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## Liver Resection for Hepatic Adenoma

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### Abstract

Between 1970 and 1978, eight hepatic adenomas were resected. Four of the eight patients took oral contraceptive pills before the hepatic adenoma was identified; one patient was male. Four patients had evidence of bleeding at the time of presentation. The original histologic diagnosis in the first five patients was malignant hepatoma. There has been no known recurrence of tumor and all patients are well. The use of oral contraceptives in these patients has been prohibited. Formal anatomic resection is recommended for hepatic adenoma when this procedure can be done without mortality or serious morbidity; however, in the future, less drastic treatments, such as occlusion of the hepatic arterial circulation to the tumor or discontinuation of oral contraceptives, may prove as effective as tumor resection.

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During the eight-year period 1970 to 1978, eight patients with hepatic adenoma have been treated on the surgical service of the University of Colorado Medical Center, Denver. They are the subject of this report.

### Subjects and Methods

Seven of the eight patients who were treated for hepatic adenomas between 1970 and June 1978 were female, and one was male (Table). Their ages at the time of operation ranged from 16 to 30 years. Six had fever as one of the presenting symptoms, six had abdominal pain, and three had palpable upper abdominal masses. One patient (case 6) was found to have gallstones and underwent her first operation elsewhere for presumed subacute cholecystitis; four additional patients (cases 3, 4, 5, and 8) underwent diagnostic laparotomies at other hospitals before the hepatic tumor was discovered. In two patients (cases 4 and 8), there was bleeding into the tumor preoperatively, with associated anemia; in two patients (cases 1 and 2), there was intraperitoneal hemorrhage and hypovolemic shock. Two patients had protracted diarrhea (cases 1 and 5) that was thought due to amebic colitis in one patient, whose home was in Mexico.

A history of oral contraceptive use prior to operation was elicited in four of the seven female patients, for durations of a few months to eight years. As far as we know, the single male patient had never taken androgens of any kind.

Radionuclide hepatography and hepatic angiography were done in some of the patients prior to transfer to Denver. In one patient (case 5) whose angiography was done in Denver, the findings were considered most consistent with malignant hepatoma.

In all patients, the tumor was single, rather than multicentric grossly and the tumor in all cases was greater than 10 cm in diameter. All eight patients were treated by formal hepatic

resection: right hepatic lobectomy in four cases, trisegmentectomy (extended right lobectomy) in three, and left lobectomy in one.

## Results

In the first two patients, subphrenic abscesses developed following operation; there have been no postoperative complications in the six patients operated on during the last seven years. The initial histologic interpretation of the resected tumors was malignant hepatoma in the first five cases. The first two patients were each given fluorouracil chemotherapy for approximately three years following operation. In 1974, the first five cases were reviewed and in all cases, the revised diagnosis was hepatic adenoma. The initial histologic diagnosis in the last three Denver cases was hepatic adenoma.

None of the patients have taken oral contraceptive pills since operation. None are known to have recurrent tumor and all are well one-half to eight years after resection of their tumors.

## Comment

In a recent review of solid liver tumors,<sup>1</sup> 323 of the 621 collected cases were primary liver tumors and 111 (34%) were benign; the records were reviewed from 127 patients at least 16 years of age who had undergone resections of primary liver tumors in 49 hospitals. Histologic review of 119 of these 127 patients resulted in reclassifying nine cases originally called malignant hepatoma as hepatic adenoma. The authors of this review commented that in no area of liver tumors is there more controversy concerning classification than in the area of benign liver tumors. Although Edmondson,<sup>2</sup> Ishak and Rabin,<sup>3</sup> and Kay and Schatzki<sup>4</sup> have described the histology and ultrastructural characteristics of the hepatic adenoma, and although in fact Edmondson's 1958 classification<sup>2</sup> is still very satisfactory, there has been chronic misunderstanding of this material and corresponding difficulty with nomenclature.<sup>5-7</sup> The initial misdiagnosis of our first five cases as malignant hepatomas, rather than hepatic adenomas, is clearly not unique.

Although the hepatic adenoma was observed prior to the introduction of oral contraceptives in 1960,<sup>2</sup> the apparent increase in recognition of this tumor in recent years has suggested that oral contraceptives may have a part in the natural history of the hepatic adenoma. In 1973, Baum et al<sup>8</sup> suggested that the development of benign liver tumors might be caused by the use of oral contraceptive pills and since then, there have been many reports concerning a possible relationship between oral contraceptives and hepatic adenoma,<sup>9-22</sup> focal nodular hyperplasia,<sup>21,23-25</sup> and malignant hepatoma.<sup>26</sup> On the other hand, Guzman et al<sup>13</sup> have pointed out that the association described by Baum and co-workers is not found in all series of cases; in fact, only three of ten patients of Guzman et al having hepatic adenomas had taken oral contraceptives before the development of their tumors. Four of our eight patients had a negative "pill" history. On the other hand, the reports of tumor regression following discontinuation of oral contraceptives<sup>10,13,16,20</sup> and tumor recurrence in two patients who continued oral contraceptives after apparently complete resections of the primary tumors<sup>17</sup> would argue for a promoting role of oral contraceptives. Edmondson et al<sup>12</sup> have suggested estrogens, particularly mestranol, rather than progesterones as the major tumor promoter, but this concept remains controversial.

