Primary Carcinoma of the Gallbladder

WILLIAM R. BELTZ, M.D.* ROBERT E. CONDON, M.D.†

From the Department of Surgery, University of Iowa College of Medicine, Iowa City, Iowa

One-hundred-and-seventeen patients with histologically proven carcinoma of the gallbladder are reviewed. The majority of the patients presented with advanced disease with extension and metastasis to the liver and to lymph nodes along the common bile duct. Four patients had localized disease recognized at the time of operation; two were treated with cholecystectomy and two with cholecystectomy and hepatic resection. There were no five-year survivals among these patients. Fourteen patients had clinically inapparent carcinoma at the time of cholecystectomy; the diagnosis being established postoperatively by histologic examination of the excised gallbladder. There were two five-year survivors in this group of patients. Both survivors had early papillary carcinoma confined to the gallbladder wall. The remaining patients with inapparent carcinoma died within three years of the time of operation with recurrent carcinoma. The present report and review of the recent literature emphasizes the poor prognosis associated with carcinoma of the gallbladder. Even with apparently localized lesions, the survival rate is extremely poor. Extended resection, while not of proven value, may improve the survival rate.

GALLBLADDER CANCER in biliary tract operations has been encountered in up to 4% of cases, with most series indicating the incidence to be about 1%.[3] Glenn[9] has stated that in patients over 65 years operated upon for cholelithiasis, 10% would be found to harbor a carcinoma of the gallbladder. The disease, while uncommon, is not rare and the poor prognosis of this tumor is widely recognized.[2]

Most patients coming to operation for suspected carcinoma of the gallbladder have advanced disease. Discovery of patients with early disease usually is fortuitous, the diagnosis of carcinoma being established only postoperatively, after histologic examination of a gallbladder excised for treatment of symptomatic cholecystitis. The further management and prognosis of patients in this clinical situation is not well established.

This report summarizes the course of patients with carcinoma of the gallbladder seen at the University of Iowa Hospitals from 1938 to 1970. It was our purpose to review the clinical features of carcinoma of the gallbladder with particular attention to the results of treatment of very early lesions by cholecystectomy.

Clinical Material

The clinical records of 117 histologically proven cases of primary carcinoma of the gallbladder were reviewed. The diagnosis had been established at operation in 103 patients; 14 were diagnosed at post mortem examination.

For the purposes of this report, the patients have been divided into four groups:

Group A (localized inapparent disease): 14 patients in whom a diagnosis of carcinoma of the gallbladder was not suspected clinically and was not made intraoperatively; cholecystectomy with or without common bile duct exploration was performed and the presence of cancer discovered later during histologic examination of the operative specimen.

Group B (localized potentially curable disease): four patients in whom the malignant nature of a localized gallbladder cancer was recognized at operation and in whom a potentially curative procedure was possible.

Group C (palliative therapy): 28 patients in whom palliative operative procedures were performed after initial exploration demonstrated disseminated carcinoma.

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* Resident in Surgery, Duke University Medical Center, Durham, North Carolina. Dr. Beltz was partially supported by a clinical fellowship awarded by the American Cancer Society.

† Professor of Surgery, The Medical College of Wisconsin, Milwaukee, and Chief, Surgical Service, VA Hospital, Wood, Wisconsin.

Reprint requests: Robert E. Condon, M.D., 8700 W. Wisconsin Avenue, Milwaukee, Wisconsin 53226.

Group D (late disease): 71 patients in whom advanced disease was found at operation or autopsy and in whom no attempt was made at palliative or definitive therapy.

The mean age of all patients was 67 years; there were 89 women and 28 men (3:1). Pain was the most frequent complaint. Jaundice and a palpable mass each were seen in more than half the patients with advanced disease and usually were present together. There were no unique clinical features of gallbladder cancer early or late in the course of the disease.

