

Carcinoma of the Gallbladder

Mustafa Şahin¹, MD, Abdullah Aydın², MD, Mustafa Erbilin¹, MD

Carcinoma of the gallbladder is a rare malignancy and cholelithiasis exists in most of the patients. The preoperative diagnosis is difficult because the clinical manifestations are nonspecific and often indistinguishable from those of cholecystitis. The majority of tumors are adenocarcinomas. Gallbladder carcinomas localized to the mucosa and submucosa can be adequately treated with cholecystectomy alone. The role of radical surgery in advanced stage disease is controversial. At present, chemotherapy and radiation therapy do not have a major role in the treatment of gallbladder carcinoma. [Journal of Turgut Özal Medical Center 1997;4(1):129-133]

Key Words: Gallbladder, carcinoma, diagnosis, treatment

Safra kesesi karsinomu

Safra kesesi karsinomu nadir görülür ve çoğu kolelityazis ile birlikte dir. Klinik belirtiler nonspesifik olduğu ve kolesistitle karıştığı için ameliyat öncesi tanı koymak zordur. Tümörlerin çoğu adenokarsinomlardır. Mukoza ve submukozada lokalize safra kesesi karsinomlarında yalnız kolesistektomi yeterli tedavi olabilir. İleri evre tümörlerde radikal cerrahinin rolü tartışmalıdır. Hali hazırda, safra kesesi karsinomlarının tedavisinde kemoterapi ve radyoterapinin major rolü yoktur. [Turgut Özal Tıp Merkezi Dergisi 1997;4(1):129-133]

Anahtar Kelimeler: Safra kesesi, karsinom, tanı, tedavi

EPIDEMIOLOGY AND ETIOLOGY

Carcinoma of the gallbladder is a rare malignancy comprising two thirds of biliary-tract cancers. It is the fifth most common cancer of the gastrointestinal tract (1). As with benign gallbladder disease, females are affected two to four times as often as males (2). The frequency of gallbladder carcinoma is maximum during the seventh decade of life (3).

The exact etiology of carcinoma of the gallbladder is not known. Several factors have been

associated with an increased risk for gallbladder cancer. Among these factors, cholelithiasis is observed most commonly and carcinoma can be found in 1-2% of all cholecystectomy specimens (4). The chronic mucosal irritation related to cholelithiasis and cholecystitis is believed to be important in the malignant degeneration of the mucosa. The duration of cholelithiasis is also believed to be of importance in this process. Gallbladder cancer is more likely to develop in patients with a single large stone than in those with multiple stones. Carcinoma of the gallbladder is also associated with calcification of the wall of the

¹ İnönü University School of Medicine Department of Surgery, Malatya

² İnönü University School of Medicine Department of Pathology, Malatya

gallbladder, the so-called porcelain gallbladder (5). Recently, Redealli et al. reported high coincidence of Mirizzi syndrome and gallbladder carcinoma (6).

Persistent presence of gallstones is not always required for the development of adenocarcinoma. Typhoid carriers are also at increased risk for all types of hepatobiliary carcinoma (7). An association with anomalous pancreaticobiliary duct union and a long common channel have been proposed (8-11). In patients with choledoccal cyst, carcinoma may develop anywhere in the biliary tree, but a significant proportion of these tumors arise in the gallbladder (12). Benign adenomatous and squamous metaplasia may be a predisposing factor for carcinoma of the gallbladder (13,14). Whether or not accompanied by gallstone disease, gallbladder polyps greater than 1 cm are most likely to become malignant and are an indication for cholecystectomy (15,16)

PATHOLOGY

Gallbladder carcinomas macroscopically exhibit two different patterns (infiltrative and papillary). Infiltrative type is the most common form (17). The tumors are usually found in fundus of the gallbladder, but may arise in corpus and neck (18). More than 75% of the gallbladder tumors are adenocarcinomas (19). Gallbladder adenocarcinomas are subdivided into three grades as well differentiated, moderately differentiated, and poorly differentiated (20). Other rare types include papillary carcinoma (5%), mucinous adenocarcinoma (5%), adenosquamous carcinoma (5%), and signet ring cell carcinoma (3%) (18,19). Small cell carcinoma, clear cell adenocarcinoma, and squamous cell carcinoma are seen in patients with gallbladder carcinoma infrequently (18-22). Although the macroscopically papillary and histologically well differentiated gallbladder carcinoma carries a better prognosis, survival depends on the stage of the tumor at the time of diagnosis (18, 19, 23).

