Liver Resection in Children with Hepatic Neoplasms

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In the past ten years, 28 patients with primary tumors of the liver have been treated. There were 11 benign tumors, including four hamartomas, three patients with focal nodular hyperplasia, and two each with congenital cysts and hemangioma. Hamartomas and masses of focal nodular hyperplasia should be excised when possible, but both are benign lesions; therefore life threatening excisions at the porta hepatis should be avoided. Cysts are often resectable, but when occupying all lobes of the liver, they can be successfully managed by marsupialization into the free peritoneal cavity. If resectable, hemangiomas should be removed; when occupying most of the liver as they often do, patients may be subject to platelet trapping or to cardiac failure. In some instances these lesions have been controlled by steroids, radiation therapy or hepatic artery ligation. Of 17 malignant tumors seen, 12 proved to be hepatoblastomas. Nine of the 12 patients underwent liver resection, of whom four are cured, (33%). There were three children with hepatocellular carcinomas and two with embryonal rhabdomyosarcoma. One child from each of these groups is cured by surgical excision. At present the only known cures in children with primary malignant liver neoplasms have been achieved by operative removal.

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HEPATIC TUMORS IN CHILDREN represent grave clinical problems as well as technical challenges for the surgeon. Benign tumors usually have a satisfactory outcome in children and most of them may be allowed to remain in part or whole, if the removal will unnecessarily jeopardize the life of the child. Malignant tumors of the liver exact a heavy toll in the childhood age. Long-term survival has thus far not been influenced by chemotherapy, radiation therapy, or immunotherapy. At present, cure of primary malignant hepatic tumors is achieved only by complete surgical removal. The following report details the surgical experience in 28 children with hepatic tumors treated at the Children's Hospital National Medical Center from 1966 through 1976.

Clinical Material

There were 28 children in this series, eleven with benign tumors and 17 with primary malignancies (Table 1). Among those with benign disease, four presented with hamartoma at three days, seven months, eight months, and five years of age. There were three children with focal nodular hyperplasia, seen at three, four an one-half and eight years, respectively. Two patients, aged three months and two years, were seen with congenital cysts. There were two infants with hepatic hemangioma. There were none in this group with simple adenoma.

In the 17 children with malignancy, 12 with hepatoblastoma comprised the largest group. They ranged in age from one to 44 months at the time of diagnosis; eight of the 12 were under one year when first seen. Three of these children had pulmonary metastasis when first seen. As has been noted in other reports, the patients with hepatocellular carcinoma were older, appearing at three, eight and 12 years, respectively.[7] Two patients in the malignant group had embryonal rhabdomyosarcoma arising in the liver; these children were seen at 18 and 30 months.

Diagnosis

Liver tumors in children are usually discovered as asymptomatic abdominal masses. Fever, abdominal pain, anorexia and weakness are symptoms of advanced malignancy and are encountered in about 25%

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TABLE 1. *Liver Tumors 1966–1976*

Hepatoblastoma	12
Hepatic cell carcinoma	3
Embryonal rhabdomyosarcoma	2
Mesenchymal hamartoma	4
Nodular hyperplasia	3
Congenital cysts	2
Hamangioma	2
	28

of children, many of whom have pulmonary metastases when first seen.[16] Anemia and thrombocytopenia are common findings but jaundice is rare. Alpha fetoprotein, a normal alpha globulin produced by embryonic hepatocytes, is a reliable biologic marker found in the serum of patients with hepatoblastoma.[1] Less frequently it is present in the serum of children with hepatocellular carcinoma. Alpha fetoprotein has usually disappeared from the serum of normal infants after a few months. The resynthesis of fetoprotein by the malignant hepatocyte is considered specific for these tumors, although it has been reported in the association with embryonal carcinoma of the testis and ovary.

