

# PRIMARY CARCINOMA OF THE GALLBLADDER

REPORT OF 29 CASES\*

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REPORTS<sup>1, 2</sup> ON CARCINOMA of the gallbladder show an associated cholelithiasis in from 86 per cent<sup>3</sup> to 100 per cent<sup>4</sup> of the cases. Gallstones could result from the carcinoma, or they could be precursors of the malignant condition. Metastatic carcinoma of the gallbladder does not appear to be associated with an increased incidence of cholelithiasis;<sup>5</sup> most reports show that from 50 to 70 per cent<sup>5</sup> of patients with carcinoma of the gallbladder have a past history of gallbladder disease. These facts indicate that cholelithiasis precedes carcinoma of the gallbladder and may be an etiologic factor.

Some authorities<sup>3, 6, 7</sup> advocate cholecystectomy in the presence of asymptomatic gallstones as a means of preventing carcinoma. They believe that the dangers and complications of gallbladder surgery are less serious than the possibility of the patient developing cancer. Other investigations<sup>8-10</sup> stress the extremely low incidence of carcinoma of the gallbladder in comparison to the high incidence of cholelithiasis, and therefore do not urge operation for the "silent gallstone."

The incidence of cholelithiasis from autopsy material has been reported to be from 8.4 per cent to as high as 32.5 per cent—50 per cent were found after the seventh decade. This evidence indicates to us that removal of the gallbladders in from 8.4 to 32.5 per cent of the people as a means of attempting to reduce the incidence of cancer of this organ is a questionable procedure.

Comfort, Gray, and Wilson<sup>10</sup> reported 112 patients with asymptomatic gallstones who refused cholecystectomy, and who were observed from ten to 25 years. Not one developed carcinoma of the gallbladder, although six of them did develop carcinoma elsewhere. More follow-up studies of this nature, observing the course of patients with asymptomatic gallstones, are clearly indicated.

Reports of operations for carcinoma of the gallbladder show that either patients are inoperable or that surgery did not appreciably prolong the life of the patient. Cures have been effected in only about 2.5 per cent of these patients.<sup>5</sup> Mattson,<sup>9</sup> as an example, reported no cures in 63 cases. The only exception to the uniformly low cure rate is that of Vadheim *et al.*,<sup>14</sup> who reported five-year survivals in 13 patients with cholecystic carcinoma of Broders' Grade One.

Carcinoma of the gallbladder presents several medical problems. First, the relationship of cholelithiasis to carcinoma of the gallbladder seems well established by previous reports. A second problem is whether greater familiarity

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with the usual clinical findings in these patients would result in more frequent and earlier diagnosis of this condition. Third is the question of the removal of asymptomatic gallbladder with cholelithiasis as a preventive measure for the subsequent development of carcinoma, and fourth, how treatment of this condition can be improved.

1. *Incidence.* The ratio of carcinoma of the gallbladder to cholelithiasis is impossible precisely to determine. Not every patient seen at the Clinic has a cholecystogram: hence the overall frequency of cholelithiasis is not accurately known. Furthermore, every patient with cholelithiasis does not have a cholecystectomy, and therefore the ratio of carcinoma of the gallbladder in patients who have had cholecystectomies is not necessarily an accurate reflection of this relationship.

Between 1932 and 1948 inclusively there have been 29 cases of carcinoma of the gallbladder operated on at the Cleveland Clinic. In the same period there have been 1488 cholecystectomies done. The incidence of carcinoma in relation to the number of cholecystectomies is therefore 1.9 per cent in this series. However, it must be remembered that most of the patients in whom cholecystectomies were not done were asymptomatic and had "silent" gallstones. Since carcinoma of the gallbladder is preceded by symptoms, it is probable that there were few if any patients with carcinoma in the unoperated group. The patient with carcinoma of the gallbladder is ill, and some operative procedure resulting in the diagnosis of the condition is usually done.

During the same time 350,000 new patients have been seen at the Clinic. Lam<sup>16</sup> reported 34 cases in a group of comparable size. The very fact that only 29 cases of carcinoma were found at operation suggests the relative rarity of this type of cancer.