The tumor has a tendency to invade surrounding structures particularly the liver, bile duct, and duodenum. Lymph node metastases are found in 50-75% of gallbladder carcinoma cases (18). The cystic duct node, at the confluence of the cystic and

hepatic ducts is the initial focus of regional lymphatic spread.

CLINICAL PRESENTATION

Carcinoma of the gallbladder is unusual in patients under the age of 40 years. Most gallbladder carcinomas are found incidentally following cholecystectomy. The most common presenting complaint is abdominal pain and nausea. Vomiting, jaundice, weight loss, fever, and anorexia are other common symptoms (24,25)

In physical examination, patients may have right upper quadrant pain with a palpable mass and is often confused with the gallbladder of acute cholecystitis. In advanced cases, patients may have cachexia and ascites.

DIAGNOSIS

The preoperative diagnosis of carcinoma of the gallbladder is very difficult because the clinical manifestations of this disease are nonspecific and often indistinguishable from those of cholecystitis. The majority of patients have advanced disease at presentation. Many patients are operated on with the preoperative diagnosis of chronic cholecystitis. A correct preoperative diagnosis of gallbladder cancer is made in 10% to 50% of cases in most series (24-26).

With the exception of patients with jaundice, no specific laboratory findings are frequently observed. Several tumor markers have been associated with gallbladder carcinoma. These include carcinoembryonic antigen, alphafetoprotein, and CA 19-9 which are common in many gastrointestinal malignancies (24). In general, the incidence of elevated tumor markers is very low and their specificity is so poor that they are not good screening tests for gallbladder cancer.

Ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and cholangiography have all been used to evaluate gallbladder carcinoma. US is the examination of choice in the diagnosis of gallbladder and biliary duct lesions, but several diagnostic problems may arise in the differentiation from polyps and acute inflammatory disease. CT better demonstrates

gastrointestinal tract invasion and lymphadenopathy, which can be a valuable finding for treatment planning.

Ultrasonography will usually reveal coexisting gallstones and is also able to identify a mass filling or replacing the gallbladder in approximately one half of patients (27,28). Other significant findings include a mass protruding into the gallbladder and asymmetric thickening or irregularity in the gallbladder wall. A CT scan can detect the presence of tumor extension into the region of the common bile duct or metastases to lymph nodes, in addition to defining irregularities within the gallbladder itself. Limited experience with the use of MRI exists in the evaluation of gallbladder carcinoma. In patients with gallbladder cancer presenting with obstructive jaundice, extension along the hepatoduodenal ligament may be evaluated by MRI. Hepatic involvement and portal vein encasement may also be seen with MRI (29).

In combination, US and CT are quite useful in evaluating patients presenting with right upper quadrant pain of short duration, vomiting, fever, and localized tenderness. It should be possible to improve the results of preoperative diagnosis in early stages (tumor-stage I and II) by using ultrasound more and more. A general awareness of the radiologic features of gallbladder carcinoma enhances preoperative diagnoses. The presence of a mass or history of weight loss should trigger suspicion of a process other than cholecystitis.

In patients with jaundice, the diagnostic evaluation should proceed as in any patient with suspected extrahepatic jaundice. Direct visualization of the biliary tree can be accomplished by percutaneous or endoscopic retrograde cholangiography. Most commonly, obstruction of the common hepatic duct will occur near the entrance of the cystic duct. The absence of filling of the gallbladder is suspicious of carcinoma of the gallbladder.

