Carcinoma* P. Bannasch, D. Keppler, G. Weber, Eds. (Boston, Kluwer Academic Publishers, Boston, 1989), pp. 499-507.

3. J.G. Fortner, B.J. MacLean, D.K. Kim, et al. The seventies evolution in liver surgery for cancer. *Cancer* **47**, 2162-2166 (1981).

4. H.H. Thompson, R.K. Tompkins, and W.P. Longmire, Major hepatic resection - A 25-year experience. *Ann. Surg.* **197**, 375-388 (1983).

5. S. Iwatsuki, and T.E. Starzl, Experience with 150 liver resections. *Ann. Surg.* **197**, 247-253 (1983).

6. S. Iwatsuki and T.E. Starzl, Personal experience with 411 hepatic resections. *Ann. Surg.* **208**, 421-434 (1988).

7. S. Iwatsuki, R. Gordon, B.W. Shaw Jr. and T.E. Starzl, Role of liver transplantation in cancer therapy. *Ann. Surg.* **202**, 401-407 (1985).

8. H.D. Bismuth, D. Castaing, B.G. Ericzon, et al. Hepatic transplantation in Europe. *Lancet* **2**, 674-676 (1987).

9. J.G. O'Grady, R.J. Polson, K. Rolles, R.Y. Calne, and R. Williams, Liver transplantation for malignant disease. *Ann. Surg.* **207**, 373-379 (1988).

10. B. Ringe, C. Wittenkind, W.O. Bechsteing, H. Bunzendhal and R. Pichlmayr, A retrospective analysis of 96 patients with particular regard to tumor stage and recurrence. *Ann. Surg.* **209**, 88-98 (1989).

11. B. Koneru, A. Cassavilla, J. Bowman, S. Iwatsuki, and T.E. Starzl, Liver transplantation for malignant tumors. *Gastroenterol. Clin. N. Am.* **17**, 177-193 (1988).

12. R.Y. Calne, Liver transplantation for liver cancer. *World J. Surg.* **10**, 76-80 (1986).

13. R. Pichlmayr, Indications for liver grafting in hepatic tumors. In *Liver Cell Carcinoma*, P. Bannasch, D. Keppler, G. Weber, Eds. (Kluwer Academic Publishers, Boston, 1989) pp. 491-497.

14. I. Yokoyama, S. Todo, S. Iwatsuki, and T.E. Starzl, Liver transplantation in the treatment of primary liver cancer. *Hepatogastroenterol.* **37**, 188-193 (1990).

15. M. Ebara, M. Ohto, T. Shinagawa, et al. Natural history of minute hepatocellular carcinoma smaller than three centimeters complicating cirrhosis: A study in 22 patients. *Gastroenterol.* **90**, 289-298 (1986).

16. J.C. Sheu, J.L. Sung, D.S. Chen, et al. Growth rate of asymptomatic hepatocellular carcinoma and its clinical implications. *Gastroenterol.* **89**, 259-266 (1985).

TABLE 1

HEPATIC CANCER AND HBV

Annual Incidence - 13,600 cases (USA)

HBV is responsible for 80% of the cases worldwide

HBsAg positive individuals have a 200-300 fold increased risk for hepatocellular cancer as compared to controls

Age at time of infection determines carrier risk

≥85% if ≤10 years

≤10% if ≥20 years

TABLE 2

FACTORS THAT AFFECT SURVIVAL OF PATIENTS WITH HEPATIC CANCER TREATED WITH LIVER TRANSPLANTATION

Factors That Improve Prognosis	Factors That Reduce Prognosis
1) incidental lesion	1) symptoms of cancer
2) < 5 cm diameter	2) vascular invasion
3) single lesion	3) multiple lesions
4) presence of a "capsule"	4) bile duct origin
5) liver cell origin	

TABLE 3

COEXISTING LIVER DISEASE IN CASES TRANSPLANTED FOR HEPATOCELLULAR CARCINOMA

Liver Disease	Percent
Hepatitis B	52.0
Non A Non B Hepatitis	5.0
Cryptogenic Cirrhosis	12.5
Metabolic Liver Disease	17.5
hemochromatosis	
α_1 antitrypsin deficiency	
tyrosinemia	

TABLE 4

LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA

Problem	1. High regional and distant recurrence rates.	
	2. Patients presenting with hepatic decompensation who cannot tolerate i/hepatic artery chemotherapy.	
Strategy	1. OLTx	
	2. Post-transplant systemic adjuvant chemotherapy with 5-FU/folinic acid/alpha-interferon.	
Results	# Patients treated since 10/89	6
	# Patients with recurrence	1 (17%)

TABLE 5

CHOLANGIOCARCINOMA

Problem:	Post-transplant regional recurrences.
Strategy	Pre-transplant radiotherapy with chemosensitization.
Results	# patients accrued since 10/89 5 liver transplants 3 cluster-liver transplants Total n = 8

No recurrence so far