The roentgenologic evaluation of the child presenting with an abdominal mass begins with plain films of the abdomen and intravenous pyelography. These studies identify renal and retroperitoneal lesions and may delineate encroachment of the tumor on adjacent abdominal structures. Ultrasonography aids in differentiating solid from cystic tumor masses. Hepatic imaging with radionucleides is useful in delineating the distribution of the tumor within the liver substances. The diagnosis is confirmed by hepatic angiography.[3,19] This definitive study is particularly useful to the surgeon because it will accurately define the arterial anatomy to the tumor and to the normal liver substance.

Treatment

Benign Disease

Several features in the handling of benign liver tumors are unique to the pediatric age group. Congenital cysts are usually detected in the early years of life. For some, a simple cystectomy or wedge resection is all that is required. Some of the cysts however, occupy the major portion of an entire lobe, necessitating formal lobectomy. If resection is not technically feasible, the cyst can be unroofed by excising the presenting surface. The edge of the remaining liver is secured with a running suture to marsupialize the cyst into the free peritoneal cavity (Fig. 1). It is not necessary to anastomose the open cyst to the gastrointestinal tract.

Hamartomas are not malignant tumors, but represent abnormal accumulations of normal tissue derived from the organ of origin.[2] Resection is the recommended treatment whenever technically feasible. Mass lesions representing focal nodular hyperplasia should be excised when surgically accessible.[27] Occasionally, these masses of hyperplastic tissue will appear grossly as malignant tumors, (Fig. 2) but they have no malignant potential.[24] When diagnostic confusion exists at the operating table, it is better to obtain a biopsy with frozen section, rather than to attempt a life-threatening excision for this benign lesion.

Hemangiomas of the liver become clinically apparent in several ways and therapy is directed accordingly.[6] Thrombocytopenia secondary to platelet trapping within the lesion, or congestive heart failure resulting from shunting in the tumor each necessitate intervention.[3,17] Surgical excision should be carried out whenever feasible, but if resection is not practical because of the location or extent of the tumor, or because there are multiple components present throughout the liver substance, alternative therapy is elected. Systemic steroids should be used in an effort to promote involution of the supporting connective tissue stroma of the hemangioma.[4,13,26] Radiation therapy may also be effective in reducing the tumor mass. Hepatic artery ligation has been shown to control the cardiac decompen-

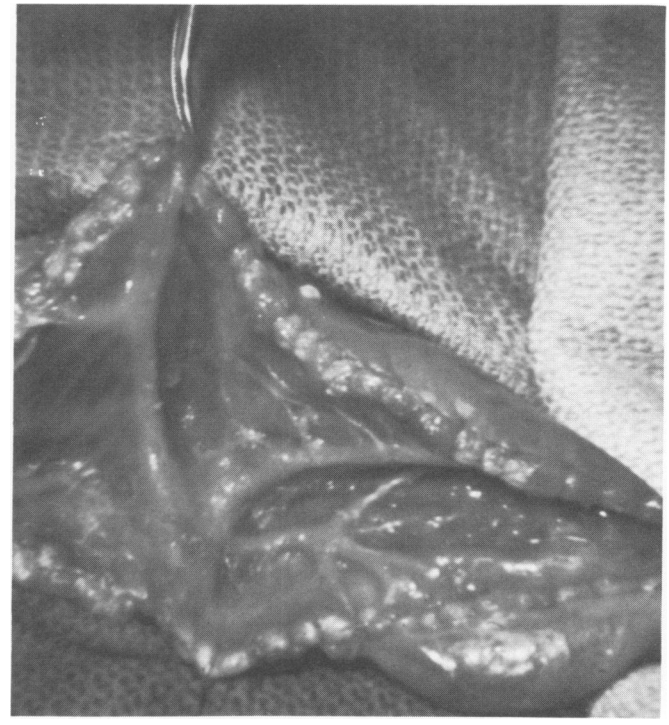

FIG. 1. Close up of the liver after resection of the anterior presenting portion of a congenital cyst. The edge has been whip stitched to marsupialize the cyst in the free peritoneal cavity. Note the internal architecture of the liver.

sation in some infants by reducing the arterial flow through the tumor.[19] The natural history of these lesions is spontaneous regression. Therefore in some patients, pharmacologic control of the cardiac systems may reduce or eliminate the need for hazardous surgery.

