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The 11-Year Pittsburgh Experience With Liver Transplantation for Hepatocellular Carcinoma: 1981–1991

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Experience with liver transplantation over a period of 11 years at the University of Pittsburgh is presented. The application of liver transplantation to cases of hepatocellular carcinoma has changed considerably over this 11-year period with the sequential introduction of adjuvant and, more recently, neoadjuvant chemotherapy.

Results with the combination of chemotherapy plus surgery appear to be better than results with either agent alone. Moreover, the early results with neoadjuvant therapy appear to be better than those achieved with adjuvant therapy.

As a result of this experience, conceptual changes in the approach to the problem of hepatic cancer and the role of both chemotherapy and liver transplantation in its management have changed at the University of Pittsburgh. These changes are identified and discussed.

KEY WORDS: hepatic cancer, total hepatectomy, surgery and chemotherapy for hepatic cancer

INTRODUCTION

During the first part of the 11-year interval encompassing this report, orthotopic liver transplantation (OLTx) as a therapy for primary liver cancer was perceived as the only therapy with any hope of clinical success. The position currently held is that liver cancer is a relative contraindication for liver transplantation [1–4]. This change in the willingness of physicians and surgeons to submit their patients to liver transplantation for the indication of primary hepatic cancer has come about as a direct result of: 1) an analysis of the effectiveness of the procedure for this condition; 2) the increasing application of liver transplantation for other disease indications having a better long-term patient survival; and 3) less donor organ availability for liver transplantation. Much of the experience obtained in Pittsburgh with OLTx for primary hepatic cancer has affected the enthusiasm of newer liver transplant programs to include hepatic cancer as an indication for transplantation. The following is a report of the experience at Pittsburgh with OLTx for primary hepatic cancer. It is presented so that the changes that have occurred in the application of OLTx at this center can be viewed both in their entirety and across time.

METHODS

The records for the 11-year period from January 1, 1981 through December 31, 1991 for the application of OLTx for primary hepatic cancer at the University of Pittsburgh were viewed using the TIMY system [5]. The overall experience for this 11-year period was determined, and then the same data were re-analyzed examining the data for three specific time periods during which no chemotherapy was used, adjuvant chemotherapy was used, and, most recently, when neoadjuvant chemotherapy was used; the results of such therapy were utilized to select patients for OLTx. For each period, the number of cases transplanted and the patient survival curves were determined, as were the type and size of the primary liver

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TABLE I. Types of Tumors for Which Liver Transplantation Was Performed in the Three Periods Studied

Type of tumors	Period (1981–1986)	(1987–1989)	(1990–1991)	Totals (1981–1991)
Hepatocellular carcinoma	15	51	36	102
Cholangiolar carcinoma	10	23	11	44
Mixed tumor	0	0	1	1
Fibrolamellar	6	3	1	10
Epithelio hemangio endothelioma	6	3	3	12
Angiosarcoma	1	2	0	3
Hepatoblastoma	0	4	2	6
Other	0	3	0	3
Totals	37	89	54	181

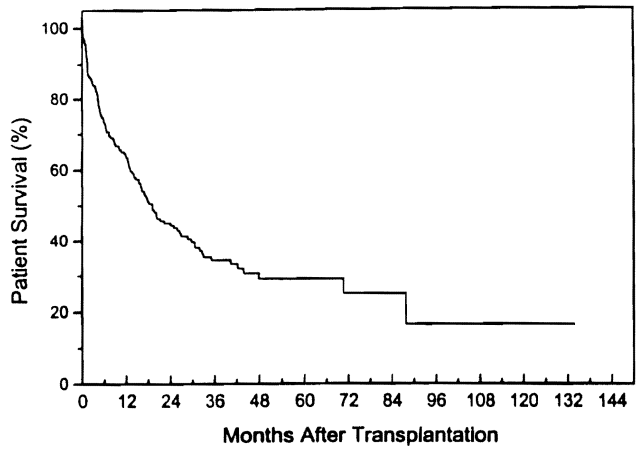

Fig. 1. Patient survival for the 181 patients transplanted for a hepatobiliary malignancy from January 1, 1981 through December 31, 1991 at the University of Pittsburgh.