Four of the eight Denver patients had fever and upper abdominal pain as the main presenting symptoms. One of our patients had gallstones (case 6) and was initially operated at another hospital for that problem, but none of the other seven patients were originally thought to have cholecystitis, although cholecystitis was part of the differential diagnosis in the early phases of evaluating most of these patients.

Four of our patients (cases 1, 2, 4, and 8) had evidence of bleeding into the tumor or peritoneal cavity and at least two of these patients had previously taken oral contraceptives; the contraceptive history is not known in one of these patients (case 1). It has been suggested that oral contraceptives may increase the frequency of bleeding in the hepatic adenoma<sup>12</sup>; the fact that only two of eight patients (25%) hemorrhaged from the tumor into the free peritoneal cavity (cases 1 and 2) is a lower frequency of hemorrhage than has been observed in some other series.<sup>8,11,12,18</sup>

Exploratory laparotomy was done at other hospitals in five of our eight patients, resulting in the diagnosis of hepatic tumor. In two of these patients, the wound was infected at the time of reoperation for tumor resection in Denver; one patient underwent trisegmentectomy (case 4) and the other patient, right lobectomy (case 6), both with wide drainage, and neither had postoperative infections.

In our first patient, needle biopsy of the liver was done at another hospital for diagnosis and the biopsy specimen was interpreted as consistent with mild hepatitis. The question of needle biopsy for diagnosis of hepatic adenomas has been recently reviewed by Terblanche,<sup>23</sup> and he agreed with the suggestion of Edmondson et al<sup>13</sup> that this procedure may not be so likely to cause hemorrhage as was originally feared. Nevertheless, a skilled and experienced surgical pathologist is needed if the needle biopsy is to have any real diagnostic value.

The central question in treating patients with hepatic adenoma is whether withdrawal of oral contraceptives is sufficient treatment for those patients who are taking such medication, or whether destruction of the tumor is necessary. In patients with no history of oral contraceptive ingestion, destruction of the tumor is the only therapeutic option other than observation in the hope of spontaneous tumor regression.

Although some hepatic adenomas will involute following withdrawal of oral contraceptive hormones,<sup>10,11,13,14,16,17,20</sup> removal of the tumor provides the most definitive therapy, if removal can be done without significant morbidity or mortality. Removal eliminates concern about the possibility of observing a malignant tumor that has been incorrectly diagnosed as benign and removal of the tumor eliminates the risk of hemorrhage from the tumor during a period of observation.

If the patient with hepatic adenoma has symptoms or signs of hemorrhage, mechanical control of the bleeding is urgently or emergently needed to save the patient's life. Terblanche<sup>23</sup> has suggested laparotomy, frozen section diagnosis of the tumor, and ligation of either the right or left hepatic artery as the initial treatment of the patient with active hemorrhage into the peritoneal cavity; he has suggested radiologic embolization of the hepatic artery for the patient with established diagnosis and pain without evidence of life-threatening hemorrhage.

The eight major anatomic resections during an eight-year period in Denver were carried out using techniques that have been described previously.<sup>27</sup> There was no mortality, no serious morbidity, and there is no known recurrence of tumor. At the present time, formal anatomic resection of the benign hepatic adenoma is recommended as the preferred treatment, regardless of the manner of presentation of this tumor, when such resection can be carried out without mortality or significant morbidity. However, in the future, less drastic ways of treating these tumors, including angiographic embolization, hepatic artery ligation, enucleation of the tumor, and discontinuing oral contraceptives, may prove to be as effective as anatomic hepatic resection. Oral contraceptive medications should be permanently prohibited in all patients with hepatic adenomas.

