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SURGICAL APPROACHES TO PRIMARY AND METASTATIC LIVER NEOPLASMS†

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Providing the anatomic conditions are appropriate, removal of as much as 85-90% of the liver is a relatively safe technique for the treatment of benign or malignant primary hepatic tumors and of isolated hepatic metastases. There have been apparent cures of malignant disease by this approach, but the paucity of concentrated experience at any one center and the failure so far to pool data from different centers effectively make a valid prognosis impossible.

Total hepatectomy and liver replacement has resulted in the apparent cure of some patients with primary hepatic malignancy. However, there has been an extremely high rate of recurrence of tumor. Small cancers which are lethal because of their strategic locations may provide an unusually good indication for liver replacement. Liver transplantation would rarely, if ever, be indicated for metastases to the liver.

Primary and metastatic liver neoplasms, Surgery, Hepatic cell carcinoma.

INTRODUCTION

The last 15 years have seen very important advances in two areas of hepatic surgery. First, techniques have been perfected which permit the relatively safe removal of as much as 85-90% of the liver. Second, it has become feasible to carry out total removal of a diseased liver and to replace it with a hepatic homograft.

How have these powerful new tools affected the treatment of primary and metastatic tumors of the liver, and to what extent will future policies of cancer therapy be shaped by their more extensive use?

DIAGNOSIS

Primary tumors

Hepatic tumors may present as asymptomatic or symptomatic masses in the liver area, or by a variety of other manifestations including distant metastases. A liver scan will help define the extent of the lesion. Since more than 90% of hepatic tumors are metastatic, it is important to search for a primary malig-

nancy elsewhere. Gastrointestinal series, barium enema, intravenous urogram, and metastatic surveys of the chest and bones are usually indicated. Unless some reason has been found with these studies not to proceed, angiographic study of the hepatic arterial supply is performed (Fig. 1). Transhepatic and retrograde (transduodenal) cholangiography are very useful procedures if jaundice is a symptom.

In all patients with hepatic masses, the presence and amount of alpha fetoprotein is important. This is a protein of the alpha₂ globulin class which is synthesized by undifferentiated hepatoma cells and which is found in the serum of 30-90% of patients with liver cell carcinoma. False positive tests from hepatic metastases have been documented only in a few pediatric patients with primary embryonal malignant lesions. Thus, not only does a positive test strongly support the diagnosis of a primary liver cell carcinoma, but later quantitative determinations are of great help in following the progress and effectiveness of treatment.¹

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5-fluorouracil = Fluorouracil[®]; cyclophosphamide = Cytosan[®]; vincristine sulphate = Oncovin[®].



Fig. 1. Arteriogram performed prior to trisegmentectomy for hepatic adenoma in a 16 year old girl. The entire liver was supplied by an anomalous artery (A) arising from the superior mesenteric artery (SMA). Branches to the right lobe and to the medial segment of the left lobe were ligated (*large arrows*), preserving the main trunk and its tiny branch to the left lateral segment (*small arrow*).

Isolated liver metastases

The diagnosis of isolated hepatic metastases after the resection of a primary malignancy elsewhere is apt to result either from careful follow-up physical examination or from serial liver scans (Fig. 2).

OPERATIVE EVALUATIONS

In the absence of contraindications such as proven metastases, abdominal exploration usually should be performed without delay to obtain a tissue diagnosis and with a view to curative resection if feasible. From the biopsy tissue, the accurate and rapid histopathologic classification of liver masses is essential. A potentially serious error is to fail to recognize a lesion known as focal nodular hyperplasia. These masses, which are not true neoplasms, do not ordinarily require major resection and usually should be left alone except for biopsy. There are exceptions to this generalization, since rupture and massive bleeding have been

reported,⁸ particularly with large areas of involvement which may cause pressure symptoms in addition. We have performed trisegmentectomy for a patient with such extensive disease. Histopathologically, the nodules, which have a cobblestone appearance, are composed of uniformly normal appearing liver cells in cords or sheets, usually without orientation to central veins or portal triads, which are sparse. There may be areas of fibrosis, infarction or hemorrhage.⁸

A particular solid hepatic neoplasm has a special place by virtue of its occasional huge size, slow natural history and failure to metastasize. These characteristics, which were particularly well recognized by Edmiston,⁴ have caused this tumor to be called benign hepatoma, minimum deviation hepatoma or adenoma. Another designation has been "pill tumor" because of the frequent association of these neoplasms in young women with the use of oral contraceptive



Fig. 2. Routine liver scans in 2 patients with hepatic metastases from colon cancer. *Top.* Anterior liver scan showing a defect in the left lateral segment which subsequently was resected. *Bottom.* Posterior liver scan. A large defect involves the right lobe and medial segment of the left lobe. Trisegmentectomy was performed.

drugs. Alpha fetoprotein determinations are negative.