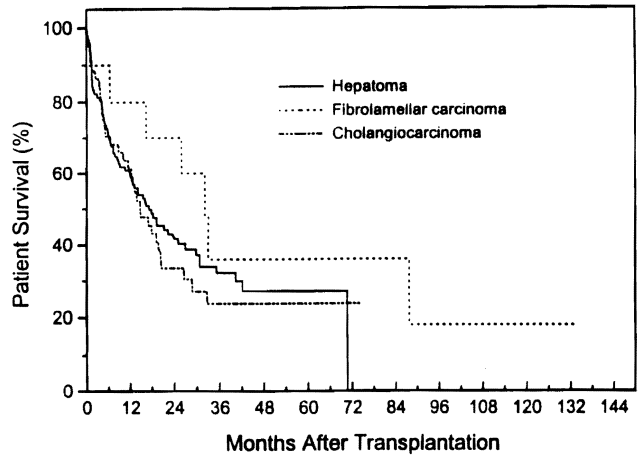

Fig. 2. Patient survival for the 181 patients transplanted as noted in Figure 1 for each of the three leading disease-specific indications for OLTx for hepatic neoplastic disease.

tumor when examined at the time of histopathologic assessment of the resected whole liver.

RESULTS

During the study period, January 1, 1981 through December 31, 1991, a total of 181 patients received a liver transplant for a malignant disease (identified in Table I). A total of 37 cases were transplanted in the first period from January 1, 1981 through December 31, 1986; a total of 89 were transplanted in the second period, January 1, 1987 through December 31, 1989; finally, a total of 54 patients were transplanted in the period from January 1, 1990 through December 31, 1991. Although there was considerable variation from year to year in the type of cases transplanted for malignant disease when segregated as to time periods of interest, the types of cases were essentially identical (Table I).

The patient survival curves for the cases included in this report are shown in Figures 1 and 2. Figure 2 demonstrates the overall patient survival curve for the 11-year period of interest. The 50% survival point is at 18 months. The 4-year survival is 30%, and 18% appear to be cured, with a survival of >6 years following OLTx. When the survivals for the three most frequently transplanted types of primary hepatic malignancies are examined (Fig. 2), it can be seen that the experiences for three types of tumors are quite different. Specifically, a 50% survival for fibrolamellar carcinoma occurs at 34 months, while a 50% survival for cholangiolar carcinoma is seen at 12 months and for hepatoma at 18 months.

The survival curve for the first period of the Pittsburgh experience from January 1981 through December 1986, when chemotherapy was not utilized, is shown in Figures 3 and 4. The overall 50% survival was approximately 15 months for all cases combined but was almost twice as long for those transplanted for a fibrolamellar carcinoma as compared with those transplanted for a primary hepatoma or cholangiolar carcinoma. The results for these latter two tumors were nearly identical, with a 50% survival at approximately 1 year.

Once chemotherapy was instituted as part of the approach to these tumors, survival began to improve as

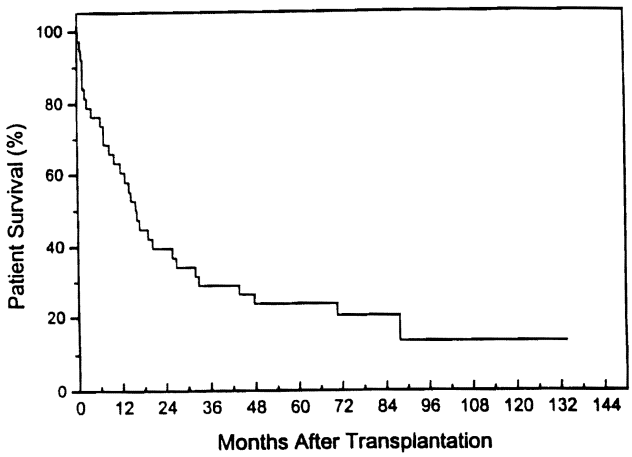

Fig. 3. Patient survival curve for cases transplanted for hepatic malignancy during the period from January 1, 1981 through December 31, 1986.