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## References

1. Foster, JH.; Berman, MM. Solid Liver Tumors: Major Problems in Clinical Surgery. Vol. 22. Philadelphia: WB Saunders Co; 1977.
2. Edmondson, HA. Tumors of the liver and intrahepatic bile ducts, in Atlas of Tumor Pathology. Armed Forces Institute of Pathology; 1958. section 7, fascicle 25
3. Ishak KG, Rabin L. Benign tumors of the liver. *Med Clin N Am* 1975;59:995–1013. [PubMed: 167242]
4. Kay S, Schatzki P. Ultrastructure of a benign liver cell adenoma. *Cancer* 1971;28:755–762. [PubMed: 4328925]
5. Galloway SJ, Casarella WJ, Lattes R, et al. Minimal deviation hepatoma: A new entity. *Am J Roentgenol* 1975;125:184–192.
6. Ishak KG. Standard nomenclature for primary hepatic tumors. *JAMA* 1977;237:1559–1560.
7. Mays ET. Standard nomenclature for primary hepatic tumors. *JAMA* 1976;236:1469–1470. [PubMed: 989111]
8. Baum JK, Holtz F, Bookstein JJ, et al. Possible association between benign hepatomas and oral contraceptives. *Lancet* 1973;2:926–929. [PubMed: 4126557]
9. Ameriks JA, Thompson NW, Frey CF, et al. Hepatic cell adenomas, spontaneous liver rupture and oral contraceptives. *Arch Surg* 1975;110:548–557. [PubMed: 1131000]
10. Anderson PH, Packer JT. Hepatic adenoma: Observations after estrogen withdrawal. *Arch Surg* 1976;111:898–900. [PubMed: 182106]
11. Christopherson WM, Mays ET. Liver tumors and contraceptive steroids: Experience with the first one hundred registry patients. *J Natl Cancer Inst* 1977;58:167–171. [PubMed: 189044]
12. Edmondson HA, Henderson B, Benton B. Liver-cell adenomas associated with use of oral contraceptives. *N Engl J Med* 1977;294:470–472. [PubMed: 173996]
13. Edmondson HA, Reynolds TB, Henderson B, et al. Regression of liver cell adenomas associated with oral contraceptives. *Ann Intern Med* 1977;86:180–182. [PubMed: 835939]
14. Fechner RE. Benign hepatic lesions and orally administered contraceptives: A report of seven cases and a critical analysis of the literature. *Hum Pathol* 1977;8:255–268. [PubMed: 192659]
15. Guzman IJ, Gold JH, Rosai J, et al. Benign hepatocellular tumors. *Surgery* 1977;82:495–503. [PubMed: 197654]
16. Kay S. Nine year followup of a case of benign liver cell adenoma related to oral contraceptives. *Cancer* 1977;40:1759–1760. [PubMed: 198104]
17. Klatskin G. Hepatic tumors: Possible relationship to use of oral contraceptives. *Gastroenterology* 1977;73:386–394. [PubMed: 194813]
18. Mays ET, Christopherson WM, Mahr MM, et al. Hepatic changes in young women ingesting contraceptive steroids. *JAMA* 1976;235:730–732. [PubMed: 175178]
19. McAvoy JM, Tompkins RK, Longmire WP Jr. Benign hepatic tumors and their association with oral contraceptives. *Arch Surg* 1976;111:761–767. [PubMed: 180932]
20. Ramseur WL, Cooper MR. Asymptomatic liver cell adenomas: Another case of resolution after discontinuation of oral contraceptive use. *JAMA* 1978;239:1647–1648. [PubMed: 204807]
21. Vana J, Murphy GP, Aronoff BL, et al. Primary liver tumors and oral contraceptives. *JAMA* 1977;238:2154–2158. [PubMed: 199752]
22. Walt AJ. Cysts and benign tumors of the liver. *Surg Clin N Am* 1977;57:449–464. [PubMed: 322342]
23. Catalano PW, Early ME, Topolosky HW, et al. Focal nodular hyperplasia of the liver: Report of six patients. *Cancer* 1977;39:587–591. [PubMed: 837340]

24. Ross D, Pina J, Mirza M, et al. Regression of focal nodular hyperplasia after discontinuation of oral contraceptives. *Ann Intern Med* 1976;85:203–204. [PubMed: 942141]
25. Terblanche J. Liver tumors associated with the use of contraceptive pills. *S Afr Med J* 1978;53:439. [PubMed: 79226]
26. Pryor AC, Cohen RJ, Goldman RL. Hepatocellular carcinoma in a woman on long-term oral contraceptives. *Cancer* 1977;40:884–888. [PubMed: 196746]
27. Starzl TE, Bell RH, Beart RW, et al. Hepatic trisegmentectomy and other liver resections. *Surg Gynecol Obstet* 1975;141:429–437. [PubMed: 1162576]

### Clinical-Pathologic Findings in Eight Patients With Hepatic Adenoma

Patient/Age, yr/Sex	Year of Operation	Initial Symptoms and Signs	Oral Contraceptive History Preoperatively	Operation	Original Histologic Diagnosis
1/27/F	1970	Fever, vomiting, jaundice, diarrhea, anemia, shock	1964 to 1970	Right lobectomy	Hepatoma
2/25/F	1970	Acute abdomen, anemia, shock	Unknown	Trisegmentectomy	Hepatoma
3/25/M	1971	Fever, epigastric pain		Left lobectomy	Hepatoma
4/19/F	1972	Fever, right upper quadrant pain, mass, anemia	None	Trisegmentectomy	Hepatoma
5/29/F	1974	Fever, right upper quadrant mass, diarrhea	Intermittent 1966 to 1974	Right lobectomy	Hepatoma
6/30/F	1975	Fever, right upper quadrant pain, gallstones	20 months (1966 to 1969)	Right lobectomy	Adenoma
7/16/F	1975	Fever, right upper quadrant pain	None	Trisegmentectomy	Adenoma
8/19/F	1977	Right upper quadrant mass, anemia	Intermittent 1975 to 1976	Right lobectomy	Adenoma