

Primary Carcinoma of the Gallbladder

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The records of patients with primary carcinoma of the gallbladder treated at Charity Hospital, New Orleans, Louisiana, from 1965 through 1978 were reviewed. Eighty patients had histologically proven primary carcinoma of the gallbladder. Sixty-nine patients had sufficient data available for evaluation. Only one patient (1.4%) was clinically free of disease at five years. Surgical procedures were performed in 45 of the 69 patients. The remainder of the patients had their disease proved at autopsy. Thirty-five patients had widespread metastatic disease at the time of operation. None of these patients survived more than one year. Only 10 patients had potentially curable lesions. The diagnosis of carcinoma of the gallbladder was not made at operation in eight of these patients. The only five-year survivor was in this subgroup. This patient had papillary adenocarcinoma confined to the mucosa and muscularis, and had a cholecystectomy alone. This report reinforces the difficulty in diagnosis and the dismal prognosis for patients with primary carcinoma of the gallbladder. Intraoperative examination of the gallbladder, earlier operation for documented gallbladder disease, and more aggressive surgical therapy should improve survival figures.

PRIMARY CARCINOMA OF THE GALLBLADDER is generally described as an unusual and an uncommon malignancy. However, it is the most common biliary tract malignancy, and it represents the fifth most common malignant disease of the digestive tract.⁷ The reported incidence of gallbladder cancer in patients who have operations on the biliary tract is approximately 1% in most series.^{2,3,15} The dismal outlook for these patients is reflected by the poor survival data that have been reported.

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Clinical Material

There were 25 males (36%) and 44 females (64%). The mean age was 68.2 years, with a range of 20 to 90 years. Two patients were in their twenties; both were

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women, and their ages were 20 and 21 years. Seventy-five per cent of the patients were greater than 60 years old at the time of diagnosis.

Clinical Findings

The presence or absence of gallstones was documented in 48 patients. In this subgroup, 60.4% of patients had gallstones. One patient had coexistent ulcerative colitis. Two patients had concomitant carcinomas at the time of diagnosis: a female with mucinous adenocarcinoma of the breast and a male with squamous carcinoma of the face. The youngest patient, a 20-year-old female, had documented IgA and IgE deficiencies.

The most common presenting complaint was pain in the right upper quadrant, or epigastrium, and was present in 36 patients (52%). Nausea and vomiting (49%), weight loss (44%), and jaundice (40%) were the next most common presenting symptoms (Table 1). One patient presented with symptoms related to an umbilical abscess, which proved subsequently to be a metastatic lesion.

The majority of patients (56.5%) had symptoms for two months or less. Eighty per cent had symptoms for less than one year. Nine patients had known gallbladder disease proved by oral cholecystography. One of these patients had been followed for six years. One patient had a history of "unexplained jaundice" 20 years prior to the diagnosis of gallbladder carcinoma.

Hepatomegaly was noted in 33 patients (45%) and represents the most common physical finding (Table 2). Jaundice was present in 40% of patients, and tenderness to palpation was noted in 36% of patients.

There were no laboratory findings that were diagnostic of gallbladder carcinoma. Hyperbilirubinemia, ranging from 2.1 mg/dl to 46.5 mg/dl, was present in 30 patients (44%). Hepatic enzyme levels were elevated in all advanced cases. Anemia, leukocytosis, and hypoalbuminemia were other frequent laboratory abnormalities.

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Oral cholecystography was performed in 24 of 69 patients. The gallbladder was not visualized in 20 patients, showed gallstones in three patients, and was reported as normal in one patient. A filling defect suggestive of carcinoma was not seen in any patient. Intravenous cholangiography was performed in ten patients. Gallstones were seen in two patients, common duct obstruction was seen in one patient, and nonvisualization was noted in the remainder. Upper gastrointestinal contrast-barium x-ray studies were abnormal in 16 of 46 patients studied. Gastric outlet obstruction was seen in eight patients, and external duodenal compression was seen in six patients. Three patients had gastric ulcers identified. A barium enema x-ray examination was performed in 30 patients. Two patients had a colon obstruction demonstrated at the hepatic flexure.

Percutaneous transhepatic cholangiography was performed in two patients. Both studies showed common bile duct compression and obstruction. A percutaneous liver biopsy was performed in seven patients, three of whom demonstrated metastatic carcinoma. The common bile duct was unable to be cannulated in all patients (5) in whom endoscopic retrograde cholangiopancreatography was attempted. A liver scan revealed evidence of metastatic disease in 14 of 21 patients studied. One patient had a right upper quadrant mass identified by ultrasonography. Selective angiography was performed in one patient, the correct diagnosis having been suspected, based on displacement of hepatic and portal blood vessels. A summary of the radiologic findings is given in Table 3.