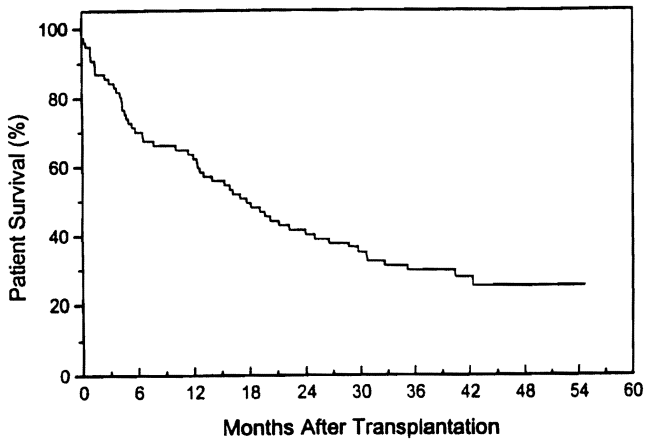

Fig. 5. Patient survival curve for cases transplanted for hepatic malignancy during the period from January 1, 1987 through December 31, 1989.

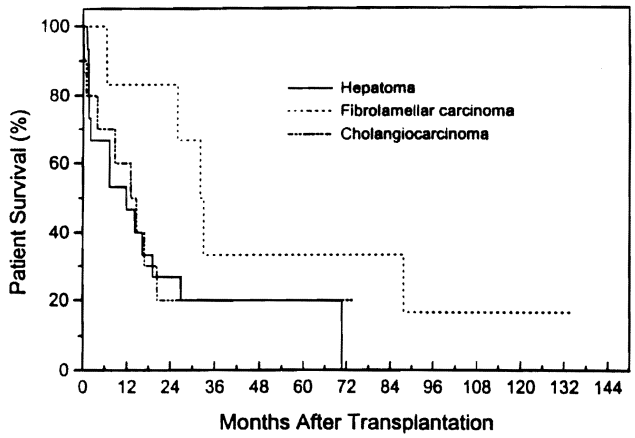

Fig. 4. Patient survival curve for the cases transplanted for the three major types of hepatic malignancy in the series noted in Figure 1. The solid line represents the data for cases with hepatocellular carcinoma; the regular broken line represents the data for cases with fibrolamellar carcinoma; and the irregular broken line represents the data for cases with cholangiolar carcinoma.

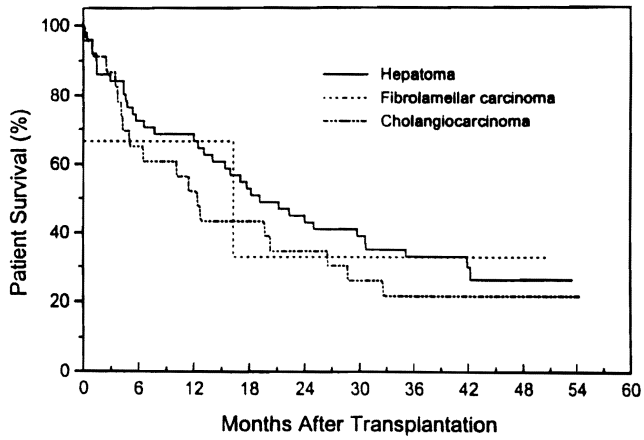

Fig. 6. Patient survival curve for the cases transplanted for the three major types of hepatic malignancy in the series noted in Figure 4. The solid line represents the data for cases with hepatocellular carcinoma; the regular broken line represents the data for cases with fibrolamellar carcinoma; and the irregular broken line represents the data for cases with cholangiolar carcinoma.

shown in Figures 5 and 6. The overall survival rate was still only at the level of 50% at 17 months. However, changes were occurring in the response of individual tumor types.