There were no diagnostic laboratory abnormalities. Serum bilirubin and alkaline phosphatase were elevated in patients with obstructive jaundice. Many patients with advanced disease had anemia, hypoalbuminemia and abnormal liver function tests. Oral cholecystograms were performed in most patients who were not jaundiced; in no case was the gallbladder visualized. Upper gastrointestinal series were performed in 77 cases; abnormalities were identified in a third of these examinations. The most common abnormality, seen in 21 patients in groups C and D, was external compression of the lateral border of the duodenum. In five patients there was a roentgenographic picture of gastric outlet obstruction which subsequently proved at operation to be due to invasion of the duodenum by tumor.

The most frequent preoperative diagnoses were cholelithiasis in early cases and pancreatic carcinoma in more advanced cases. A correct preoperative diagnosis was made in only 11 instances, a diagnostic accuracy of less than ten per cent.

The operative procedures are listed in Table 1. There were 119 operations performed in 103 patients. The operative mortality (30 days) for all procedures was 18%. Most of the patients who died postoperatively were in an advanced stage of disease (Group D) at the time of exploratory laparotomy. There were no operative deaths in Group A patients.

TABLE 1. *Operations Performed in Patients with Gallbladder Cancer*

Laparotomy and Biopsy		62
Cholecystectomy: alone	19	
with common duct exploration	7	
with right hepatic lobectomy	1	
with excision of hepatic bed	1	
Total		28
Cholecystostomy		3
Cholecystojejunostomy		3
Choledochoduodenostomy		1
Excision of biliary-enteric fistula		2
Gastroenterostomy		7
Drainage of abscess		3
Hepatic artery cannulation		3
Other procedures		7

TABLE 2. *Extent of Spread of Carcinoma at the Time of Diagnosis*

	Group B	Group C	Group D	Total
Total Patients	4	28	71	103
Liver	1	27	70	98
Common Duct Lymph Nodes	1	19	64	84
Omentum & Peritoneum	0	10	19	29
Duodenum and Stomach	0	4	10	14
Colon	0	1	11	12
Pleura & Lung	0	0	7	7
Other*	0	0	6	6

Excluding Group A, 89 patients were diagnosed at operation and 14 at postmortem examination.

* Includes intracranial metastasis (3 patients) and adrenal metastasis (5 patients).

Cholecystectomy was performed in 28 cases; in 14 patients, it was done without intraoperative recognition of the presence of carcinoma (Group A). A small group of four patients, in whom carcinoma grossly was localized to the gallbladder and was correctly diagnosed intraoperatively, had cholecystectomy as part of definitive excisional therapy for their tumor (Group B). In two of these patients no further procedures were carried out; one other patient had a right hepatic lobectomy and another had a wedge resection of the hepatic bed of the gallbladder in addition to cholecystectomy. The one postoperative death in Group B occurred in the patient in whom hepatic lobectomy had been performed. In ten further patients, cholecystectomy was carried out as a part of the operative palliation of disseminated carcinoma.

The majority of tumors were adenocarcinoma (98 of 117); of these, only three were papillary in type. There were seven epidermoid carcinomas and 12 tumors were classified as undifferentiated. The most frequent site of invasion or metastasis was to the right lobe of the liver (98 of 117) and to lymph nodes along the common bile duct (84 of 117). Many patients also had hepatic metastases at a distance from the gallbladder bed or tumor implants in the peritoneum or omentum. Direct invasion of the duodenum by tumor was found in 14 patients, the hepatic flexure of the colon was involved in 12 cases. The extent of invasion or metastasis at the time of diagnosis is summarized in Table 2.

Survival

The five-year survival rate for all patients was 1.7%. Three-fourths of the patients who had their diagnosis established preoperatively or intraoperatively had succumbed to their disease within six months. The mean survival of the four patient groups is summarized in Table 3.