Malignant Tumors

At present, the only successful therapy is operative excision of all of the malignant growth. In the past, the presence of pulmonary metastases have countermanded a decision for surgical removal of the tumor. However, the well-being of the patient after removal of the large primary mass and the potential for control of metastases by Adriamycin[10] suggest that resection of the primary mass in the liver should be carried out except in terminal disease states. X-ray therapy of very large tumors has been recommended as a preoperative measure to reduce the size and enhance the operability of the tumor. We believe it unlikely that tumors can be removed from one lobe by irradiation and therefore, doubt that operability is truly altered. Large tumors can usually be as safely removed as smaller ones.

Technical considerations in liver resection. For maximum safety major hepatic resection implies the need for intraoperative monitoring, which includes arterial access for blood pressure and blood gases, central venous pressure, and Doppler flow sensor. Adequate quantities of type-specific blood, platelets and fresh-frozen plasma must be available in advance of surgery. Preoperative preparation includes review of the angiograms with formulation of a surgical plan based upon the vascular anatomy.

Adequate exposure for safe resection can be obtained through a generous transverse abdominal incision. For children, it is rarely necessary to enter the chest, even for resection of the largest hepatic tumors. Disseminated disease through both lobes is obviously not resectible; however, enormous lesions arising in one lobe often displace the other without invading it, or involvement of the adjacent lobe by contiguous spread is amenable to surgical resection. An aggressive surgical approach is encouraged. The first step in resection is the mobilization of the liver by dividing its ligamentous attachments to the abdominal wall and diaphragm. In smaller children, the liver can be displaced almost out by the abdominal cavity, providing access to the retrohepatic vena cava. Caution must be exercised since vena caval angulation may occur if the liver is mobilized too far anteriorly. A sudden fall in cardiac output and central venous pressure signifies the need to replace the liver into its normal anatomic position until hemodynamic stability returns.

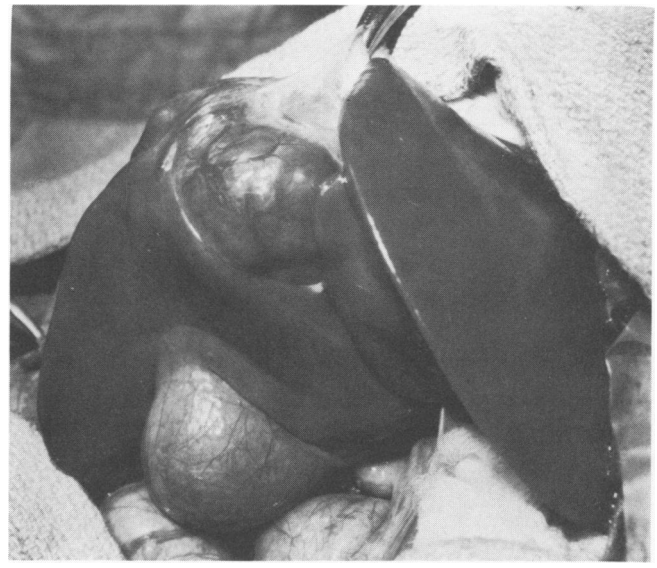

FIG. 2. Liver in 4½-year-old child with focal nodular hyperplasia. Note large veins on surface which resemble those seen in malignant tumors. This tumor was easily excised, but if located in the porta hepatis, such a tumor should be allowed to remain.

Routine canulation of the vena cava with an internal shunt is not advised, but appropriate tubes should be available should this maneuver be required in the event of catastrophic hemorrhage during dissection of the hepatic veins. These shunts can be placed from below the renal veins and passed upward to lie in the suprahepatic vena cava, or they can be inserted through the right atrium downward where, the canula is secured within the caval lumen below the liver.

