International Advances in Surgical Oncology 5:163-171 (1982)

Hepatectomy in Children

Shunzaburo Iwatsuki, MD and Thomas E. Starzl, MD, PhD

Tumors of the liver in infants and children are uncommon. A committee of the Surgical Section of the American Academy of Pediatrics surveyed liver tumors in children who were operated upon during the 10 years preceding 1974. They collected only 375 liver tumors of which 252 were malignant and 123 benign [1]. The most common malignant tumor was hepatoblastoma followed closely by hepatocellular carcinoma. Complete excision of the tumor was achieved in a little less than a half of the children with hepatoblastoma or hepatocellular carcinoma [1].

Because of the infrequency with which partial hepatic resections are done, there are few pediatric surgeons who are experienced with such operations. However, in the personal series of 129 subtotal hepatectomies compiled by us since 1963, there have been 14 patients in the pediatric age group. The treatment in these 14 cases will be discussed.

In addition, eight children with primary malignant liver tumors were treated by total hepatectomy and liver replacement (orthotopic liver transplantation) during the same period. This latter experience has shown that cure of a liver tumor is a possibility after transplantation.

SUBTOTAL HEPATECTOMY

Technical Considerations

The four kinds of liver resection commonly used are shown in Figure 1. They consist of true right lobectomy, true left lobectomy, excision of the lateral segment of the left lobe, and right trisegmentectomy. With a right trisegmentectomy, the true right lobe is removed in continuity with the medial segment of the left lobe. The surgical techniques have been described by which these procedures can be performed safely [2, 3].

A fifth resection may be applicable, namely left trisegmentectomy. With this operation, the true left lobe is removed, in continuity with the anterior segment of the right lobe. We have performed such an operation four times with success on each occasion. One patient was a 10-year-old boy (Fig. 2). To our knowledge, these are the only examples of this radical operation being performed in humans. The patient shown in Figure 2 is free of disease after 12 months.

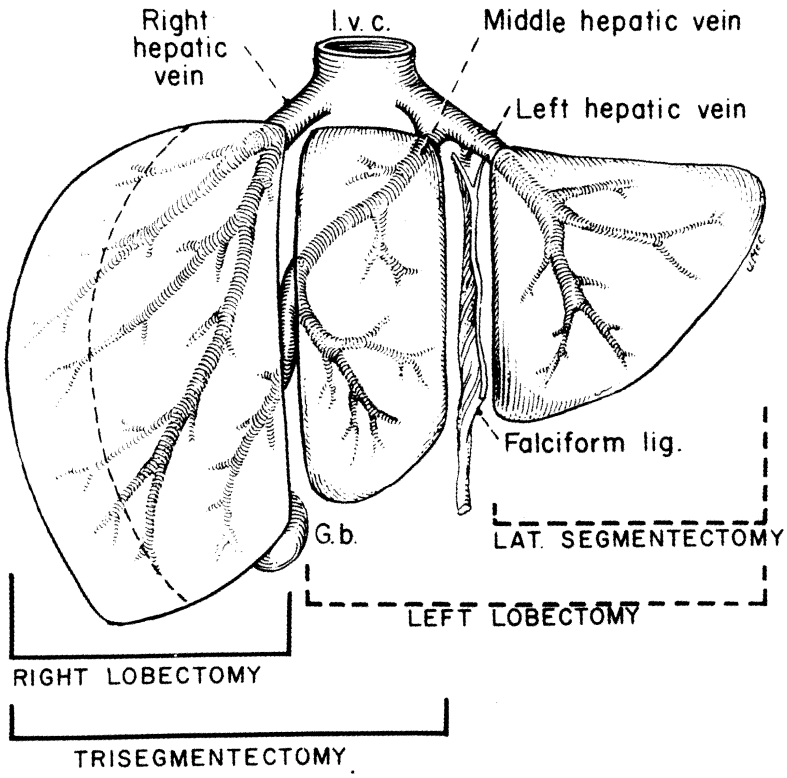

Fig. 1. Conventional hepatic resections.

