Chapter 32

Liver Transplantation in the Treatment of Liver Cancer

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The treatment of choice for hepatic malignancy has been total surgical removal of tumor(s). Extensive liver resection such as right and left trisegmentectomies can now be performed with an operative mortality of less than 5% [1]. Five-year survival of primary liver malignancy after subtotal liver resection has been as high as 46% [1]. On the other hand, the prognosis of liver cancer which cannot be treated with the conventional technique of subtotal liver resection because of extensive hepatic involvement of tumors or coexisting nonneoplastic liver disorders has been quite poor. Total hepatectomy with hepatic replacement (orthotopic liver transplantation) is, at least in concept, an ideal approach for the "unresectable" liver cancer.

The world's first attempt to treat "unresectable" liver cancer by total hepatectomy with hepatic replacement was made in Denver on May 5, 1963. The patient was a 48-year-old man with hepatocellular carcinoma in a cirrhotic liver. He died 22 days after transplant from pulmonary emboli and sepsis. The postmortem examination did not reveal any residual tumors. The first patient to live more than 1 year after liver transplantation also had hepatocellular carcinoma. This 1-year 7-month-old girl was the eighth recipient in Denver and lived 400 days after transplantation on July 23, 1967. Her tumor first recurred in the lungs 3 months after transplant and then disseminated into the liver homograft, other abdominal organs, and the brain. Despite [redacted] efforts to control the tumor by chemotherapy, radiation therapy, and surgical debulking procedure, she died from carcinomatosis on August 26, 1968. These early two cases clearly illustrated the issues involved in liver transplantation for hepatic malignancies. By the time the early Denver experience in liver transplantation was reported in the monograph in 1969 [2], the enthusiasm for treating so-called unresectable liver cancer with orthotopic liver transplantation had been dampened because of the high incidence of aggressive tumor recurrence after potentially curative total hepatectomy with liver replacement. Nevertheless, the treatment of malignant tumors by liver transplantation has continued because of: (1) the lack of other effective therapy; (2) rare examples of cure of malignancy by total hepatectomy with hepatic replacement; and (3) the improved overall survival after liver transplantation with [illegible] recent years.

The Denver-Pittsburgh experience in orthotopic transplantation in the presence of primary hepatic malignancy during the last 23 years from March 1963 to March 1986 will be summarized in this chapter. There have been several publications on this subject, reporting individual results in detail by the OT code numbers of the patients for interested readers to review [2–7]. Prof. Calne has provided a similar detailed account of his experience in England [8].

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1 Selection of candidates

There are two different situations where patients who have primary hepatic malignancies require total hepatectomy with hepatic replacement (orthotopic liver transplantation). In the first, liver transplantation is needed primarily because of endstage nonmalignant liver disease, but a coincidental primary hepatic malignancy is identified either before transplantation or after examination of the excised liver. Such tumors could have been totally removed by subtotal hepatectomy if the liver were not so seriously diseased. Here, the selection of candidates is essentially the same as that of candidates with nonmalignant disease.

In the second situation, liver transplantation is needed because of a hepatic malignancy which cannot be removed by conventional techniques of subtotal hepatectomy. In such patients, an extensive search for extrahepatic metastases must be carried out before the patient is accepted as a candidate. Tumor metastases are investigated with chest X-ray, bone survey, CT scan of the chest, abdomen, and brain, bone marrow examination, and other sophisticated modern diagnostic procedures. A history of slow growth, good response to chemotherapy or radiation therapy, and of known favorable histology may also play an important role in selecting a candidate. A final decision for or against hepatic replacement is often made after a donor liver graft becomes available, at which time definitive exploration is carried out. If a tumor is found outside the liver, long-term survival of the patient is so unlikely that the attempt usually is abandoned and the liver is given to a "backup" candidate.

The differentiation of primary hepatic malignancies (particularly cholangiocarcinoma) from liver metastases can be extremely difficult, even with adequate biopsy material for histological examination. There have been only a handful of examples of liver transplantation for metastatic liver tumors [2, 8, 9]. In general, patients with metastatic liver malignancies are not suitable candidates for liver transplantation, at least at the present time. However, there may be occasional patients who develop metastases only in the liver, years after complete local control of carcinomas or carcinoids of the intestinal tract. It is possible, but not proven, that such rare patients with metastatic liver disease can benefit by orthotopic liver transplantation.

2 Histological considerations

Hepatocellular carcinoma is the most common primary hepatic malignancy. It can develop in the normal liver. Many such tumors can be treated by subtotal hepatectomy. In many others, extrahepatic metastases have already developed by the time the diagnosis is made. Since hepatocellular carcinoma tends to metastasize relatively early in its clinical course, it is uncommon to find the disease in a stage where subtotal hepatectomy would not be curative, but where total hepatectomy would be.

