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TREATMENT OF FIBROLAMELLAR HEPATOMA WITH PARTIAL OR TOTAL HEPATECTOMY AND TRANSPLANTATION OF THE LIVER

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Fourteen patients with fibrolamellar hepatoma were treated with radical excision. In eight, a subtotal hepatic resection was performed from 16 months to more than 16 years ago. None of the patients have died and recurrences have been seen in only one patient. Six other patients had total hepatectomy and hepatic replacement. Two of these six patients have died of metastases and a third is living with recurrent tumor. This experience has justified the continuing use of quite aggressive extirpative procedures for the treatment of fibrolamellar hepatoma.

16 years by a single group, namely the hepatic transplant team which was at the University of Colorado until December 1980 and subsequently at the University of Pittsburgh. Six resections were by total hepatectomy, followed by orthotopic hepatic transplantation. The other eight involved subtotal removal of the liver with right or left trisegmentectomy. By examining these instances, for which follow-up studies are available of 11 months to almost 16 and one-half years, it has been possible to show what can be achieved with this disease using these two therapeutic options.

RECOGNITION of fibrolamellar hepatoma as a special pathologic entity dates from the description made by Edmondson in 1956 of a tumor sent to him by Brunschwig of New York (1). Further descriptions were written by one of Edmondson's associates, Peters (2). However, the clinical importance of this hepatoma variant was not generally appreciated until 1980 when, in nearly simultaneous publications (3, 4), the emphasis was on the indolent growth often exhibited by such tumors and the good results that sometimes could be obtained with aggressive surgical therapy. Because the material in these two series had been contributed on an individual patient by patient basis by many surgeons, the standards of management and the choices of operative procedures were variable.

METHODS

University of Colorado series. Until late 1979, the surgeons and pathologists alike at the University of Colorado were unaware of the existence of fibrolamellar hepatomas or the clinical significance of this diagnosis. In November of that year, Doctors Shires and Popper of New York City called one of us about Patient No. 3 in the Subtotal Resection Series, as given in Table I, who was being referred either for right trisegmentectomy or transplantation of the liver. Doctors Shires and Popper explained the favorable prognosis with the lesion and Doctor Popper described the characteristic histopathologic findings of eosinophilic polygonal liver cells and interlacing bands of tightly packed collagen from which the descriptive term fibrolamellar derived. From that time onward, the question was frequently asked if specific patients from past experience had, in fact, had this kind of hepatoma, including a hepatic transplant recipient (Patient No. T2, Transplantation Series) whose survival in spite of extremely adverse gross findings at operation far exceeded expectations.

We present herein a series of 14 patients with fibrolamellar hepatoma treated during more than

It remained for Farhi and associates in their exhaustive retrospective analysis of hepatomas in

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young people at the University of Colorado (5) to clarify questions that had been unanswered at that institution for almost two decades. Ten (44 per cent) of the 23 hepatomas seen in patients less than 35 years old between 1963 and 1981 had been of the fibrolamellar variety, including four treated on the general surgical service. The hepatic transplantation team had treated the six other patients with partial hepatic resection (Patients No. 1, 2, 3 and 4, Table I) or with total hepatectomy and orthotopic hepatic transplantation (Patients No. T1 and T2, Table I).

University of Pittsburgh series. By 1981, the articles by Craig and Berman and their co-workers had been published (3, 4). There was no longer any ambiguity about the diagnosis of fibrolamellar hepatoma and all tumors of the liver were looked at by the pathologists with this diagnosis in mind. In the three years between January 1981 and December 1983, four fibrolamellar hepatomas were removed by partial hepatic resection. In addition, four complete livers containing fibrolamellar hepatomas were removed from patients who underwent orthotopic transplantation of the liver.

Decisions about subtotal hepatectomy versus transplantation. Subtotal hepatectomy was considered the procedure of choice. If it was technically possible to encompass the tumor without devitalizing the residual hepatic remnant, this was done. The operation of right trisegmentectomy which became a standardized procedure less than a decade ago (6) was used in six instances (Table I). The first reported left hepatic trisegmentectomy was used for a nine year old child (Patient No. 4) with a fibrolamellar hepatoma (7) and this same operation was used later for an adult (Patient No. 8, Table I). In the early instances, the sheer bulk of the tumors in those patients undergoing partial hepatectomy and the proximity of the lesions to portal triad structures or the major outflow veins made it difficult until the pathologic factors were later clarified to understand why the patients were alive and free of tumor many years later.

Highly unfavorable conditions were also present in four of the patients undergoing total hepatectomy and transplantation. In Patient No. T1, the tumor probably was cut through at the level of the suprahepatic vena caval cuff. In Patient No. T2, a tumor thrombus was found floating in the retrohepatic inferior vena cava. Its superior end was pulled back from the heart into the operating field. The portal vein was completely occluded by a tumor less than a centimeter from the site of

transection in Patient No. T3. Patient No. T4, who had undergone a right trisegmentectomy four and one-half years earlier at another institution, had multiple metastases in the remaining lateral segment with invasion of the left diaphragm in the raw area encompassed by the left triangular ligament. Most of the left diaphragm was taken out with the specimen and replaced with Marlex mesh (polypropylene).

Chemotherapy. Adjuvant chemotherapy with cyclophosphamide, vincristine and actinomycin-D was given prophylactically to Patient No. 2 after partial hepatectomy. Patient No. 5 was given the same drugs plus Adriamycin (doxorubicin hydrochloride) because a tumor was found at the site of parenchymal transection as well as the site of adhesions to the diaphragm.

Because of pulmonary metastases, chemotherapy with Adriamycin, 5-fluorouracil, mitomycin and vincristine was given to Patient No. T4 15 months after total hepatectomy and transplantation. Seven months later, the drug treatment was changed to dichloromethotrexate.