Case Material

Fourteen children were treated with subtotal hepatectomy (Table I). Six were male and eight female. The age ranged from 11 months to 16 years. Ten children had primary malignant liver tumors; one hepatoblastoma, six hepatocellular carcinomas, and three sarcomas. Two children had metastatic liver tumors, one from a neuroblastoma of the right adrenal gland and another from a Wilms' tumor of the kidney. One child had an adenoma. One child had a liver resection for trauma. Follow-ups here have been for 1 to 15 years (Table I).

There were nine right trisegmentectomies, one left trisegmentectomy, one right lobectomy, two left lobectomies, and one nonanatomical resection of the liver (Table I). There were no operative deaths nor any serious complications such as bleeding, subphrenic abscess formation, or bile duct injury. The earliest death after hepatic resection occurred 6 months after a left hepatic lobectomy, due to the recur-

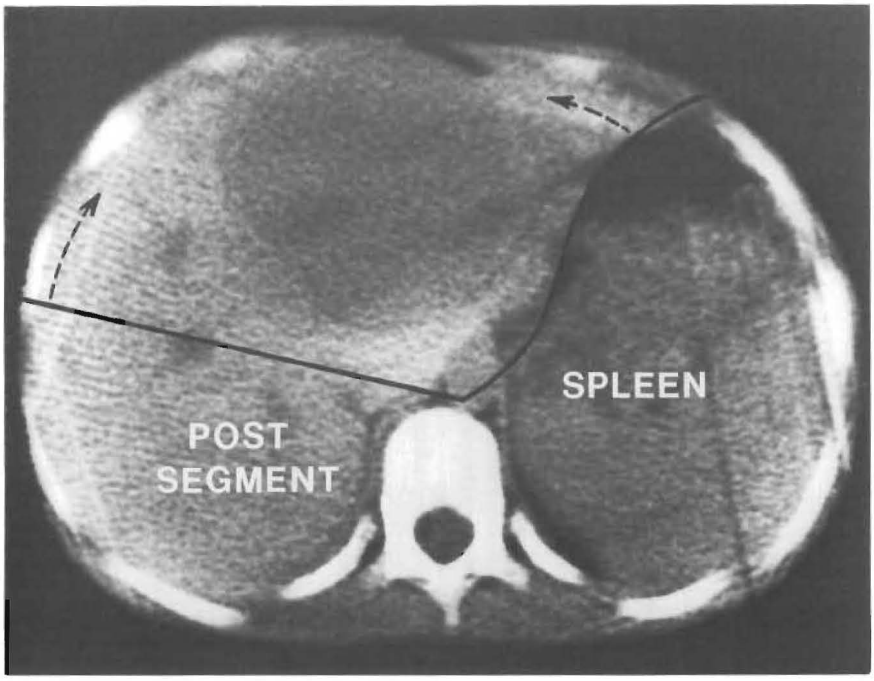

Fig. 2. A child with a large hepatoma dominant in the true left lobe could not be treated by conventional left lobectomy. A left trisegmentectomy was carried out along the line.

rence of hepatoblastoma (Table I). Minor bile leaks through the drain site were common, but these were all closed spontaneously.

Adjuvant Therapy

Eleven of the 12 patients with malignant disease received chemotherapy after hepatic resection, and four were given radiation therapy (Table I). One patient had chemotherapy before, but not after resection.

The agents used for chemotherapy were variable and were influenced by the histopathology (Table II). Initially, the most common treatment for hepatomas and hepatoblastomas was cyclophosphamide, 5-fluorourcil, and vincristine, as described by Holton and co-workers [4]. This was followed with adriamycin, if necessary, for recurrences. Later, those four agents were begun simultaneously as soon as the children recovered from the surgical procedure. The time after surgery usually ranged