The tendency of hepatic adenomas to rupture has made their presence in the liver like a time bomb. Berg *et al.* noted 4 cases of this tumor in the Iowa State Cancer Registry; in 3 the tumor ruptured and lethal hemorrhage occurred.² Two of our 6 women with hepatic adenomas have presented with massive bleeding. Both cases illustrated that serious errors of treatment-planning or interpretation of results are possible without an accurate diagnosis. After emergency hepatic lobectomy, the 2 women carried the diagnosis of hepatoma and were treated with 5-fluorouracil

for more than 2 years before the pathologic specimens were reviewed and reclassified. If there are doubts about the diagnosis, specimens should be sent to reference centers such as the Armed Forces Institute of Pathology, Washington, DC 20305.

Hepatic cell carcinoma (hepatoma) accounts for 80–90% of the malignant primary hepatic neoplasms. Cholangiocarcinoma is next in frequency. Both tumors may be multifocal. The list of unusual or rare malignancies is a long one, including hemangioendothelial sarcoma, squamous cell carcinoma in an intrahepatic cyst and carcinoma of the larger intrahepatic ducts. Patients with the last kind of neoplasm may be candidates for liver transplantation (see below).

PARTIAL HEPATECTOMY

The limits of safe removal

The human liver consists of four segments. The units which lend themselves to excision (Fig. 3) include the right and left true lobes (each consisting of two segments), the true right lobe plus the medial segment of the left lobe (trisegmentectomy or extended right lobectomy) and the lateral segment of the left lobe. In planning the appropriate operation, the dissection is so greatly facilitated by preoperative arteriography (Fig. 1) that this

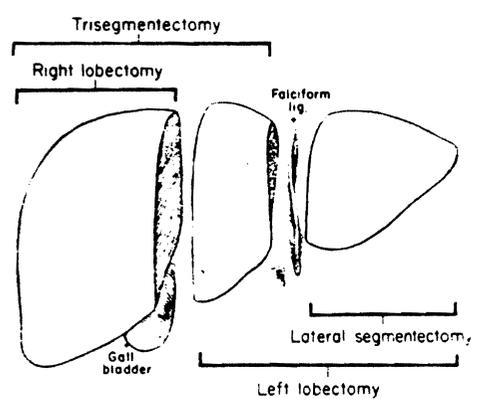


Fig. 3. The common hepatic resections, of which there are only four. The most radical procedure, trisegmentectomy, involves removal of the true right lobe plus the medial segment of the left lobe. The least radical procedure, lateral segmentectomy, was incorrectly termed left lobectomy in the older literature.

study is performed in every candidate for partial hepatectomy, unless it is contraindicated.

The historically high risk of hepatic resection has been reduced drastically in recent years. In the personal experience of the senior author with about 30 cases at the University of Colorado no patient has died after partial hepatectomy since 1962. The numbers of hepatic resections have increased steadily; 20 of our partial hepatectomies have occurred since 1970, including only one segmentectomy. Of these last 20 patients, trisegmentectomy was performed in 8, and removal of conventional lobes in the rest.

Surgical treatment

As has already been emphasized, a final diagnosis is frequently impossible until operation, and sometimes not even then. If, at exploration, the lesion in question is thought to be: other than focal nodular hyperplasia; resectable; and localized to the liver, enough liver is removed by one of the formal resections shown in Fig. 3 to excise the mass with as full a margin as possible. The piecemeal removal of hepatic masses, even those thought to be benign, is almost never justifiable from a technical point of view if the amount of excised tissue is more than 100 or 200 g.

The special question of metastases

If there is a resectable primary hepatic tumor, no one would seriously argue against its removal with as wide margins as possible. Although large series cannot be cited as the basis for a prognosis, numerous reports have proved that both hepatomas and cholangiocarcinomas can be cured.^{6,7}

The expectations after resection for hepatic metastases are even less clear. With the exception of carcinoid tumors, there is surprisingly little actual experience with partial hepatectomy for metastatic disease. The world literature was surveyed by Flanagan and Foster in 1967.⁵ They found 32 reports involving 72 patients who had survived liver resection. The primary malignancy was colonic in 45 instances. The overall 5-year survival for the 72 patients was 24%. The

correlation of the time interval between primary and secondary operation with prognosis was not good. The kind of primary tumor was influential; metastases from sarcomas and colon carcinomas were most effectively treated.

Since the lure of describing successes exceeds the temptation to report failures, the compilation of Flanagan and Foster may be an overstatement of the therapeutic expectations. In a personal series of 11 cases Longmire *et al.*⁷ report that 10 of their patients died of recurrent disease 2–18 months after hepatic resection. The single survivor was alive after 16 months. On the other hand, in a similar series of eight, Dillard³ recorded 5 long term survivors; 4 of these had lived from 4 to 10 years after partial hepatectomy without evidence of recurrence.