Specifically, the 50% survival for patients transplanted for hepatoma had increased to 20 months, while the 50% survival for those with fibrolamellar tumors declined to 16 months. No change in the prognosis for cases transplanted for cholangiolar carcinoma was evident.

For the most part, when both pre- and post-OLTx chemotherapy were utilized and the response to chemotherapy used to identify cases for OLTx, overall survival was increased to 19 months, and the largest gain appears to have occurred in the cases with cholangiolar carcinoma (Figs. 7 and 8).

DISCUSSION

The role of OLTx in the treatment of hepatocellular carcinoma has evolved from a treatment offered in desperation to an individual with no other hope for survival or medical care in the 1960s and 1970s to a procedure offered only to a highly selected group based upon restrictive criteria developed as a consequence of empiric observation over almost 3 decades of study.

Specifically, for nearly 2½ decades, from 1963 through 1986, patients with hepatic cancer were considered to be the ideal patients for OLTx, as no other therapy existed that had potential for a cure let alone a disease-free interval prior to the patient's death [1,2,4,6]. This situation was true world-wide as well as in Pittsburgh from the inception of the program in 1981 through the

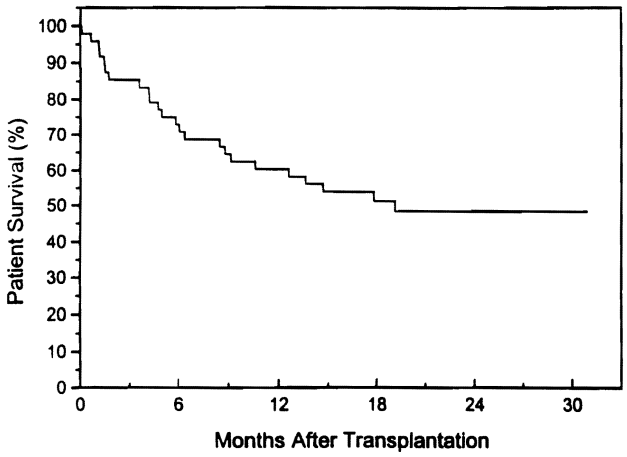

Fig. 7. Patient survival curve for cases transplanted for hepatic malignancy during the period from January 1, 1990 through December 31, 1991.

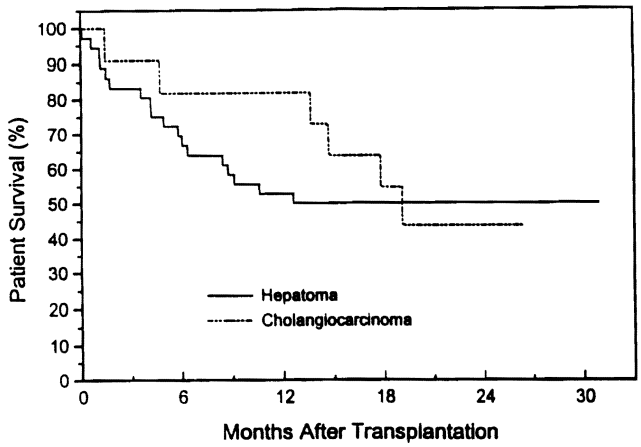

Fig. 8. Patient survival curve for the cases transplanted for the three major types of hepatic malignancy in the series noted in Figure 7. The solid line represents the data for cases transplanted for hepatocellular carcinoma while the broken line represents the data for cases with cholangiolar carcinoma.

first 5 years of the program. During this period, several facts became evident: 1) essentially all cases (>80%) recurred by 1 year; and 2) nearly all cases died within 2 years (>70%), with only a minority surviving beyond 2 years with no evidence of disease (~30%). A closer examination of this data revealed several additional facts—first, that the incidental lesions, those <5 cm in diameter and those discovered as a result of a pathologic examination of the resected liver not originally thought to have a tumor but nonetheless having one, were the only cases to be cured, with a cure defined as a patient being alive and disease free beyond 2 years from the date of transplantation [6–9]. The second finding was that the patients with bilobar disease, lymphatic metastasis, and vascular invasion documented pathologically by examination of the resected liver did worse (recurred within 1 year) as compared with those who did not have these conditions [8–10].