During this same interval, a diagnosis of cholelithiasis by roentgen-ray examination was made in 4459 patients. The incidence of carcinoma of the gallbladder in relation to the incidence of cholelithiasis as determined by roentgen-ray examination is calculated to be 0.66 per cent. This indicates that cancer of the gallbladder is a relatively uncommon disease, whereas cholelithiasis is common, the ratio being 154 to 1.

The true incidence of carcinoma of the gallbladder in patients with cholelithiasis is almost certainly much lower than 0.66 per cent, since many patients with asymptomatic gallstones did not have cholecystograms. The autopsy incidence of cholelithiasis (8.4 to 32.5 per cent) has already been cited. Bockus<sup>5</sup> estimates the incidence of cholelithiasis to be 10 per cent. On this basis, with 350,000 new patients seen during this time, many patients with asymptomatic gallstones evidently did not have cholecystograms and the diagnosis of gallstones was not made. Consequently, the true ratio of neoplasm to calcareous disease of the gallbladder is probably actually less than the figure (0.66 per cent) previously cited.

Cholecystectomy still carries with it some mortality and morbidity. The operative mortality for cholecystectomy probably exceeds the incidence of carcinoma of the gallbladder. We believe that more lives would be lost postopera-

tively by routine cholecystectomy in the presence of asymptomatic gallstones than would be lost, years later, by the subsequent development of cholecystic carcinoma. It must also be remembered that the patient who dies postoperatively does so immediately, while the patient who develops neoplasm of the gallbladder will probably not do so for a considerable length of time.

The age and sex incidence in our series is presented in Table I. The sex ratio was four women to one man. No case occurred in a patient under 40 years of age, while 21 of the 29 cases were in patients over 60 years of age.

TABLE I.—*Age and Sex Distribution.*

Age	Female	Male	Total
40-49 .....	1	1	2
50-59 .....	6	0	6
60-69 .....	9	5	14
70-79 .....	7	0	7
Total .....	23	6	

2. *History.* A history of pre-existing biliary colic was obtained from 17 patients, antedating the present illness by nine months to six years. A consensus of reports<sup>5</sup> indicates that from 50 to 70 per cent of patients have a past history of benign biliary disease.

TABLE II.—*Symptoms in Primary Carcinoma of the Gallbladder.*

Symptom	Number of Cases	Average Duration of Symptom
Weight loss .....	23	5.5 months
Pain .....	21	3.5 months
Constipation .....	21	3.6 months
Nausea or vomiting .....	16	2.5 months
Jaundice .....	16	5.4 weeks
Anorexia .....	16	2.5 months
Dyspepsia .....	13	3.5 months
Weakness .....	10	5.5 months
Mass in abdomen .....	4	5 months
Fever and chills .....	3	2.2 months
Anemia .....	1	8 months
Hematemesis .....	1	6 weeks

The presenting symptoms in our series are tabulated in Table II. Weight loss and weakness were the earliest symptoms. Weight loss was present in 23 cases, the average loss of weight being 22 pounds in 5.5 months. Mattson<sup>9</sup> found that 70 per cent of his patients lost an average of 27.5 pounds. It is significant that Vadheim *et al.*,<sup>14</sup> in their series of early carcinomas in which no preoperative diagnoses were made, found that 67 per cent suffered loss of weight.

Pain was also an early and important symptom. Twenty-one patients complained of pain as a predominant symptom. In other series<sup>3, 4, 7, 9, 17-19</sup> pain has been reported in about 80 per cent. The pain was described as a dull ache located in the epigastrium in ten patients, in the right upper quadrant in nine

patients, and solely in the lower abdomen in two patients. Characteristically it began as colicky or cramplike pain in 11, then rapidly assumed a constant nature in ten patients. Radiation of pain occurred in half of the cases, spreading to the scapula, back, shoulder, chest, and in one patient to the left breast. The pain was usually of moderate severity. The average duration of this symptom was 3.5 months.

Jaundice was present in 16 cases. In a few patients it was the first symptom drawing attention to the biliary tract. The average duration of the jaundice in our series was five weeks, identical with the findings of Cooper. In all of our patients the jaundice was of the continuous, obstructive type. Jaundice most commonly was caused by obstruction of the common duct; rarely is the jaundice caused by liver metastases. Painless jaundice was present in only five patients.