In contast, hepatocellular carcinomas in livers affected with some other disease may be much less advanced but not treatable by partial hepatectomy because of impaired hepatic function. Total hepatectomy with liver replacement may be the ideal treatment in such cases in which the primary diagnosis is macronodular or micronodular cirrhosis (posthepatitic cirrhosis, Laennec's cirrhosis), tyrosinemia, hemochromatosis, biliary atresia, Thorotrast liver disease, and other advanced liver diseases. Orthotopic liver transplantation has been effective in treating such coincidental hepatocellular carcinomas.

Although it develops in the normal liver, fibrolamellar carcinoma carries a better prognosis than other hepatocellular carcinomas. This tumor is a histological subtype of hepatocellular carcinoma and is composed of large polygonal eosinophilic cells dispersed throughout a fibrolamellar stroma. It is characterized by its prevalence in young patients, its indolent growth, and an increased resectability rate and survival in comparison with other types of hepatocellular carcinoma [10–14]. Because metastases occur late in its clinical course, fibrolamellar carcinomas which cannot be resected (even by the most extensive subtotal hepatectomy, such as right or left trisegmentectomy) may be treated effectively by total hepatectomy and replacement.

Cholangiocarcinoma is the second most common primary hepatic malignancy. It usually arises in the normal liver and, like hepatocellular carcinoma, it metastasizes relatively early in its course. Therefore, it is rare to find this tumor in a stage suitable for liver transplantation.

Hepatoblastoma is the most common hepatic malignancy in early childhood. It grows rapidly and spreads outside the liver early in its clinical course. It is rare for hepatoblastoma to be effectively treated by liver transplantation, unless the tumor has been under good chemotherapeutic control.

There are other unusual primary hepatic malignancies, such as hemangiosarcoma, rhabdomyosarcoma, and leiomyosarcoma. These sarcomas, like hepatoblastoma, grow rapidly and metastasize early. It is exceptional that these sarcomas can be effectively treated by liver transplantation.

Although classified as sarcomas, epithelioid hemangioendotheliomas or epithelioid hemangioendothelial sarcomas of the liver possess distinct clinical and pathological features. This type of tumor was originally described as intravascular bronchioloalveolar tumor (IVBAT) of the lung by Dail and Liebow in 1975 [15]. The angiogenic nature of IVBAT was subsequently confirmed by light-microscopic and ultrastructural observations. Factor VIII-related antigen, an endothelial cell marker, was first identified in tumor cells of IVBAT by Weldon-Linne et al. [16]. In 1982, the term "epithelioid hemangioendothelioma" was proposed by Weiss and Enzinger [17]. Involvement of the liver was first thought to be metastatic from IVBAT of the lung or its soft tissue counterpart, but later it was confirmed that this tumor can originate in the liver as well. Ishak et al. [18] reported 32 cases of epithelioid hemangioendothelioma of the liver in 1984. The clinical course of this tumor is between that of hemangioma and conventional angiosarcoma. Nine of the 32 patients in this report survived 5 years or longer regardless of the treatment, but the same number of patients developed metastases during follow-up. This tumor may be effec- [illegible] placement when conventional techniques of subtotal hepatectomy cannot be applied.

A carcinoma arising from the junction of the right and left hepatic ducts is called Klatskin's tumor. Because of the location, signs of obstructive jaundice appear when the tumor is still small, usually less than a few centimeters in diameter, and the diagnosis of malignancy can be made relatively early. This tumor usually grows slowly and metastasizes late in its clinical course. It can often be resected, with or without partial hepatectomy, and the bile duct can be reconstructed. However, in many cases, the tumor is located too high in the liver tissue and complete resection is

not possible. In such patients, the bile duct can be intubated surgically or under radiological control to relieve obstructive jaundice, followed by radiation therapy. This palliative measure has been successful both in prolonging life and in improving the quality of life for 1–2 years on average [19]. Although this Klatskin's tumor would appear to be an excellent indication for orthotopic liver transplantation because of its small size, slow growth, and relatively late metastasis, the survival after transplantation has been disappointing and not significantly better than that after palliative procedures, as will be discussed later in this chapter.

3 Denver-Pittsburgh experience with transplantation

During the 23-year period from March 1963 to March 1986, 750 patients received orthotopic liver transplantation at the University Health Sciences Center of Colorado (1963–1980) and the University Health Center of Pittsburgh (1981–1986). The first 170 patients were treated by azathioprine and steroids with or without antilymphocyte globulin, and the following 580 patients were treated by cyclosporine and steroids with or without monoclonal anti-T-lymphocyte antibody. Of the 750 patients, 63 (8.4%) had transplantation in the presence of a primary hepatic malignancy. For analysis, the 63 patients were divided into two groups.