The most common staging system used for

Table 1. Nevin staging of carcinoma of the gallbladder

Stage I	Intramucosal involvement only
Stage II	Involvement of the mucosa and muscularis
Stage III	Involvement of all three layers of gallbladder
Stage IV	Involvement of all three layers and cystic duct lymph nodes
Stage V	Involvement of liver or metastases to other organs

gallbladder carcinoma, as described by Nevin, is based on the depth of invasion and the spread of the tumor (Table 1) (30).

TREATMENT

Carcinoma of the gallbladder has always been associated with unfavorable prognosis. The majority of patients with gallbladder carcinoma present with advanced disease. Stage I carcinoma of the gallbladder can be adequately treated with cholecystectomy alone with 5-year survival rates as high as 100% in several series. The management of stage II patients is not so clearly defined. Several studies suggest that cholecystectomy alone is the sufficient treatment. On the other hand, a number of authors report higher rates of recurrence and lower rates of survival for stage II patients treated with cholecystectomy alone. The optimal treatment for patients with stage III and IV tumors is an extended cholecystectomy. This procedure includes cholecystectomy, regional lymph node dissection in the hepatoduodenal ligament, and a wedge resection of the gallbladder bed with at least a 3-cm margin of normal parenchyma. The dismal prognosis for patients with stage V has made many surgeons advocate palliative procedures rather than resection (1,4).

A combined resection of the involved organs (hepatectomy, pancreatoduodenectomy etc.) may be appropriate in carefully selected patients with advanced gallbladder carcinoma to improve both survival and the quality of life. (31,32). Obstructive jaundice is a common but late complication of gallbladder cancer. Endoscopic or percutaneous stenting is the choice of palliation in patients with advanced disease with jaundice.

Incidental gallbladder cancer has been reported in laparoscopic cholecystectomy (LC) series (33,34). Additional treatment of gallbladder cancer incidentally found by LC should be decided according to the depth of invasion and the range of mucosal spread. If available, frozen sections for pathologic analysis should be utilized during LC. In cases with subserosal or serosal involvement, LC should be converted to open laparotomy for radical resection. If the frozen section analysis shows an early carcinoma only with involvement of the mucosa or the muscular layer not reaching the cut

end of the cystic duct, it may be wise to perform LC without further treatment (33).

Tumor cells of clinically inapparent gallbladder carcinomas can be implanted at the trocar sites during laparoscopic cholecystectomies. Seeding of tumor cells at the umbilical port during laparoscopic surgery for staging malignant disease or laparoscopic cholecystectomy has been reported (35). When laparoscopic techniques are used for the resection of tumors, the excised specimen should be enclosed in a nonporous bag for removal through the abdominal wall and port sites should be washed with normal saline to prevent port site recurrence in patients with laparoscopic cholecystectomy (36).

The use of single and multiple chemotherapeutic agents either as primary therapy or as adjuvant therapy has been disappointing (1). Radiotherapy has shown promise when used in the postoperative adjuvant setting. Patients with advanced disease and locally symptomatic tumors should be offered radiation therapy (37).