Anorexia, nausea, vomiting or all three were found in 16 patients, of whom 12 also had jaundice. In no case did these symptoms, or that of dys-

TABLE III.—*Physical Findings in Carcinoma of the Gallbladder.*

Finding	Number of Cases
Palpable liver .....	22
Palpable gallbladder or mass .....	17
Nodular or hard .....	16
Fluctuant .....	1
Jaundice .....	16
Tenderness .....	14
Ascites .....	2
Elevated temperature .....	2
Metastatic lesion in skin in inguinal region .....	1

pepsia, antedate the weight loss, pain or jaundice. In addition to the symptoms mentioned, one patient complained of frothy stools, one of pyrosis, and one of diarrhea. Anemia constituted the chief complaint in one patient.

3. *Physical Findings.* In Table III, it will be seen that 22 patients had a palpable liver which was usually over 4 cm. below the costal margin. In other reports the incidence of this finding varies but little from 50 per cent; however, Vadheim, *et al.*<sup>14</sup> noted a palpable liver in only 23 per cent. A palpable mass was present in 17 patients and was found in each case to represent either the carcinomatous gallbladder or direct invasion of the liver. In no patient was the abdominal examination negative, but in three patients there was a single finding of tenderness or distention.

4. *Laboratory Findings.* Routine laboratory findings were usually non-contributory. Anemia is not a characteristic feature in this type of cancer. The average hemoglobin in 23 women was 12.5 Gm. per 100 cc., and the average in six men was 11.7 Gm. per 100 cc. The hemoglobin was below 12 Gm. in seven patients, and less than 11 Gm. in four patients. One man had a hemoglobin of 6.0 Gm.; he was found to have a pyonephrosis secondary to adjacent metastases. The leukocyte count was normal except in two patients who had a count of 20,000 per cu. mm. Prothrombin times were done in 13 patients, averaging 74 per cent.

Little mention is made in the literature regarding liver function tests in carcinoma of the gallbladder. Lam<sup>16</sup> had two patients with bromsulfalein retention, each of whom had liver extension. In our series, bromsulfalein retention was determined in four patients. Three patients without jaundice had definitely positive tests; these patients were found to have liver metastases, invasion of the portal vein, or invasion into the liver. The fourth patient had a normal test, but did have invasion of the liver.

5. *Roentgen Ray Findings.* Cholecystograms were done in 16 cases, all of which revealed non-functioning gallbladders. Twenty-three plain gallbladder films were done, disclosing three cases with opaque stones and one case with a calcified gallbladder. Reports of a normally functioning gallbladder in the presence of cholecystic cancer are indeed rare in the literature, and we have been unable to find any report of the tumor being visualized through cholecystographic dye, as is possible with a papilloma of the gallbladder.

Pressure from extension of the tumor may reveal defects in the roentgen ray examination of adjacent organs. Three patients in our series had pressure defects on the stomach or duodenum as determined by barium meal examination. Urologic examinations demonstrated pyonephrosis in one patient with metastases to the right adrenal gland, and hydronephrosis in one patient with metastases to the retroperitoneal space.

6. *Diagnosis.* It is frequently stated that a preoperative diagnosis of carcinoma of the gallbladder is seldom made; Danzis<sup>4</sup> and Vadheim, *et al.*<sup>14</sup> found that none in their series had been diagnosed preoperatively. Sainburg and Garlock<sup>7</sup> stated that 23 per cent in their series were diagnosed preoperatively. Correct preoperative diagnoses were recorded in eight cases in our series. In many cases the operation was performed because of mistaken diagnoses of carcinoma of the pancreas or ducts, cholelithiasis, carcinoma of the stomach, and common duct stone. However, two of Lam's<sup>14</sup> cases, and one of ours carried a diagnosis of cirrhosis of the liver for a period prior to operation.

Carcinoma of the gallbladder should be suspected particularly in women over 60 years of age who give a history of biliary colic during the past three years, and who complain of epigastric or right upper quadrant pain of three months' duration, and with weight loss of approximately 20 pounds. Vomiting and constipation are frequently present. If the patient is jaundiced this is the latest symptom to appear. The presence of a palpable liver and/or a mass in the right upper quadrant, together with a non-functioning gallbladder on roentgen ray study should suggest this diagnosis.