Hepatic resection proceeds with isolation of the portal vein, common bile duct, and hepatic artery to the lobes and segments being resected. Extreme care must be exercised to protect the vascular and biliary structures to that portion of the liver which will remain.

Ligation of the hepatic veins is the most difficult and hazardous part of the resection. Particularly in infants, these veins are inaccessible, short and fragile. Avulsion or injury can result in serious hermorrhage. The middle hepatic vein is vulnerable to damage during either a right or a left lobectomy. The location of this vein should be established and the plane of resection planned to spare it. After securing the vascular and biliary structures, division of the liver substance remains to complete the resection. Several techniques, including finger fracture, knife handle dissection and sharp dissection have their proponents. We have used large vascular clamps to compress the liver substance at the line of resection. After the dissection is completed the clamps are applied along the line of proposed resection (Fig. 3). The large intersegmental ves-

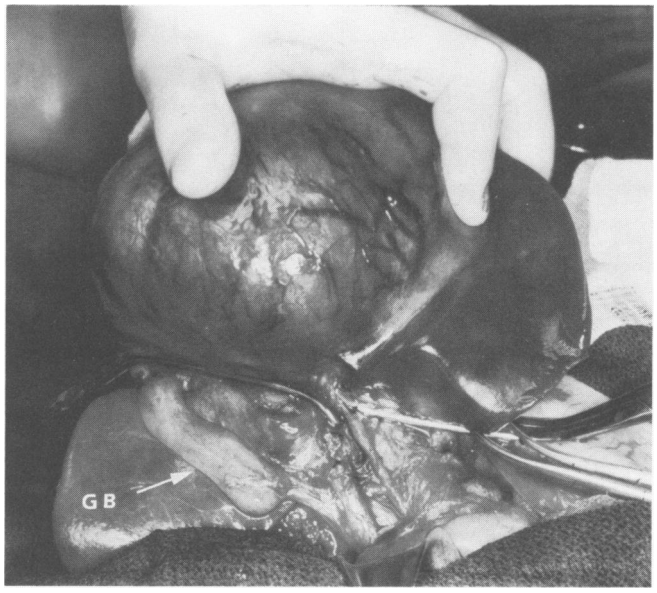

FIG. 3. Application of large aortic clamps, placed from above and below after the dissection has been completed.

sels and ducts are held securely by the clamps. These are subsequently suture ligated individually. Resection is thus expedited and blood loss minimized (Fig. 4). The area of resection is drained liberally.

After surgery the child is taken to the intensive care unit and monitored for postoperative fluid shifts, abnormalities of the clotting mechanism and electrolyte balance. Even after extensive hepatic resection, serum electrolyte and clotting factors are usually well maintained. Ten per cent glucose solutions are provided initially until glycogen stores are replenished. Hepatic regeneration proceeds rapidly, and biochemical parameters of liver function quickly return to the normal range even following the most radical resections.[20]

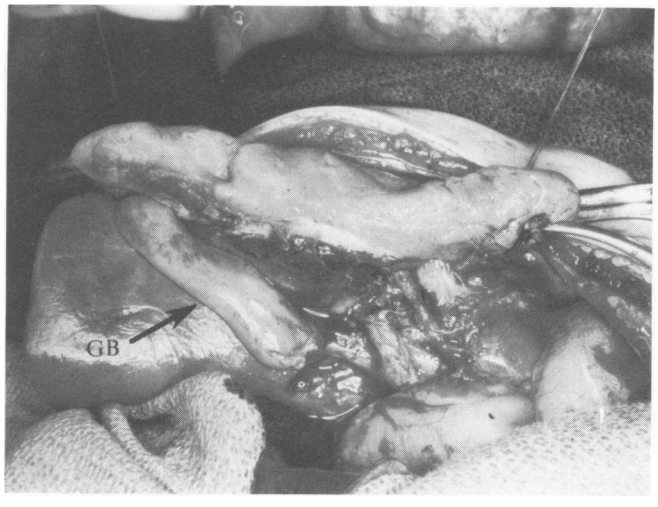

FIG. 4. Control of resection margin by large clamp after removal of tumor and left lobe.