RESULTS

After partial hepatectomy. None of the seven patients with clean surgical margins and follow-up periods of 11 months to more than 16 years have had a recurrence (Table I). Patient No. 5 with a tumor that was incompletely removed had slow growing recurrences within an eight month period. After three and one-half years, metastases in the celiac lymph nodes, on the thoracic and abdominal surfaces of the diaphragm and in the middle part of the mediastinum, were removed through separate abdominal and thoracic incisions. No gross tumor was left behind.

After replacement of the liver. Metastases from the fibrolamellar hepatomas were directly responsible for the deaths of two patients 14 and more than 32 months after transplantation. These recipients were not given chemotherapy. A third patient who underwent hepatic transplantation (Patient No. T4) had already survived for four and one-half years after undergoing a right trisegmentectomy at another institution. She had pulmonary metastases develop one year after removal of the hepatic remnant and hepatic replacement. The pulmonary metastases have been moderately responsive to chemotherapy, and she remains in good condition 31 months after transplantation.

The other three surviving transplant recipients have no obvious metastases after 12, 17 and 40 months. However, it is far too soon to pronounce

TABLE I.—CLINICAL FEATURES

Patient No.	Age, yrs., race and sex	Date of resection	Extent of resection	Time postresection to metastases	Adjuvant therapy postoperatively	Survival in months
PARTIAL HEPATECTOMY						
1	20/W/F	7/20/68	Right trisegmentectomy	—	None	196
2	9/W/M	9/28/73	Right trisegmentectomy	—	Multiple chemo.	134
3	31/W/F	12/11/79	Right trisegmentectomy	—	None	59
4	9/W/M	6/13/80	Left trisegmentectomy	—	None	53
5	40/W/M	4/13/81	Right trisegmentectomy	Tumor at margins	Multiple chemo.	44 (Living with disease)
6	14/W/M	2/03/83	Right trisegmentectomy	—	None	21
7	33/I/M	12/20/83	Right trisegmentectomy	—	None	11
8	40/W/M	12/30/83	Left trisegmentectomy	—	None	11
TRANSPLANTATION						
T1* (OT 14)	16/W/F	3/17/68	Total	12 Months†	None	14 (Died)
T2 (OT 172)	24/W/M	3/10/80	Total	30 Months‡	None	32½ (Died)
T3 (OT 194)	26/W/M	7/12/81	Total	—	None	40
T4 (OT 231)	23/W/F	4/18/82	Total§	13 Months	Multiple chemo.	31 (Living with disease)
T5 (OT 300)	25/W/M	6/06/83	Total	—	None	17½
T6 (OT 338)	24/W/M	11/06/83	Total	—	None	12½

*OT, Orthotopic Transplantation; OT code numbers have been used in previous publications

†Metastases proved at time of retransplantation. Death, two months later, was caused by a duodenal fistula. Metastases in diaphragm, retroperitoneal space and hepatic graft.

‡Extensive intraperitoneal seeding with "frozen" pelvis. No tumor in graft.

§Right trisegmentectomy in December 1977. Hepatectomy completed with orthotopic transplantation four and one-half years later. Has multiple pulmonary metastases.

I, Indian; W, white; F, female; M, male, and chemo., chemotherapy.

them safe since the diagnosis of recurrence had been made from one to two and one-half years after transplantation (Table I).

DISCUSSION

The results in our experience with subtotal hepatic resections have verified the expectations of good survival reported by others (3, 4). It is noteworthy that not a single recurrence has been seen among the seven patients with lesions that could be removed completely with partial hepatectomy.

An eighth patient, with a tumor that was incompletely removed, has survived for more than three and one-half years and has undergone late resection of metastases in the abdomen and chest. The presence of survivors for more than a decade after undergoing surgical treatment has provided retrospective justification for procedures which at the time were considered overly zealous by some.

The less satisfactory behavior of patients undergoing total hepatectomy and hepatic transplantation was not surprising. By definition, such patients were rejects for partial hepatectomy by virtue of the more extensive disease. However, this may not be the only explanation for the poorer results. An additional adverse factor after

hepatic transplantation has been performed may have been the necessity for continuous immunosuppression.

More than 15 years ago, consequences of iatrogenic weakening of the immunologic surveillance apparatus with immunosuppression were examined in several oncologic situations (8). The possible effects included: 1, an increased incidence of *de novo* malignant conditions in patients without previous neoplasia; 2, a greater ability to transplant malignant cells which could become autonomous in a host which normally would reject them, and 3, an augmentation or promotion of metastases which might otherwise have failed to become established.

In the succeeding years, the evidence that immunosuppression can be influential in the first two of the aforementioned circumstances has been so overwhelming that it may be naive to believe that the same does not apply in the third. Even with the possibility that immunosuppression may have contributed to the growth of metastases, the meaningful prolongation of life that has been achieved by transplantation of the liver in those patients with fibrolamellar hepatoma and the fact that as many as one-half of the recipients may have been cured justify the continuing efforts at replacement of the liver for this type of lesion

as has been suggested in an earlier publication (9).

SUMMARY

Eight patients with fibrolamellar hepatoma were treated with subtotal hepatic resections from 11 months to more than 16 years ago. Although the resections were at the extreme limits of technical feasibility, recurrences have been observed in one patient; none of the patients died.

Six other patients with fibrolamellar hepatomas were treated with total hepatectomy and orthotopic transplantation of the liver. The incidence of a recurrence of the tumor has been 50 per cent and two of the six patients have died of metastases.

The poorer incidence of tumor control may reflect the advanced nature of the lesions at surgical removal, an adverse effect of immunosuppression upon natural host defenses against malignant growths or a combination of both. Nevertheless, continued use of replacement of the liver to treat this hepatoma variant seems justified.

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