TABLE I. Hepatic Resections in Pediatric Patients

Case No.	Age (yr)	Sex	Diagnosis	Surgery	Adjuvant therapy	Results
Primary malignant tumor						
1	$1^{6}/_{12}$	M	Hepatoblastoma	Lt. Lobectomy	Chemotherapy	Died 6 mos. with disease
2	7	M	Hepatocellular ca	Rt. trisegmentectomy	Chemotherapy	Alive without disease over 5 years
3	9	M	Hepatocellular ca	Rt. trisegmentectomy	Chemotherapy	Alive without disease over 7 years
4	5	M	Hepatocellular ca	Rt. trisegmentectomy	Chemotherapy	Died 19 mos. with disease
5	15	F	Hepatocellular ca	Rt. trisegmentectomy	Chemotherapy	Alive with disease at 4 years
6	15	F	Hepatocellular ca	Rt. trisegmentectomy	Chemotherapy, radiation	Died 17 mos. with disease
7	10	M	Hepatocellular ca	Lt. trisegmentectomy	Chemotherapy (before operation)	Alive without disease at 1 year
8	12	F	Sarcoma	Rt. trisegmentectomy	Chemotherapy	Alive without disease over 5 years
9	11/12	F	Rhabdomyosarcoma	Nonanatomical resection	Chemotherapy, radiation	Alive without disease over 2 years
10	12	F	? Sarcoma	Rt. trisegmentectomy	Chemotherapy	Alive without disease over 5 years
Metastatic malignant tumor						
11	2	M	Neuroblastoma of rt. adrenal gland	Rt. trisegmentectomy and rt. adrenalectomy	Chemotherapy, radiation	Alive without disease over 6 years
12	12	F	Wilms' tumor	Lt. lobectomy	Chemotherapy, radiation, and pulmonary resection	Died 10 mos. with disease
Benign disease						
13	16	F	Adenoma	Rt. trisegmentectomy	_____	Alive over 6 years
14	16	F	Trauma	Rt. lobectomy	_____	Alive over 15 years

TABLE II. Adjuvant Chemotherapy

Case No.	Diagnosis	Chemotherapy agents
1	Hepatoblastoma	Cytoxan, vincristine, 5-FU
2	Hepatocellular ca	Cytoxan, vincristine, 5-FU
3	Hepatocellular ca	Cytoxan, vincristine, 5-FU
4	Hepatocellular ca	Cytoxan, vincristine, 5-FU
5	Hepatocellular ca	Cytoxan, vincristine, 5-FU, Adriamycin
6	Hepatocellular ca	Cytoxan, vincristine, 5-FU, Adriamycin
7	Hepatocellular ca	None after resection
8	Sarcoma	Cytoxan, vincristine, 5-FU
9	Rhabdomyosarcoma	Vincristine, dactinomycin, cytoxan
10	Sarcoma (?)	Cytoxan, vincristine, dactinomycin, DTIC, adriamycin
11	Neuroblastoma	Cytoxan, vincristine, CCNU, adriamycin
12	Wilm's tumor	Dactinomycin, vincristine

from a few days to several weeks. The heterogeneity of agents, dosage, and timing of adjuvant therapeutic protocols and small number of cases precluded conclusions about effectiveness beyond the observation that good long-term survival was obtained with adjuvant therapeutic treatment, even in some patients who had known recurrences.

Late Results

Primary hepatic malignant tumor. The results are summarized in Table I. Nine of 10 children survived at least 1 year. Seven of the 10 children are alive with follow-up periods of 1 to 7 years, and six of them are free of disease. Another with stable pulmonary metastasis is under new chemotherapy after 4 years. Three children died with disease 6, 17, and 19 months after hepatic resection. Four children are alive and free of disease for more than 5 years and are considered to be cured.

Metastatic malignant tumor. One child with neuroblastoma is alive more than 6 years after resection and is considered to be cured. Another child with Wilms' tumor died with disease after 10 months (Table I).

Benign disease. These two children recovered completely and have no complaints or hepatic function abnormalities after many years (Table I).

TOTAL HEPATECTOMY AND LIVER REPLACEMENT (ORTHOTOPIC LIVER TRANSPLANTATION)

Primary liver malignancy which cannot be treated with conventional techniques of subtotal hepatectomy could theoretically be cured by total hepatectomy and liver replacement. Eight children with primary liver malignancy received orthotopic liver transplantation since 1963.

TABLE III. Eight Children with Primary Liver Malignancy Who Were Treated by Total Hepatectomy and Liver Replacement (Orthotopic Liver Transplantation)

Case No.	Age (yr)	Sex	Diagnosis	Survival
15.	3	F	Biliary atresia, incidental hepatocellular carcinoma	Alive 12 years without disease
16.	7	F	Biliary atresia, incidental hepatocellular carcinoma	Operative death
17.	5	F	Alpha-1-antitrypsin deficiency incidental hepatoblastoma	Alive 3 years without disease
18.	11	F	Biliary atresia, concomitant hepatocellular carcinoma	Died 3 months with disease
19.	9	F	Tryosinemia, concomitant hepatocellular carcinoma	Died 3 months with disease
20.	$1^{7}/_{12}$	F	Hepatocellular carcinoma	Died 14 months with disease
21.	16	F	Hepatocellular carcinoma	Died 15 months with disease
22.	15	M	Hepatocellular carcinoma	Died 5 months with disease

Case Material

Three children received liver transplantation for end-stage liver disease. In the excised livers were found incidental primary liver malignancies (Table III).