Group 1 consisted of 14 patients who had liver replacement primarily to treat an endstage nonmalignant liver disease, but who were found to have a coincidental primary hepatic malignancy either before transplantation or after examination of the excised whole liver. The tumor could have been totally removed by the conventional technique of partial hepatectomy if the liver had not been so seriously diseased.

Group 2 consisted of 49 patients whose sole or principal reason for liver replacement was a malignancy which could not be removed by partial hepatectomy. The patients in both groups 1 and 2 were further classified according to whether immunosuppression was with azathioprine and corticosteroids (subgroup A) or cyclosporine and corticosteroids (subgroup B).

3.1 Histological diagnosis

The histological diagnoses of 63 primary liver malignancies treated with orthotopic liver transplantation are listed in Table 32.1. There were 42 hepatocellular carcinomas (HCCs), of which nine were of the fibrolamellar variant. The other tumors were ten bile duct carcinomas (Klatskin's tumors), five epithelioid hemangioendothelio- [illegible] cholangiocarcinomas, and one each of hepatoblastoma, angiosarcoma, adenocarcinoma of unknown primary site, and epithelioid tumor of undetermined histology.

Of the 14 primary liver malignancies in group 1 (coincidental tumors), 13 were HCCs and one was a hepatoblastoma. These coincidental hepatic malignancies were found in tyrosinemia (four cases), biliary atresia (three cases), alpha-1-antitrypsin deficiency disease (two cases), post-hepatitic cirrhosis (two cases), Laennec's cirrhosis (one case), Neville's disease (one case), and familial cholestatic syndrome (one case).

Of the 49 primary liver malignancies in group 2 (unresectable tumors), 14 developed in livers that had underlying serious hepatic diseases. Six HCCs were in livers that had postnecrotic cirrhosis. The underlying disease in two cases was tyrosinemia, and in one case each the diagnoses were Thorotrast liver and biliary atresia. Three patients with bile duct carcinoma (Klatskin's tumor) had sclerosing cholangitis. One case of cholangiocarcinoma had developed against a background of postnecrotic cirrhosis. The remaining 35 malignancies had developed in an apparently normal liver.

3.2 Residual tumor

No patient with primary liver malignancy who underwent liver transplantation was known preoperatively to have had extrahepatic involvement. However, five patients of group 2 (unresectable tumor) were found to have metastases at the time of transplantation. One patient with epithelioid hemangioendothelioma had fine metastases to the lung and peritoneum. This patient is still alive and well without any sign of tumor regrowth more than 9 years later. The second patient with hemangiosarcoma had metastases to the lungs and the omentum at the time of emergency transplantation for intra-abdominal bleeding, which was thought to be from ruptured multiple hemangiomas. When this patient died 3 months after operation as a result of pneumonia and liver graft failure, the autopsy also revealed metastases to the bone marrow. The third patient had adenocarcinoma of unknown primary site and was found to have metastases to many abdominal lymph nodes during surgery; some were not removed. This patient developed radiological evidence of bone metastases at 11 months but is still alive with a tumor 15 months after transplantation. The fourth patient with fibrolamellar HCC had tumor invasion of the diaphragm. Microscopic examination of the excised whole liver also revealed tumor-positive hilar lymph nodes. This patient died 1 month after transplantation from liver failure and infectious complications. The autopsy revealed no residual fibrolamellar HCC, but there was an incidental small adenocarcinoma of the lung. The fifth patient had bile duct carcinoma and primary sclerosing cholangitis. Several regional lymph nodes were involved at the time of surgery. This patient is alive without evidence of tumor regrowth 3 months after transplantation.

Eleven other patients in group 2 (unresectable tumor) died within 2 months from various complications of liver transplantation. Preoperatively and at the time of operation, all 11 were thought to be free of extrahepatic tumor. At autopsy, only one had gross or microscopic evidence of residual neoplasm. This patient, who survived only 5 days after liver transplantation, had metastatic cholangiocarcinoma in the lungs, vertebrae, kidneys, and some abdominal lymph nodes. The remaining ten patients were free of tumor insofar as this could be determined from complete postmortem examination, indicating that screening for candidacy had been grossly accurate in the great majority of cases.

3.3 Tumor recurrence

3.3.1 Incidental malignancies

In group 1, there have been no tumor recurrences among the 14 patients whose excised liver contained incidental primary liver malignancies. Thirteen patients had HCC and one had hepatoblastoma. Two patients died after liver transplantation—one on the 1st postoperative day from hyperkalemia and the other almost 2 years after the operation from lung cancer. The remaining 12 patients are alive and free of tumor recurrence from 3 months to more than 16 years after liver transplantation (median 24 months).