The course of patients in whom the diagnosis of carcinoma was not apparent to the surgeon at the time of

TABLE 3. *Mean Survival from Time of Diagnosis (Operation) in Patients with Gallbladder Cancer*

Group A	Inapparent Disease	16.7 months*
Group B	Localized Disease	24.7 months†
Group C	Palliative Therapy	15.4 weeks
Group D	No Operative Treatment Possible	8.5 weeks

* Excludes patient dying 21 years later of unrelated cause.
† Excludes postoperative death.

operation and was established by histologic examination of the excised gallbladder is summarized in Table 4. Two of the 14 patients in this group survived more than five years; a group survival rate of 14.3%. Both survivors had papillary adenocarcinoma. In one, the tumor involved only the mucosa of the gallbladder; in the other, there was evidence of perineural spread but no involvement of the gallbladder serosa. Of the 12 Group A patients who did not survive five years, three had carcinoma confined to the gallbladder wall without serosal involvement. Recurrent gallbladder carcinoma was the cause of death in 11 of the 12 nonsurviving Group A patients. The other patient returned to the hospital 11 months after cholecystectomy with superior mesenteric artery occlusion. At laparotomy, in addition to advanced necrosis of small bowel, two small tumor implants were noted in the gallbladder bed; the patient died two days later of sepsis. Post mortem examination demonstrated additional small metastatic implants in the left liver lobe and in a splenic pedicle lymph node.

Discussion

The association of gallbladder carcinoma and cholelithiasis is well established. In his collective review, Arminski[3] found gallstones present in 73% of patients with gallbladder cancer; similar figures of stone incidence are noted in the later reviews of Strauch,[26] Litwin[17] and Hart and colleagues.[14] Gallstones were definitely present in 69% of our patients; in only four was there definite mention that stones were absent.

The etiologic relationship between gallstones and gallbladder carcinoma is unclear. Wenkert and Robertson[30] followed 781 patients with "silent gallstones" and noted that over an 11-year period only 0.4% developed carcinoma. Similarly, Lund[18] found that of 526 patients being followed with nonoperative management of asymptomatic cholelithiasis, only 1% developed a carcinoma of the gallbladder; but, most clinical reports of gallbladder cancer take pains to point out the frequent association of gallstones and gallbladder carcinoma.

The clinical features of carcinoma of the gallbladder are indistinguishable from those of cholecystitis and cholelithiasis. In the later stages of gallbladder cancer, the clinical picture is most frequently one of metastatic liver disease and obstructive jaundice. Most patients who present with early lesions have symptoms because of cholecystitis rather than their tumor. Seven of the 14 patients in our Group A (inapparent disease) presented with acute or subacute cholecystitis. The difficulty of diagnosing cancer under these circumstances is apparent.

Among our patients, 45% gave a history of symptoms of cholecystitis which had existed for more than one year prior to operation. Of those patients who were considered potentially resectable for cure (Groups A and B), 61% had a history of longstanding biliary tract symptoms. Three patients, all with advanced disease, had had a cholecystostomy up to 23 years previously as treatment of complicated cholelithiasis. The high frequency of longstanding symptoms attributable to the biliary tract in patients with gallbladder carcinoma has been noted by others.[2,3,12,16,23]

Preoperative roentgenographic studies were of little value in establishing a diagnosis of gallbladder carcinoma. Hardy and Volk[12] have described a patient in whom a subsequently proven carcinoma presented as an intramural filling defect in a visualizing oral cholecystogram. Mooring[21] has described a variant of cystic duct obstruction seen on intravenous cholangiography which he believes is diagnostic of carcinoma of the gallbladder. Although other authors[1,11] have reported the presence of gallbladder cancer in patients with normal oral cholecystograms, there were no such instances among our patients.

It is of interest that a third of our patients in whom an upper gastrointestinal series was performed showed abnormalities, the most common of which was compression of the lateral part of the duodenum. Invasion of the duodenum by tumor was documented in 14 cases and,

TABLE 4. *Clinical Features of Patients with Inapparent Carcinoma of Gallbladder (Group A)*

Age	Sex	Histologic Diagnosis	Survival (months)
83	F	Adenocarcinoma	7.5
66	F	Adenocarcinoma	14
83	F	Adenocarcinoma	9
81	M	Adenocarcinoma	23
57	F	Adenocarcinoma	4
70	F	Epidermoid carcinoma	13
83*	F	Adenocarcinoma	11
67	F	Adenocarcinoma	14
59	F	Papillary Adenocarcinoma	35
61	F	Adenocarcinoma	18
65†	F	Adenocarcinoma	34
47†	F	Undifferentiated carcinoma	10
72	F	Papillary Adenocarcinoma	alive 6 yr.
60	F	Papillary Adenocarcinoma	died 21 yr.‡