Two other children had end-stage liver disease and concomitant primary liver malignancy which was known prior to transplantation (Table III). The three final children had primary liver malignancy which was not resectable by conventional technique of subtotal hepatectomy (Table III). Transplantation was decided upon as a means of extending the limit of resection.

There were seven hepatocellular carcinomas and one hepatoblastoma. The age ranged between 1 year and 7 months old to 16 years old.

Surgical and Medical Therapy

The surgical techniques of orthotopic liver transplantation have been described elsewhere [5]. The new liver was placed in the anatomical position.

For immunosuppression, these eight patients were given azathioprine, prednisone, and horse antilymphocyte globulin.

TABLE IV. Tumors or Tumor-like Lesions of the Liver in Infants and Children

Malignant group
1. Liver cell carcinoma
   - Hepatoblastoma
   - Hepatocellular carcinoma
2. Hepatic mixed tumors
3. Mesenchymoma (malignant)
4. Sarcoma
5. Metastatic tumor

Benign group
1. Tumor-like epithelial lesions
   - Focal nodular hyperplasia
   - Multiple nodular hyperplasia
   - Accessary lobe
2. Benign eipithelial tumors
   - Adenoma
   - Adrenal rest tumor
3. Cysts and tumor-like mesenchymal tumor
   - Mesenchymal hamartoma
   - Nonparasitic cyst
4. Benign mesenchymal tumors
   - Cavernous hemangioma
   - Infantile hemangioendotheliomas
5. Teratoma

Survival

There was one operative death (12.5% operative mortality). Five children died with recurrent tumor between 3 and 15 months after transplant, after a mean survival of 8 months (Table III). These five children all had advanced stages of liver malignancy with bulky tumors. Two children are alive and free of disease 3 years and 12 years, respectively, after transplant. In both children, primary liver malignancy was discovered at the pathological examination of the removed organ (Table III), and thus the tumors were incidental findings.

COMMENT

Edmondson [6], classified liver neoplasms in his classic paper in 1956 (Table IV). In the 1974 survey of the American Academy of Pediatrics [1], the ratio of malignant to benign lesions was 2 to 1. Among the benign lesions hemangioma, hamartoma, epithelioma, benign cyst, and adenoma were the most common in that order of frequency. Ninety percent of the malignant tumors were hepatoblastomas or hepatocellular carcinomas. Hepatoblastoma occurred largely in the infant population; almost half the patients were 18 months of age or younger. In the patients with

hepatocellular carcinoma, there appeared to be two age peaks, one in the age below 4 years, and another in age between 12 and 15 years.

An unacceptably high (20-30%) operative mortality from hepatic resection has been reported in the literature. Ishak and Glunz [7], reported that 4 of the 18 patients with hepatoblastoma or hepatocellular carcinoma died on the operating table during hepatic resection. The survey by the American Academy of Pediatrics, Surgical Section, also reported that 25 of 223 patients with hepatoblastoma or hepatocellular carcinoma who had exploratory celiotomy died on the operating table or in the immediate postoperative period. Since definitive resections were carried out in less than half the cases, the operative mortality from resection apparently exceeded 20%. At an earlier time at the Boston Children's Hospital there was an 18% operative mortality [8], and at the Hospital for Sick Children in London, the death rate was 31% [9].

Major hepatic resections can now be done quite safely. In our 14 hepatic resections, there was no operative mortality. The earliest death occurred 6 months after operation due to recurrence of tumor. The authors' personal series of 129 major hepatic resections were carried out with the operative mortality of only 3% during the last 18 years. Wilson, Adson, and Weiland from Mayo Clinic also reported the operative mortality of less than 5% [10, 11]. Thus, major hepatic resection has become a safe operative procedure at places where hepatic operations are performed rather frequently.