3.3.2 Unresectable malignancies

In group 2, 36 of 49 patients whose main reason for liver transplantation was primary liver malignancy survived for at least 3 months after transplantation and thus became suitable for meaningful observations with respect to recurrence. The 36 patients included four of the five who were found at the time of transplantation to have extrahepatic involvement as described in the preceding section. The other 32 were all considered to have had a gross tumor removed by total hepatectomy.

In 20 (63%) of the 32 patients who were made potentially tumor-free by liver transplantation, the original tumor recurred after 1–42 months (median 9 months). HCC that was not fibrolamellar in type recurred in 8 (62%) of 13 patients, all within 1 year (median 4 months; Table 32.2). Recurrence of fibrolamellar HCC was also seen in five (71%) of seven patients (Table 32.2), but all after 1 year (median 16 months). Four of the seven bile duct carcinomas recurred, two before and two after 1 year; the exceptional patient who did not have a recurrence died of other causes 3 months after operation. Two of the four epithelioid hemangioendotheliomas recurred within 1 year. One patient with cholangiocarcinoma developed a tumor recurrence in the 15th postoperative month. One-year tumor-free rates are also shown in Table 32.2.

3.4 Location of recurrences

The first location of tumor recurrence and the organs ultimately involved by tumors were examined in the 20 patients of group 2 who rendered potentially tumor-free at the time of transplantation but who later developed metastases. The grafted liver and the lung were the two organs most commonly affected by tumro recurrences (Table 32.3).

The liver was the first site of recurrence in eight patients, the lung in six patients, both the liver and the lung simultaneously in two patients, the bone in two patients, and the skin and the pelvic peritoneum in one patient each.

The liver was ultimately involved by recurrent tumors in 12 patients. Other locations within the abdomen, such as the abdominal lymph nodes and the peritoneum, were affected in 13 patients. The lung [illegible] involved in 11 patients, and the brain and bone in three patients each.

3.5 Patient survival

The overall survivals after liver transplantation have greatly improved since the introduction of cyclosporine-steroid therapy in March 1980 [6]. Since that time, the survival rate at 1 year after operation and each year thereafter for at least 5 years has more than doubled compared with that previously obtained with azathioprine and steroid therapy (Fig. 32.1). The actuarial 5-year survival in all patients treated since 1980 is slightly better than 60%.

3.5.1 Survival of patients with group 1 tumors

Of the 14 patients who had incidental hepatic malignancies, 12 are still alive and free of tumor from 3 months to 16 years after operation. Two patients died after transplantation. One patient with biliary atresia and an incidental HCC died on the 1st postoperative day from hyperkalemia. Another patient with a micronodular (Laennec's) cirrhosis and incidental HCC died 23 months after transplantation from disseminated oat cell cancer of the lung, which was discovered 16 months after transplantation. Actuarial survival curves of patients with incidental primary liver malignancy are shown in Fig. 32.2.

3.5.2 Survival of patients with group 2 tumors (unresectable tumors)

Of the 20 patients of subgroup A who were treated with azathioprine and steroids, 13 (65%) had died by the end of the first 6 months. At the end of the year, only six (30%) remained alive, of whom all but one have subsequently died (Fig. 32.3). The single survivor, now 9½ years after transplantation, had epithelioid hemangioendothelioma with peritoneal and pulmonary metastases at the time of transplantation.

The patients of subgroup B who were treated with cyclosporine and steroids had greatly improved early postoperative results with a 6-month actuarial survival of 80%. This reflected the better overall prognosis for early recovery using cyclosporine-steroid therapy. However, after the half-year mark, survival continued to decline, primarily because of the recurrent malignancies, as will be described in the following sections. The actuarial 1- and 3-year survivals of patients with unresectable tumors after liver transplantation with cyclosporine-steroid therapy (group 2B) are projected at 58% and 24%, respectively (Fig. 32.3). As of April 1986, only 12 (41%) of the original 29 recipients in group 2B are still alive after 2 months to 4½ years. Three of the surviving patients at 2, 3, and 13 months, respectively, had tumor-positive regional lymph nodes at the time of transplantation, and five others are living with known recurrences.

3.6 Main causes of deaths in group 2

Of the 49 patients whose principal reason for liver transplantation was the presence of unresectable primary liver malignancy (group 2), 36 had died before April 10, 1986. Of the 36 deaths, 26 were within 1 year after transplantation. Seven of the 26 deaths were due to nonneoplastic complications such as liver graft failure of infections or both: The majority of these nonneoplastic deaths occurred among the patients transplanted before 1970 [2–7]. Of the ten deaths that occurred a year or more after transplantation, nine were directly caused by tumor recurrence. Thus, the shape of the survival curves both before and after the introduction of cyclosporine

nated from the 6th month onward by the fatal effects of tumor recurrence (Fig. 32.3).