Recognition of a recent change of symptoms suggesting early cholecystic neoplasm, in a patient with known gallbladder disease, provides the best chance for effective cholecystectomy. Particular inquiry should be made regarding recent biliary colic, change in frequency and duration of pain, and the onset of weight loss. Should these symptoms be recognized within the first months after onset, instead of at three and one-half months, cholecystectomies might result in a higher percentage of cures.

An additional diagnostic measure is peritoneoscopy, but no details regarding observations have been noted in the literature. This procedure was used in four of our cases, and enabled correct gross diagnosis in two patients. In the other two patients, biliary cirrhosis was diagnosed in one, and the examination was inconclusive in the other. This simple procedure may enable a diagnosis to be made in those advanced cases in which an exploratory laparotomy might hasten the patient's demise.

TABLE IV.—*Malignant Spread of the Tumor.*

Site	Metastases	By Direct Invasion
Liver .....	10	6
Omentum .....	8	1
Ducts (biliary) .....	6	9
Pancreas .....	6	1
Peritoneum .....	5	1
Transverse colon .....	2	0
Portal vein .....	1	2
Adrenal .....	2	0
Skin of thigh .....	1	0
Duodenum .....	1	1
Stomach .....	0	1

It might prove profitable to use more liver function tests in evaluating the status of possible cholecystic cancer. Liver function tests showing severe hepatic damage should suggest that the carcinoma is inoperable, and save the patient the necessity of an unsuccessful exploratory procedure.

7. *Pathology.* All of the 29 patients in this series had some operative procedure. In addition, three patients were examined at autopsy. In our series

TABLE V.—*Operative Procedures.*

Operation	Number of Cases
Exploration .....	10
Cholecystectomy .....	7
Cholecystostomy .....	7
Peritoneoscopy .....	2
Choledochostomy .....	1
Biopsy of skin metastases .....	1
Exteriorization of the gallbladder .....	1

grossly one case presented the papillary type of tumor, while all others were scirrhous or infiltrative. Microscopically, adenocarcinoma with columnar or cuboidal epithelium was present in 27 cases. The rare squamous cell carcinoma, which has a tendency to form a hard, localized, rapidly metastasizing tumor, was found in two cases. In one of these the gallbladder had perforated, and in the other a cholecystectomy had been performed with recurrence one month later at the ampulla of Vater.

Metastases or direct extension of the tumor occurred in all the cases in our series. These are tabulated in Table IV.

Nineteen of 22 patients had gallstones associated with the carcinoma. In seven patients the gallbladder was not opened and stones were not palpated at

operation. It has been adequately established<sup>5</sup> that cholelithiasis is associated with cholecystic neoplasm.

8. *Surgery.* Surgery for this condition is unsatisfactory, and seldom results in cure. None of the cases in this series had a five-year cure. The operative procedures that were performed in our series are tabulated in Table V. It will be noted that cholecystectomy was possible in only seven of the 29 cases. Surgery for carcinoma of the gallbladder would seem to have little to offer the patient who has had symptoms of this condition for as long as three months.

#### SUMMARY

Carcinoma of the gallbladder is an uncommon disease. At the Cleveland Clinic there have been 29 cases of carcinoma of the gallbladder among 350,000 new patients. In the same length of time 1488 cholecystectomies have been done, giving an incidence of 1.9 per cent carcinoma of the gallbladder in the cholecystectomies performed. A diagnosis of cholelithiasis was made in 4459 patients. The percentage of patients with carcinoma of the gallbladder among those having cholelithiasis as determined by roentgen-ray examination was 0.66. The sex ratio in 29 patients was four women to one man; 21 of the 29 cases occurred in patients over 60 years of age.

A history of pre-existing biliary colic was obtained in 17 patients. The earliest symptom was loss of weight, which was present in 23 cases. Pain was present in 21 patients. Nausea or vomiting and jaundice, the last symptom to appear, were present in 16 cases. The liver was enlarged in 22 patients, and there was a palpable mass in 17.