Surgical resection offers the only chance of survival for patients with malignant hepatic neoplasms. Ishak and Glunz [7] reported that none of the children who did not have the benefit of surgical resection survived more than 1 year, but that 9 of the 11 children whose tumors were resected were alive; 6 of these 9 children had survived for 4, 5, 6, 8, 9, and 13 years, respectively, without evidence of recurrence. The survey by the American Academy of Pediatrics [1] also reported that there were no survivors at 2 years after biopsy only or incomplete resection of tumors, but that 60% of the children with hepatoblastoma and 35% of them with hepatocellular carcinoma survived. The prognosis of hepatocellular carcinoma has been said to be poorer than that of hepatoblastoma [1, 7, 12]. In our present series 7 of the 10 children who had curative hepatic resections for primary hepatic malignancy are alive for 1 to 7 years including 4 of 6 with hepatomas and 3 of 3 with sarcomas.

The role of adjuvant chemotherapy and radiation therapy has been questioned for a long time [1, 7]. The lack of significant numbers of cases has precluded a meaningful conclusion. However, our satisfactory long-term results of hepatic resection with adjuvant therapy have been noted and defended elsewhere [3].

The limits of resectability can be extended by treating primary liver malignancy with total hepatectomy and orthotopic liver transplantation. However, a high recurrence rate of the original malignancy after successful transplantation has dampened enthusiasm for this approach. Nevertheless, a small but significant palliation has been achieved with this approach, even in some patients who eventually have died of recurrence [13-15]. Further gains will be possible only with extremely discriminating selec-

tion of prospective recipients and better immunosuppressive therapy. Effective adjuvant therapy to prevent recurrence is awaited.

REFERENCES

1. Exelby PR, Filler RM, Grosfeld JL: Liver tumors in children in particular reference to hepatoblastoma and hepatocellular carcinoma: American Academy of Pediatrics Surgical Section Survey, 1974. J Ped Surg 10:329, 1975.
2. Starzl TE, Bell RH, Beart RW, Putnum CW: Hepatic trisegmentectomy and other liver resections. Surg Gynecol Obstet 141:429, 1975.
3. Starzl TE, Koep LJ, Weil R III, Lilly JR, Putnum CW, Aldrete JA: Right trisegmentectomy for hepatic neoplasms. Surg Gynecol Obstet 150:208, 1980.
4. Holton CP, Burrington JD, Hatch EI: A multiple chemotherapeutic approach to the management of hepatoblastoma. Cancer 35:1083, 1975.
5. Starzl TE: "Experience in Hepatic Transplantation." Philadelphia: W.B. Saunders Co., 1969.
6. Edmondson HA: Differential diagnosis of tumors and tumor-like lesions of liver in infancy and childhood. AMAJ Dis Children 91:168, 1956.
7. Ishak KG, Glunz PR: Hepatoblastoma and hepatocarcinoma in infancy and childhood: Report of 47 cases. Cancer 20:396, 1967.
8. Taylor PH, Filler RM, Nebesar RA, Tefft M: Experience with hepatic resection in childhood. Am J Surg 117:435, 1969.
9. Howat JM: Major hepatic resections in infancy and childhood. Gut 12:212, 1971.
10. Wilson SM, Adson MA: Surgical treatment of hepatic metastases from colorectal cancers. Arch Surg 111:330, 1976.
11. Adson MA, Weiland LH: Resection of primary solitary hepatic tumors. Am J Surg 141:18, 1981.
12. Randolph JG, Atlman RP, Arensman RM, Matlak ME, Leikin SL: Liver resection in children with hepatic neoplasms. Ann Surg 187:599, 1978.
13. Starzl TE, Koep LJ, Halgrimson CG, Hood J, Schröter GP, Porter KA, Weil R III: Fifteen years of clinical liver transplantation. Gastroenterology 77:375–388, 1979.
14. Iwatsuki S, Klintmalm GBG, Starzl TE: Total hepatectomy and liver replacement (orthotopic liver transplantation) for primary hepatic malignancy. World J Surg 1982, in press.
15. Calne RY, Williams R: Liver transplantation. In Ravitch MN (ed): "Current Problems in Surgery." Chicago: Year Book Medical Publishers, 1978, pp 1–44.