3.7 Histology, recurrence, and survival in group 2

Of the eight patients with fibrolamellar HCC, two died of nonneoplastic transplant complications in the 2nd and 7th months without any evidence of residual or recurrent tumors. The remaining six patients lived for at least 1 year. These six 1-year survivors were thought to be free of tumor when they passed the 12-month mark. However, metastases subsequently developed in four of the six patients, two of whom died 21 and

36 months after operation. The other two are living with known metastases after more than 2 and 4 years. A fifth patient died from liver graft failure and infectious complications just less than 3 years after operation. The sixth patient is alive, free of tumor recurrence more than 4 years after transplantation.

In contrast, patients with nonfibrolamellar HCC had earlier and more lethal metastases. Of 21 such patients, eight died within 3 months, too soon to allow meaningful evaluation for recurrence. Of the 11 patients with a longer follow-up, eight developed a recurrent tumor within a year and subsequently died from tumor recurrence within 18 months after transplantation; two more patients died from nonneoplastic causes 3 and 6 months after transplantation. As of April 1986, only three patients are alive and free of tumor recurrence 3, 11, and 27 months after transplantation; the follow-ups of two of these three are too short to be meaningful. Thus, the conventional HCCs carried a far poorer prognosis than the fibrolamellar variant.

Of the ten patients with bile duct cancer (Klatskin's tumor), four died from nonneoplastic causes within 3 months after transplantation. Two patients died directly from recurrent tumors within a year, and two others developed tumor recurrences after a year and died from recurrent malignancy 25 and 54 months after liver transplantation. Two others who are alive and free of tumor after 3 and 6 months have too short a follow-up to be considered.

Of the five patients with epithelioid hemangioendothelioma, two developed recurrent tumors 2 and 11 months after transplantation and died directly from a recurrent tumor 3 and 16 months after transplantation, respectively. Three others are alive and free of tumor more than 6 months, 2 years, and 9 years after transplantation.

Of the five patients with other primary liver malignancies, two lived more than a year. One with cholangiocarcinoma developed tumor recurrence 15 months after transplantation and died directly from a recurrent tumor 5 months afterward. Another with adenocarcinoma of unknown primary site developed a recurrence 11 months after transplantation, but he is alive more than 5 months later.

4 Past reflections and future prospects

Remarkable progress has been made in the field of organ transplantation since the introduction of cyclosporine in the late 1970s. More than 70% of liver recipients now survive at least a year after operation, and approximately 60% overall are expected to live for 5 years after liver transplantation. However, the survival of patients who received liver transplantation because of unresectable primary hepatic malignancies has been poor and less than a quarter of these patients will [illegible] after liver transplantation even with cyclosporine therapy. Two-thirds of the patients developed tumor recurrence even though they were thought to have been rendered tumor-free after total hepatectomy. Recurrent tumors were the most frequent cause of death among these patients, and nearly all of the deaths after a year were directly caused by or attributed to recurrent neoplasms.

The high recurrence rate after liver transplantation for unresectable tumors reflects in part the advanced defvelopment of the neoplasms by the time a decision was made to attempt therapy with transplantation. However, the immunosuppression necessary to prevent graft rejection

might actually have expedited the growth of residual nests of malignant cells left after the total hepatectomy, as was suggested a number of years ago [2] and has since been supported by many recent investigations of host factors promoting tumor metastases [20–22].

The tendency of the metastases from hepatic malignancies to recur in the liver grafts is of particular interest in reflecting on the mechanisms of tumor metastasis. One possible explanation is that the malignant cells of primary hepatic tumors may find the best microenvironment to be in the liver itself. Another explanation could be that the grafted liver, which is itself under constant attack from the host immune system, may provide the location of the weakest antitumor defense where circulating neoplastic cells can nest and grow. Further investigations are needed to explain this peculiar and dangerous phenomenon.

Of all the tumors with which experience has been accumulated so far, fibrolamellar HCC has emerged as the best for treatment with transplantation. This tumor is known to behave less aggressively than most other malignant hepatic neoplasms [10–14]. Although it recurred in more than half the patients after transplantation, the metastases tended to appear late and to grow relatively slowly. Two of our patients with recurrence have been in good condition for more than 1 and 3 years after multiple pulmonary metastases were first proved.

Epithelioid hemangioendothelioma is a peculiar malignant neoplasm which can originate in the lung, soft tissue, and liver [15–18]. Our experience in this tumor has been mixed with aggressive recurrences and potential cures. Two of the five patients died from aggressive recurrent tumors. The remaining three, including one with distant metastases at the time of transplantation, are alive and well without any clinical evidence of tumor more than 6 months, 2 years, and 9 years after transplantation.