Laboratory findings did not help in the diagnosis of this condition. Only one patient had an appreciable anemia. Liver function tests may be of value in determining the operability of patients with this condition.

Roentgen-ray findings are nondiagnostic, cholecystograms showing only a non-filling gallbladder. Five patients had evidence of extrinsic pressure on other organs.

Peritoneoscopy was of help in the diagnosis of two patients and saved them from the necessity of an exploratory operation.

Adenocarcinoma was present in 27 cases, and squamous cell carcinoma in two patients. All cases had evidence of extension of the tumor or metastases at the time of operation.

Surgery for this condition is unsatisfactory. There were no five-year cures, and cholecystectomy was possible in only seven patients.

#### CONCLUSIONS

We believe that the incidence of carcinoma of the gallbladder is too low to warrant routine cholecystectomy as a prophylactic measure in all patients with gallstones. Furthermore, the operative mortality from cholecystectomy as a purely preventive procedure would probably at least equal the number of patients who would be expected to develop carcinoma of the gallbladder in later years.

## BIBLIOGRAPHY

- 1 Boyce, F. F., and E. M. McFetridge: Carcinoma of Gallbladder; Critique Based on Analysis of 25 Cases for Charity Hospital in New Orleans. *Internat. S. Digest*, **21**: 67, 1946.
- 2 Illingworth, C. F. W.: Carcinoma of Gallbladder. *Brit. J. Surg.*, **23**: 4, 1935.
- 3 Benjamin, E. G.: Carcinoma of Gallbladder; An Analysis of 70 Cases. *Minnesota Med.*, **31**: 537, 1948.
- 4 Danzis, M.: Carcinoma of Gallbladder; a Report of 26 Cases. *J. Med. Soc. New Jersey*, **45**: 274, 1948.
- 5 Bockus, H. L.: *Gastroenterology*, vol. 3, Philadelphia, 1943, W. B. Saunders.
- 6 Graham, E. A.: Prevention of Carcinoma of Gallbladder. *Ann. Surg.*, **93**: 317, 1931.
- 7 Sainburg, F. P., and J. H. Garlock: Carcinoma of Gallbladder; Report of 75 Cases. *Surgery*, **23**: 201, 1948.
- 8 Cole, W. H.: In F. Christopher: *Textbook of Surgery*, 4th ed., p. 1143, Philadelphia, 1945, W. B. Saunders.
- 9 Mattson, H.: Carcinoma of Gallbladder: Study of 60 Cases. *Minnesota Med.*, **25**: 985, 1942.
- 10 Comfort, M. W., H. K. Gray, and J. M. Wilson: Silent Gallstone; a Ten to Twenty-five Year Follow-up Study of 112 Cases. *Ann. Surg.*, **128**: 931, 1948.
- 11 Gross, D. M. B.: Statistical Study of Cholelithiasis. *J. Path. and Bact.*, **32**: 503, 1929.
- 12 Crump, C.: Incidence of Gallstones and Gallbladder Disease. *Surg., Gynec. and Obst.*, **53**: 447, 1931.
- 13 Robertson, H. E.: Silent Gallstones. *Gastroenterol.*, **5**: 345, 1945.
- 14 Vadheim, J. L., H. K. Gray, and M. B. Dockerty: Carcinoma of Gallbladder; Clinical and Pathologic Study. *Am. J. Surg.*, **63**: 173, 1944.
- 15 Cooper, W. A.: Carcinoma of Gallbladder. *Arch. Surg.*, **35**: 431, 1937.
- 16 Lam, C. R.: Present Status of Carcinoma of Gallbladder; Study of 34 Clinical Cases. *Ann. Surg.*, **111**: 403, 1940.
- 17 Lichtenstein, G. M., and W. Tannenbaum: Carcinoma of Gallbladder; Study of 75 Cases. *Ann. Surg.*, **111**: 411, 1940.
- 18 Hamilton, F. G.: Primary Carcinoma of Gallbladder; Review of Cases at St. Alexis Hospital. *Ohio State M. J.*, **42**: 378, 1946.
- 19 Kelly, F. J., and T. Speed: Primary Carcinoma of Gallbladder. *Texas State J. Med.*, **42**: 327, 1946.