TABLE 2. *Survival of Benign Liver Tumors*

	No.	Alive
Mesenchymal hamartoma	4	3
Nodular hyperplasia	3	3
Congenital cysts	2	2
Hemangioma	2	2
	11	10 (90%)

Postoperative radiation therapy is essential in rhabdomyosarcoma of the liver as is treatment with chemotherapy with Actinomycin, Vincristine and Cytoxan. There has, however, been no salutory effect on hepatoblastoma or hepatic cellular carcinoma by radiation therapy or chemotherapy.[14] A new protocol, developed by the Children's Cancer Study Group which employs Adriamycin, has yielded some encouraging early results.[10] At preset, the only hope for cure in children with hepatic malignancy lies in complete surgical extirpation of tumor. This can usually be accomplished and should be the surgical objective.

Results

Benign Tumors—Table 2

Eleven patients had surgery for benign liver tumors. There was one death. This occurred in a three day old baby who underwent right hepatic lobectomy for a mesenchymal hamartoma and succumbed to postoperative hemorrhage 24 hours later because of an uncontrollable coagulopathy. In the other three patients one had biopsy only because of an unresectable position in the porta hepatis; one had wedge resection and one had extended lobectomy.

There were three patients with focal nodular hyperplasia. One was treated successfully by lobectomy, one by wedge resection, and one who had biopsy only because of the location of the tumor in the porta hepatis.

Two patients had congenital cysts, one of whom was treated successfully by lobectomy. The other had extensive involvement of the liver substance by this cystic mass and therefore a marsupialization procedure was done. She remains completely well four and a half years after surgery. Both children treated for hemangioma had biopsy only. In one the hemangioma has been asymptomatic and the child is well. The other child had significant congestive heart failure which has been controlled by Digitalis. Radiation therapy and oral steroids administration has resulted in regression of the tumor.

Malignant Tumors

Hepatoblastoma. Of 12 children with hepatoblastoma nine have been treated with lobectomy. Three

TABLE 3. *Survival of Malignant Tumors*

	No.	Cured
Hepatoblastoma	12	4
Hepatic cell carcinoma	3	1
Rhabdomyosarcoma	2	1
	17	6 (35%)

patients, treated early in the series had pulmonary metastases at the time they were diagnosed and had biopsy only. Five of the nine patients subjected to lobectomy are surviving but one is known to have metastases. The other four are free of disease at two, two, three, and four years, respectively. The two year cure rate is 33%, and recurrence is unlikely in this group of very young patients.

Three patients had hepatic cell carcinoma. A 12-year-old child died shortly after biopsy with extensive pulmonary metastases. Another child underwent successful left lobectomy but died a year later with pulmonary metastases. An eight-year-old presented with multicentric carcinoma arising from a regenerative nodule in a liver with postnecrotic cirrhosis. Because of underlying liver disease, lobectomy was not practical. This patient has had three separate wedge resections. The unique biologic behavior of this tumor which characteristically recurs locally with pulmonary metastasis occurring rarely or only in terminal stages of the disease lends itself to treatment by limited local excision.

One of the two patients treated for rhabdomyosarcoma of the liver is alive and presumed cured by lobectomy. The other underwent combined lobectomy and Whipple operation but succumbed after two years from recurrent disease.