With all other kinds of tumor, metastases tended to appear early and led to death promptly. The prognosis with nonfibrolamellar HCC has been very poor. None of our patients with proximal duct cell carcinomas (Klatskin's tumors) have lived 5 years and, to our knowledge, this has not been accomplished in any other center [8, 23].

It is sometimes tempting during the acquisition of this experience to conclude that liver transplantation for malignant hepatic malignancy is conceptually unsound, except for coincidental malignancies and probably for fibrolamellar HCC, and to abandon such efforts. However, the most encouraging aspect of this experience was the almost uniform survival of patients with coincidental hepatic malignancy. The fact that none of these patients developed a recurrence during the follow-up proved that the mere presence of a hepatic malignancy is not an absolute contraindication for liver transplantation.

Even in the patients of group 2, arrest and control of the malignant process have been accomplished under some of the least likely circumstances, as with the patient who had distant metastases at the time of transplantation from hepatic epithelioid hemangioendothelioma and a patient with nonfibrolamellar HCC. There has been no identifiable reason why some patients were spared recurrence and why others were not.

The poor results so far have made it clear that liver transplantation for unresectable cancer will have to be tied to some other kind of therapeutic effort in future trials. The usual approach of giving adjuvant chemotherapy or radiation therapy will not be sufficient to prevent tumor

recurrence for a long time as was experienced in two of our four recent patients who developed aggressive recurrences of nonfibrolamellar HCC within a few months in spite of prophylactic treatment with adriamycin and other chemotherapeutic agents. Huber et al. [9] have described a novel approach in which patients with metastatic liver malignancies had liver replacement as well as total body irradiation and ultradose chemotherapy, followed by autotransplantation of stored bone marrow. One of their patients whose original disease was a carcinoma of the breast was alive, free of tumor, more than 3 years after liver transplantation (personal communication).

Further experiences and more effective adjuvant therapies are required for liver transplantation to establish a firm role in the treatment of hepatic malignancies.

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Table 32.1. Histological diagnosis of 63 primary liver malignancies

	Group				Total
	1A	1B	2A	2B	
Hepatocellular carcinoma (fibrolamellar type)	2	11 (1)	13 (1)	16 (7)	42 (9)
Bile duct cancer (Klatskin's tumor)	0	0	5	5	10
Epithelioid hemangioendothelioma	0	0	2	3	5
Cholangiocarcinoma	0	0	1	1	2
Hepatoblastoma	1	0	0	0	1
Angiosarcoma	0	0	0	1	1
Adenocarcinoma of unknown primary site	0	0	0	1	1
Epithelioid tumor, histology undetermined	0	0	0	1	1
Total	3	11	21	28	63

Table 32.2. Incidence of tumor recurrence and 1-year tumor-free survival among the patients in group 2 who survived over 3 months after liver transplant; all gross tumors were removed by total hepatectomy

	Tumor recurrence		1-year tumor-free	
	No.	Percent	No.	Percent
Hepatocellular carcinoma	12/20	60	7/15	47
Nonfibrolamellar	(8/13)	62	(1/9)	11
Fibrolamellar	(4/7)	57	(6/6)	100
Bile duct cancer	4/7	57	2/4	50
Epithelioid hemangioendothelial sarcoma	2/4	50	1/3	33
Cholangiocarcinoma	1/1	100	1/1	100
Total	20/32	63	11/23	48

(G.T25)

Table 32.3. Location of recurrence of original primary liver malignancy in 20 patients

	First location of recurrence	Organ ultimately involved
Liver	10 (2)[b]	12
Abdomen other than liver[a]	1	13
Lung	8 (2)	11
Bone	2	3
Brain	0	3
Skin	1	1

[a] Abdominal lymph nodes, peritoneum
[b] Two patients had recurrences both in the liver and the lung discovered simultaneously

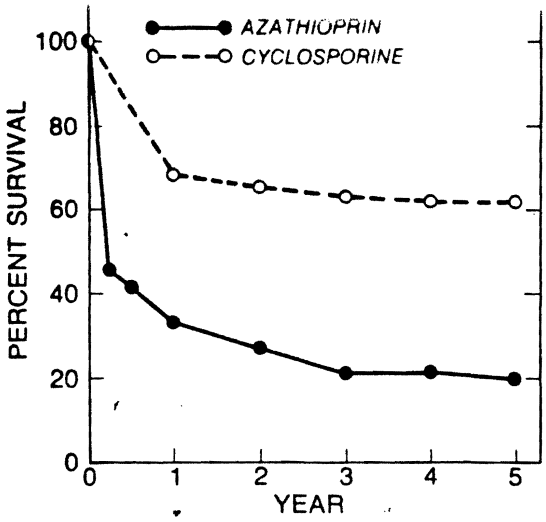


Fig. 32.1. The survivals after liver transplantation have more than doubled since the introduction of cyclosporine in 1980