In the last 13 years, we have performed partial hepatectomy for metastatic disease only upon the patients shown in Fig. 2. The paucity of our experience and that elsewhere undoubtedly reflects the tendency of liver metastases to be widespread once they occur. However, a further factor could be a bias against using secondary partial hepatectomy because of its reputed high mortality. The reduction in operative risk in recent times should encourage an aggressive approach.

A need for pooled data

Even major oncology centers have a similar problem accumulating sufficient cases to draw valid conclusions about the value of hepatic resection for both primary and secondary neoplasms; therefore the use of pooled registries to develop prognostic data should be obvious objectives of oncology centers springing up under the stimulus of federal funding. Furthermore, information is needed about the postresectional role of adjuvant therapy with drugs or irradiation. The tacit assumption is usually made that neither irradiation or chemotherapy are safe or effective following subtotal hepatectomy, but such negative attitudes may eventually prove to be completely unjustifiable. Several of our recent patients have been treated with the triple drug regimen of cyclophosphamide, 5-fluorouracil and vincristine sulphate.

Therapy was not started for several weeks after operation until regeneration had a chance to begin and good wound healing was evident. Two of these patients who had massive tumors with blood vessel invasion are clinically free of tumor after 1-2 years.

TOTAL HEPATECTOMY AND TRANSPLANTATION

The appeal of liver replacement for the treatment of hepatic cancers is that the boundaries of permissible resection could be considerably expanded. Some liver tumors which cannot be completely excised by standard techniques of subtotal hepatectomy would become removable if the whole organ could be extirpated.

A potentially self-defeating aspect

Of course, the extension by this means of the surgical procedure would not insure against metastases. Indeed there is the possibility that the growth of residual tumor could actually be accelerated as a consequence of the immunosuppressive therapy which is necessary for prevention of homograft rejection. This would be expected if the concept is valid that the immunologic system provides a surveillance function by which mutant neoplastic cells are identified and either eliminated or restricted in their growth potential. The individuality of such cells which allows their recognition as foreign has been thought to result from tumor specific antigens.

It has been thoroughly documented elsewhere⁹ that immunosuppression leads to a striking incidence of new tumors and that it permits the transplantation of malignant tumors in humans which may become autonomous and, therefore, deadly even if immunosuppression is stopped. It has not been proven that metastases are enhanced by immunosuppressive therapy but the strong possibility has been raised from observations with patients treated with hepatic replacement for primary malignancies of the liver.⁹

In our own experience, seven patients with malignant liver tumors, exclusive of three with carcinomas of intrahepatic bile ducts, have undergone surgery for hepatic replacement with subsequent survival for long enough to

permit meaningful observations about tumor recurrence. The diagnoses were hepatoma in 6 cases and hemangioendothelial sarcoma in the other. Six of the patients developed metastases and all were dead 2.5-14 months after transplantation, usually as the result of the neoplasm. The only exception was a 3 year old child whose liver, which had been destroyed by biliary atresia, contained a 2 cm incidental hepatoma. After transplantation, the elevated serum alpha fetoprotein disappeared and more than 5 years later, there is no evidence of recurrence.

R. Y. Calne of Cambridge, P. Daloze of Montreal (oral communication, London, March 4, 1975) and J. B. Fortner of New York (oral communication, Mexico City, October 18, 1974) collectively have also had a few long survivals after liver replacement in patients with primary liver tumors. However, the salvage rate, which is not yet satisfactory after transplantation even for the treatment of



Fig. 4. Transhepatic cholangiogram with which a cholangiocarcinoma obstructing the main hepatic ducts was diagnosed. The patient is well, without evidence of recurrent disease, 1 year after orthotopic liver transplantation.

non-neoplastic liver disease, will obviously be drastically further depreciated in cancer patients.

It is hard to imagine for the same general reasons already stated that liver replacement will ever play much of a role in the treatment of metastatic liver disease.

A possible exception

Carcinomas at the junction of the right and left hepatic ducts are being accurately diagnosed at an earlier time, with increased use of transhepatic and transduodenal cholangiography. Because of the strategic location of the lesion (Fig. 4), jaundice develops early and

often prompts medical evaluation when the tumor is still very small and potentially highly curable.

We have performed liver replacement for 3 such patients. One died of surgical complications a few weeks later. Another died after 2 years of recurrent tumor in the homograft. The third patient is well without evidence of recurrent tumor 1.75 years after transplantation. Further experience will be necessary to determine if this approach will be preferable to the palliative methods designed to decompress the obstructed biliary passages that have been used in the past.

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