Discussion

This experience would seem to indicate that a therapeutic plan individualized for the patient on the basis of the histologic lesion is best for the management of children with benign hepatic tumors. Conversely, malignant disease can be successfully treated only by aggressive surgical resection. Since the original work by Quattlebaum in 1952[22] improvements in liver resection have been steadily seen over the past 25 years. Excision of a lobe of the liver or extended resection involving two of the major components of the liver are now standard operations.[5,9,11,15,18,21] Liver resection in children is easier in some respects than in adults; in particular, exposure, mobility of the organ, the elasticity of the surrounding viscera, and the parenchymal mass which must be traversed all make for a simpler technical operation. On the other hand, blood loss can rapidly plunge the small subject into shock. Therefore, precise monitoring, accurate blood replacement, and awareness of the child's vulnerability to cardiac arrest are all highly important facets of hepatic surgery in children. The use of clamps at the resection margin is controversial and can be complicated. We have felt them to be beneficial in these resections. They are not applied until after all dissection of the porta hepatis, the vena cava, and the hepatic venous outflow have been completed. Then we have used two simple large aortic clamps, one placed from above and one placed from below along the line of resection. This has minimized blood loss and provided control of the major vessels at the site of transection. The clamps are easy to remove and the operation has been safer with their use.

Because the location of benign tumors may be such that surgical resection may be impossible or unduly hazardous, an operative biopsy is recommended rather than proceeding with a life threatening resection which is not mandatory. Intraperitoneal seeding from operative manipulation or after rupture of hepatic tumors has not been seen in children's hepatic malignancies, so this deviation from cancer surgery principles is not unwise. Adenomas, hamartomas and focal nodular hyperplasia behave in a biologically benign fashion and all or any portion of these tumors can be allowed to remain *in situ*. However, when confined to a single lobe which lends itself to extirpation, resection of benign tumors is preferable because of possible symptoms or complications, such as encroachment on the surrounding viscera, bleeding or necrosis.

This series of patients confirms the view that surgical resection represents the only hope of cure for children with malignant liver disease. Vigorous surgical resection of rhabdomyosarcoma occurring in the liver and biliary system should be carried out even when the

TABLE 4. *Surgery for Liver Tumors*

	Biopsy (8)		Wedge (4)		Lobectomy (13)		Extended Lobectomy (3)	
Type	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
Benign	4	0	3	0	2	1	1	0
Malignant	0	4	1	0	4	6	2	0

tumor is not completely accessible.[23] Improved survival for this lesion, in the liver as elsewhere in the body, has been realized with the addition of triple drug chemotherapy and radiation therapy. While chemotherapy has been disappointing for the management of primary hepatic tumors, current studies by the Children's Cancer Study Group suggest that Adriamycin may have a salutory affect on pulmonary metastases in some patients.[10] Therefore we would recommend surgical resection in the primary tumor even when pulmonary metastases have occurred as long as the patient is not in a terminal state.

A number of workers have spoken to the benefit of preoperative radiation, particularly because of its ability to shrink large tumors. However, there is no evidence that a tumor can be eliminated from a lobe of the liver into which it has grown. Therefore, the only beneficial affect of the radiation therapy is to shrink the tumor in size. It is our strong belief that large tumors can be handled safely and that radiation therapy is of little benefit in the preoperative phase. It has been well shown that radiation therapy after operation may damage the small amount of remaining liver after a major resection or may impede liver regeneration.[12,24] Therefore this modality must be used judiciously after liver resection in infants and children.

Conclusions

Complete excision of childhood malignant tumors of the liver has been possible in the majority of children in this series, resulting in a 35% cure rate. No benefit has been recognized from chemotherapy or radiation therapy in the children with hepatoblastoma or hepatic cell carcinoma. As in other locations, hepatic rhabdomyosarcoma is affected favorably by these adjunctive measures. Surgical approach to benign liver tumors should be individualized according to the type and location of the tumor.

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Discussion

Dr. Jonathan A. van Heerden (Rochester, Minnesota): I rise briefly to bring to the attention of this group an instance which we recently encountered which we believe to be the first such incident recorded in the world's literature. Perhaps it isn't, and perhaps this group can tell us so.

We recently operated on a 4½-year-old girl with a large tumor of the right hepatic lobe. (Slide) This was a gigantic tumor, as seen here, which was a low grade hepatocellular carcinoma. The interesting thing about this was that at the time of right hepatic lobectomy, I could not find the portal vein. It's very difficult to lose the portal vein during a right hepatic lobectomy, but it was not to be found.