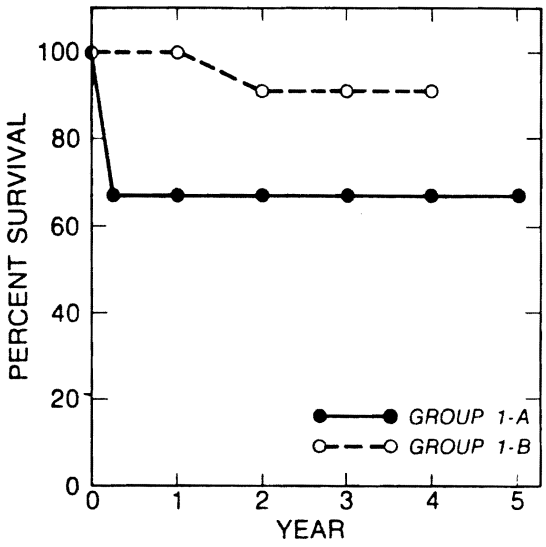


Fig. 32.2. The survivals of patients with incidental primary malignancy. Group 1A—incidental tumor treated by azathioprine and steroids; group 1B—incidental tumor treated by cyclosporine and steroids

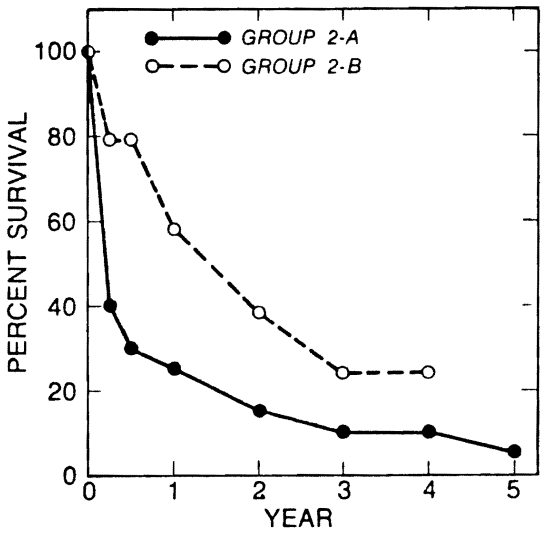


Fig. 32.3. The survivals of patients with unresectable primary liver malignancy. Group 2A—unresectable tumor treated by azathioprine and steroids; group 2B—unresectable tumor treated by cyclosporine and steroids