* Died of unrelated cause 11 months postop but had recurrent and metastatic carcinoma (see text).
† Received chemotherapy after recurrence of carcinoma.
‡ Death due to unrelated cause.

as previously mentioned, five of these patients had a clinical and roentgenologic picture of gastric outlet obstruction. Tanga and Ewing[27] have reported three patients with carcinoma of the gallbladder presenting as gastric outlet obstruction. Khilnani[15] has described compression of the first portion of the duodenum with loss of mucosal folds as a characteristic finding in duodenal involvement by gallbladder carcinoma. These x-ray findings occur with advanced disease and are of little help in early diagnosis of potentially curable cancers.

The most frequent sites of spread of gallbladder cancer are to the adjacent liver and to lymph nodes along the cystic and common bile ducts. In our patients, metastases to the gallbladder bed were present in 84 per cent and to lymph nodes along the common bile duct in 72%. Fahim and colleagues[6] elaborated on the mode of spread of carcinoma of the gallbladder; nodes along the common bile duct were involved in 20% of early cases which potentially were curable. Because of this finding, they recommended that operations for cure should include wedge resection of the hepatic gallbladder bed combined with en-bloc excision of lymph nodes along the common bile duct to the upper border of the duodenum. More extended resection in patients in whom the disease is grossly apparent does not increase the survival rate.[3,16,22]

Both of our long term survivors had a well differentiated papillary adenocarcinoma. Similarly, the only five-year survivor reported by Frank and Spjut[7] had a papillary adenocarcinoma as did two of the long term survivors reported by Fahim and colleagues.[5] Hart and Modan[13] have emphasized the better prognosis of papillary adenocarcinoma of the gallbladder. However, Glenn and Hayes[10] have found no influence of histologic tumor type on survival rates. In the experience of some authors,[10,18] papillary lesions are frequently anaplastic at their base.

Discovery of patients at an early stage of gallbladder cancer is fortuitous and not common. Only 17% of our patients were considered potentially curable. A similar low incidence of early lesions has been reported by others.[12,20,27,28] In many series, the only survivors are those in whom the carcinoma is not apparent at the time of operation. Both of the five-year survivors among our patients were diagnosed only by histologic examination of the excised gallbladder. Table 5 summarizes survival rates in patients with early carcinoma of the gallbladder treated by cholecystectomy. Even with early lesions, survival after cholecystectomy has been disappointing.

What can be done to improve the survival of patients having carcinoma of the gallbladder? Obviously, once dissemination from the gallbladder has occurred, even extensive resectional therapy will not improve survival. However, in those lesions which are still confined to the gallbladder and its immediate environs, extended resectional therapy should improve end results. The difficulty is in making the diagnosis when the lesion is still so confined.

Patients over 65 years have an appreciable risk of harboring a gallbladder carcinoma. If every gallbladder removed in older patients were examined by the surgeon in the operating room prior to completion of the operation, surely some "inapparent" carcinomas would be noted and extended resection of the gallbladder bed and common duct nodes could be carried out immediately. Although extended resection has done little to improve overall survival rates,[10,22] there has been an inadequate clinical trial in patients with localized carcinomas.

TABLE 5. *Results of Cholecystectomy in Treatment of Localized Gallbladder Carcinoma*

Author	Total Cases	Localized Cases	No. of 5 Year Survivors
Chandler and Fletcher[4]	66	10	2
Fahim *et al.*[5]	151	25	8*
Frank and Spjut[7]	16	16	1
Gerst[8]	132	22	7
Gradisar and Kelly[11]	41	5	1
Marcial-Rogas and Medina[19]	28	14	1
Ram[23]	47	10	0
Salwan[24]	96	15	2
Strauch[26]	70	10	3
Thorbjarnarson and Glenn[29]	90	23	3
Present Report	117	16	2
Totals	838	166	30

* Two of these patients developed recurrence more than 5 years postoperatively.

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