Treatment and Results

Forty-five of the 69 patients reviewed had surgical procedures performed (Table 4). The diagnosis of carcinoma of the gallbladder was the major preoperative diagnosis in only three of these patients. The major preoperative diagnosis in the remainder of the patients was cholelithiasis (9), carcinoma of the pancreas (9), carcinoma of the liver (9), obstructive jaundice—un-

TABLE 2. Presenting Physical Findings (n = 69).

Findings	Number of Patients	Per Cent
Hepatomegaly	33	48
Jaundice	28	41
Abdominal tenderness	25	36
Right upper quadrant mass	14	20
Cachexia	9	13
No signs	4	6

known etiology (8), acute cholelithiasis (5), and not stated (2).

Fifteen patients had exploratory laparotomy and biopsy only. Cholecystectomy was performed in 15 patients. In eight of these patients the diagnosis of carcinoma was not suspected until it was demonstrated on permanent histologic section. The one five-year survivor in this series was in this group. One patient had a cholecystectomy combined with right hepatic lobectomy and regional node dissection, and one patient had cholecystectomy with gallbladder bed hepatic wedge resection, in what were felt to represent curative procedures. These procedures were performed after the gallbladder had been opened in the operating room and a carcinoma was identified. The operative mortality for all procedures was 17.7%.

Thirteen patients received postoperative chemotherapy. Seven patients received intravenous 5-fluorouracil, two patients received intra-arterial 5-fluorouracil, and two patients received intravenous 5-fluorouracil, methotrexate, vincristine, and cytoxan. One patient received bleomycin and cytosine arabinoside. Subjective palliation was reported in three of the patients who received intravenous 5-fluorouracil alone.

The most common histological type of primary gallbladder carcinoma was adenocarcinoma (82.2%), and of these, two were papillary adenocarcinoma. There were five cases of squamous cell carcinoma, and there were four cases classified as undifferentiated carcinoma. The tumor was felt to be confined to the gallbladder in 11 patients. The tumor was confined to the mucosa and muscularis in only one patient, the long-term survivor.

Invasion of the liver at the gallbladder bed was the most common area of spread in this series (Table 5). Regional metastasis to the porta hepatis and the pericholedochal nodes was common. Sites of distant metastases included small bowel, bone, adrenals, ovary, bladder, umbilicus, and thyroid.

The overall five-year survival was 1.4%. The mean survival was 4.5 months. Causes of death were varied, but were most frequently secondary to inanition and hepatic failure secondary to diffuse carcinomatosis.

TABLE 1. Presenting Symptoms (n = 69).

Symptoms	Number of Patients	Per Cent
Right upper quadrant and epigastric pain	36	52
Nausea and vomiting	30	43
Weight loss	27	39
Jaundice	24	35
Weakness, fatigue	17	25
Fatty food intolerance	12	17
Fever	7	10

TABLE 3. *Roentgenographic Studies*

Radiologic Study	Number of Patients	Per Cent
Oral Cholecystogram	24	35
Gallstones present	3	4
Gallbladder nonvisualized	20	29
Normal visualization	1	1
Intravenous cholangiogram	10	14
Gallbladder nonvisualized	7	10
Gallstones present	2	3
Common duct obstruction	1	1
Transhepatic cholangiogram	2	3
Common duct compression	2	3
Liver scan	21	30
Metastatic disease	14	20
Nonspecific hepato-cellular disease	2	3
Normal	5	7
Angiography	1	1
Hepatic arterial & portal venous displacement	1	1
Ultrasound	1	1
Right upper quadrant mass	1	1
Upper gastrointestinal series	46	67
Gastric outlet obstruction	8	12
External duodenal compression	6	9
Normal	32	

Discussion

Primary carcinoma of the gallbladder presents the surgeon with a most difficult and challenging situation. Its cause is unknown, and a correct preoperative diagnosis is seldom made. Despite the advances in modern medicine, survival rates remain frustratingly low.

The etiologic factors most often implicated are gallstones and chronic inflammation of the gallbladder. Balaroutsos et al.³ noted the presence of gallstones in 77% of patients, while Priehler and Crichlow,¹² in a review of the literature, reported a 73.9% incidence in 2,000 cases. Sixty per cent of patients in our series had associated gallstones.

An association between primary carcinoma of the gallbladder and chronic ulcerative colitis had been reported.¹⁴ One patient in this series had both diseases.