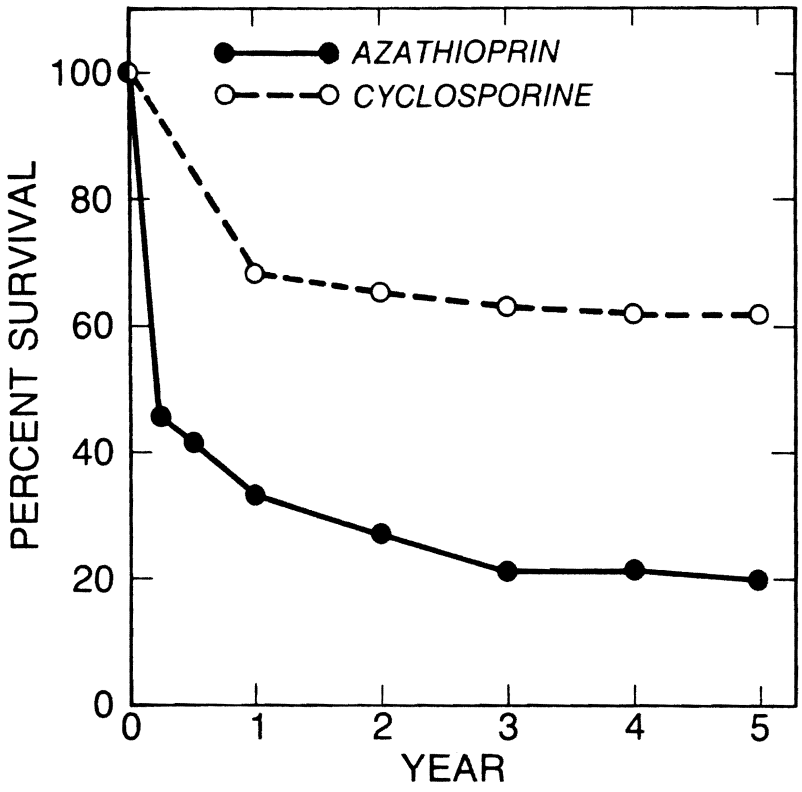
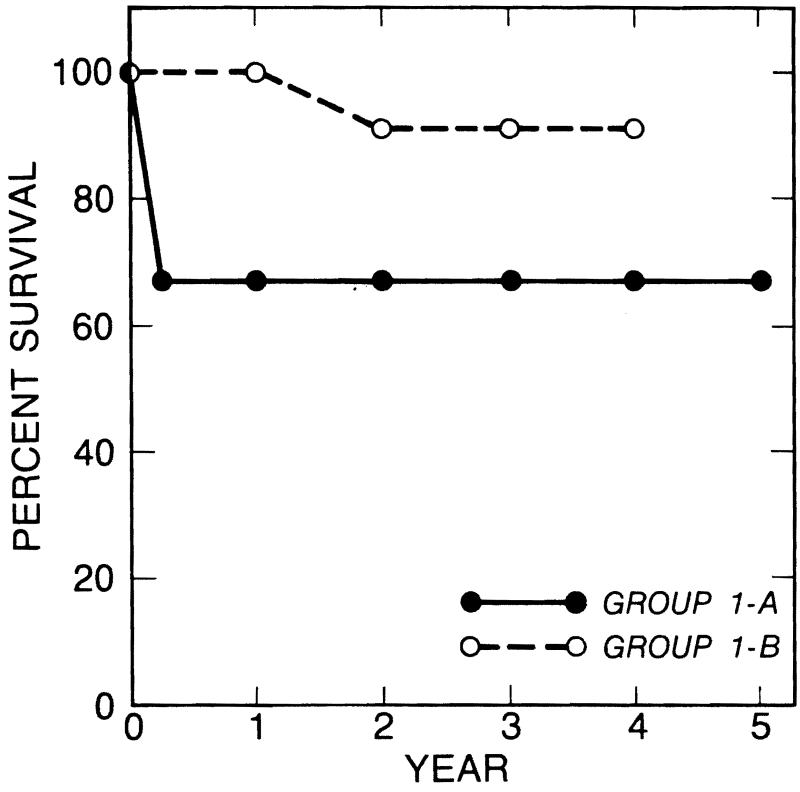

AZATHIOPRIN
CYCLOSPORINE
PERCENT SURVIVAL
100
80
60
40
20
0
0
1
2
3
4
5
YEAR

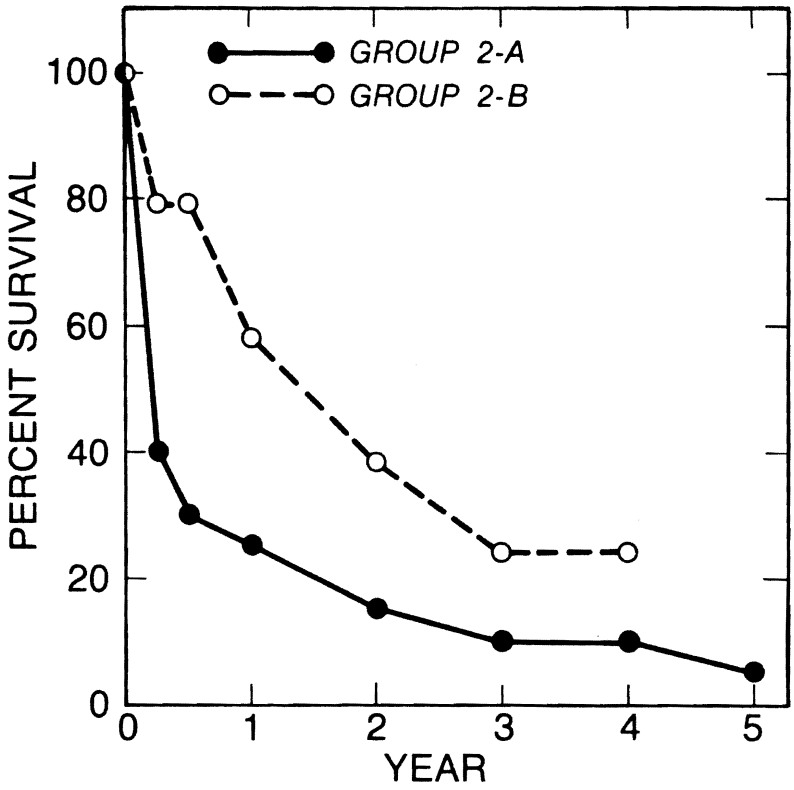
Figure 1



32.2

Figure 2

68.4



32.3

68%

Figure 3