Based upon these findings, two important recommendations were made that affected changes in the field. The first was the recommendation that small tumors, those that would have been classified as incidental tumors earlier, be treated preferentially with OLTx, as the recurrence rate with a major hepatic resection was 60% at 2 years while it was well below 5% when treated with total hepatectomy and OLTx [9]. This recommendation has not yet been implemented widely because of its presumed excessively aggressive approach but is gradually becoming more widely accepted by transplant centers worldwide. The second recommendation was that large tumors (>5 cm diameter), should they be submitted to OLTx, should receive adjuvant chemotherapy to treat micrometastasis that would otherwise have escaped resection and would ultimately lead to the death of the patient in question. The simultaneous development of chemotherapeutic agents reported to be effective in at least some cases of primary hepatic cancer has allowed this latter recommendation to proceed to fruition. Despite the application of adjuvant chemotherapy, disease recurrence still occurred and led inevitably to the loss of patient life. This was the state of the art during the middle period in Pittsburgh (1987–1989) and most other large transplant centers that were still accepting tumor patients for OLTx.

The most recent period (1989 to the present) grew out of the experience of the middle period with adjuvant chemotherapy, as investigators began to use chemotherapy prior to, as well as after OLTx (neoadjuvant) rather than simply after the transplant procedure (adjuvant). With this approach, three groups of patients with hepatic cancer being considered for OLTx became clinically recognizable: 1) those who experienced a true oncologic response to the neoadjuvant chemotherapy, with a 50% or greater reduction in their tumor burden; 2) those who appeared to respond to the chemotherapy but did not meet the criteria for a true response with less than a 50% reduction of the tumor burden; and 3) those who failed to respond to the chemotherapy altogether. When OLTx was applied to the first group, 2-year survival rates jumped dramatically to 86% from a pre-neoadjuvant level of 40% if the chemotherapy was continued post-operatively for a full three cycles [7]. For those who failed to achieve an oncologic remission but responded, the chemotherapy has been continued continuously at monthly intervals. Some of these latter cases, after a full year of such therapy, have had no additional disease progression and have been transplanted after 1 year of chemotherapy and stable disease. The results in this group are as yet too small to be anything but anecdotal but appear to be quite promising. For those failing to respond to chemotherapy, the chemotherapy has been stopped and either α-inter-

feron or hormonal therapy, principally tamoxifen, has been used. As expected, the results in this latter group have been quite poor, with only four survivors beyond 3–4 months of secondary therapy.

The observations that hepatic resections for primary hepatoma have only a 40% survival rate as compared with an essentially 100% 2-year survival rate for incidental lesions with OLTx alone and an 86% survival at 2 years for clinically obvious tumors showing a response to chemotherapy and OLTx has dramatically changed the thinking about the role of hepatic resection (subtotal resections) and OLTx in the management of primary liver cancer.

Based upon the recent experience with neoadjuvant chemotherapy and the role of total hepatectomy for incidental lesions (<5 cm in diameter), it may be best to pursue the following course:

1. Utilize OLTx for all small tumors <5 cm in diameter
2. Utilize neoadjuvant chemotherapy for three cycles in all cases with tumors >5 cm in diameter
3. Transplant those responding to the chemotherapy and continue the chemotherapy for another three cycles post-OLTx
4. Continue on the chemotherapy for a full 1 year those having a partial response to the chemotherapy but not achieving the predetermined criteria of a full response (>50% reduction in tumor volume). Completely re-evaluate those continuing to have a partial response and stable disease for the presence of extra-hepatic disease and if none is found, proceed to OLTx. Obviously, those with extrahepatic disease should be rejected for any further consideration for OLTx but should continue to receive the chemotherapy until the tumor develops clinical resistance to the therapy, as evidenced by the development of overt tumor progression
5. Deny OLTx to those failing to respond to the chemotherapy and offer some experimental therapy other than chemotherapy

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