The signs and symptoms of carcinoma of the gallbladder frequently are those of advanced malignant disease and unfortunately represent unresectable lesions. The presence of obstructive jaundice and weight loss are particularly ominous. The presentation of an early, potentially curable gallbladder carcinoma is usually identical to that of chronic cholecystitis and cholelithiasis, and, thus, a correct preoperative diagnosis is extremely rare. Pehler and Crichlow¹² reported a mean correct preoperative diagnosis of 8.6%. In this

series, 4.3% (3 patients) had the correct preoperative diagnosis.

The majority of patients in this series reported symptoms for only two months or less. However, nine patients had nonvisualizing oral cholecystograms from six months to six years prior to diagnosis. Other reports^{4,11,15} demonstrate an even higher percentage of patients (up to 50%) with symptoms attributable to gallbladder disease of greater than one year's duration.

Laboratory and radiological studies are seldom helpful in the diagnosis of gallbladder carcinoma. Liver function studies were normal in all cases of this series in which the carcinoma was confined grossly to the gallbladder.

The presence of obstructive jaundice in conjunction with other findings such as right upper quadrant mass and weight loss may arouse suspicion of gallbladder carcinoma, but this is certainly nonspecific.

Although gallbladder carcinoma has been demonstrated by a filling defect on oral cholecystography,¹² this is an unusual finding;^{4,13} the high reported rate of nonvisualization is the probable explanation. Oral cholecystography resulted in 83% nonvisualization for those patients studied in this series. In no case did this study help to differentiate between malignant and nonmalignant disease. Several reports^{4,5,11} have emphasized that abnormalities on an upper gastrointestinal series usually indicate late disease. Fourteen of 46 patients in this series demonstrated either lateral compression of the duodenum or gastric outlet obstruction on upper gastrointestinal x-rays. All of these patients were later found to have large unresectable tumors.

Olken and colleagues¹⁰ reported a case of primary carcinoma of the gallbladder in a nonjaundiced patient, correctly diagnosed by ultrasonography. Ultrasonography was performed in only one patient in this series, and a nonspecific right upper quadrant mass was identified.

TABLE 4. *Operative Procedure (n = 45)*

Operation	Number of Patients	Per Cent
Exploratory laparotomy and biopsy only	15	22
Cholecystectomy only	8	12
Cholecystectomy, common bile duct exploration	5	7
Cholecystectomy, right hepatic lobectomy, regional lymphadenopathy	1	1
Cholecystectomy, hepatic bed excision	1	1
Cholecystostomy	4	6
Choledochoduodenostomy or jejunostomy	3	4
Gastrojejunostomy	1	1
Hepatic artery cannulation	2	3
Partial colectomy	1	1
Other procedures	4	6

TABLE 5. Sites of Extension and Metastasis (n = 69)

Location	Number of Patients	Per Cent
Liver (gallbladder bed)	39	57
Porta hepatis	31	45
Pericholedochal lymph nodes	29	42
Lung	9	13
Duodenum	8	12
Colon	6	9
Pancreas	5	7
Stomach	3	4
Small bowel	3	4
Bone	2	3
Other	12	17

The most common areas of initial spread in this series were the gallbladder bed, the porta hepatis, and the pericholedochal nodes. This was not different from the modes of spread reported by others.^{2,4,6,8,11}

At the time of exploration, 70 to 80% of patients with gallbladder carcinoma are found to be nonresectable.^{4,9} Successful resection for cure is generally limited to those cases in which the carcinoma was not noted at operation and was only later diagnosed by pathologic examination. Eight patients in this series had a cholecystectomy alone for presumed benign disease. In none of these patients was the gallbladder opened and examined at the time of operation. The only five-year survivor in this report was in this subgroup.

Only two patients in this series had cholecystectomy combined with regional resection. Neither patient survived five years. Piehler and Crichlow,¹¹ Adson,¹ and others^{7,13,15} have recently made a plea for cholecystectomy combined with removal of tissue along the known paths of spread in those cases in which grossly localized carcinoma is found. To date, there has been no reported series in which cholecystectomy combined with hepatic wedge resection and regional lymphadenectomy for early carcinoma of the gallbladder have been given a thorough evaluation.

The five-year survival rate of 1.4% in this report does

not differ greatly from other investigations, which yield from 0 to 10% survival, with an average of 4.3%.^{4,6,7,12,13}

The extremely dismal survival rates for carcinoma of the gallbladder emphasize the need for a more aggressive approach. The gallbladder should be opened and examined in the operating suite in every cholecystectomy, and suspicious lesions should be submitted for immediate histologic examination. Strong consideration for more extensive surgery in cases of apparent localized carcinoma should be entertained. Further, earlier surgery for documented gallbladder disease, especially in elderly patients, represents the most logical prophylaxis.

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