REFERENCES

- Jones RS. Carcinoma of the gallbladder. *Surg Clin North Am* 1990;70:1419-28.
- Whetstone MR, Saltztein EC, Mercer LC. Demographic characteristics of gallbladder cancer in an area endemic for biliary calculi. *Am J Surg* 1986;152:728.
- Black WC, Key CR, Carmany TB, Human D. Cancer of the gallbladder in a population of southwest American Indians. *Cancer* 1977;39:1267-79.
- Piehler JM, Crichlow RW. Primary carcinoma of the gallbladder. *Surg Gynecol Obstet* 1978;147:929.
- Polk HC. Carcinoma and the calcified gallbladder. *Gastroenterology* 1966;50:582-5.
- Redaelli CA, Buchler MW, Schilling MK, et al. High coincidence of Mirizzi syndrome and gallbladder carcinoma. *Surgery* 1997;121:58-63.
- Welston JC, Marr JS, Friedman SM. Association between hepatobiliary cancer and typhoid carrier state. *Lancet* 1979;1(8120):791-4.
- Chijiwa K, Kimura H, Tanaka M. Malignant potential of the gallbladder in patients with anomalous pancreaticobiliary ductal junction. The difference in risk between patients with and without choledochal cyst. *Int Surg* 1995;80:61-4.
- Chijiwa K, Tanaka M. Surgical strategy for patients with anomalous pancreaticobiliary ductal junction without choledochal cyst. *Int Surg* 1995;80:215-7.
- Kimura K, Ohto M, Saisho H, et al. association of gallbladder carcinoma and anomalous pancreaticobiliary ductal union. *Gastroenterology* 1985;89:1258-63.
- Chao TC, Jan YY, Chen MF. Primary carcinoma of the gallbladder associated with anomalous pancreaticobiliary ductal junction. *J Clin Gastroenterol* 1995;21:306-8.
- Aoki H, Sugaya H, Shimazu M. A clinical study on cancer of the bile duct associated with anomalous arrangements of the pancreaticobiliary ductal system: analysis of 569 cases collected in Japan. *J Bile Tract Pancreas* 1987;8:1539-51.
- Yamagiwa H, Tomiyama H. Intestinal metaplasia-dysplasia-carcinoma sequence of the gallbladder. *Acta Pathol Jpn* 1986;36:989-95.
- Aldridge MC, Gruffaz F, Castaing D, et al. Adenomyomatosis of the gallbladder: a premalignant lesion? *Surgery* 1991;109:107-10.
- Kozuka S, Tsubone M, Yasui A, et al. relation of adenoma to carcinoma in the gallbladder. *Cancer* 1982;50:2226-34.
- Chijiwa K, Tanaka M. Polypoid lesion of the gallbladder. Indication of carcinoma and outcome after surgery for malignant polypoid lesion. *Int Surg* 1994;79:106-9.
- Crawford JM. The liver and biliary tract. In: Cotran RS, Kumar V, Robbins SL, eds. *Robbin's Pathologic Basis of the Disease*. 5th ed. Philadelphia: WB Saunders 1994:831-96.
- Scott HS. Gallbladder and extrahepatic biliary tree. In: Sternberg SS, ed. *Diagnostic Surgical Pathology*. 2nd ed. New York: Raven Press 1994:1581-612.
- Henson DE, Saavedra JA, Corle D. Carcinoma of the gallbladder. *Cancer* 1992; 70:1493-97.
- Saavedra JA, Henson DE, Sobin LH. The WHO histological classification of tumors of the gallbladder and extrahepatic bile ducts. *Cancer* 1992;70:410-14.
- Johnstone AK, Zuch RH, Anders KH. Oat cell carcinoma of the gallbladder. *Arch Pathol Lab Med* 1993;117:1009-12.
- Vardaman C, Saavedra JA. Clear cell carcinoma of the gallbladder and extrahepatic bile ducts. *Am J Surg Pathol* 1995;19:91-9.
- Ouchi K, Owada Y, Matsuno S, Sato T. Prognostic factors in the surgical treatment of gallbladder carcinoma. *Surgery* 1987;101:731-7.
- Cubertafond P, Gainant A, Cucchiari G. Surgical treatment of 724 carcinomas of the gallbladder. *Ann Surg* 1994;219:275-80.
- Arnaud JP, Casa C, Georgeac C, et al. Primary carcinoma of the gallbladder-review of 143 cases. *Hepato-Gastroenterology* 1995;42:811-5.
- Ouchi K, Suzuki M, Saijo S, et al. Do recent advances in diagnosis and operative treatment improve the outcome of gallbladder carcinoma? *Surgery* 1993;113:324-9.
- Weiner SN, Koenigsberg M, Morehouse H, Hoffman J. Sonography and computer tomography in the diagnosis of carcinoma of the gallbladder. *Am J Radiol* 1984;142:735-9.
- Tsuchiya Y. Early carcinoma of the gallbladder: macroscopic features and US findings. *Radiology* 1991;179:171-5.

29. Wilbur AC, Gyi B, Renigers SA. High-field MRI of primary gallbladder carcinoma. *Gastrointest Radiol* 1988;13:142-4.
30. Nevin JE, Moran TJ, Kay S, et al. Carcinoma of the gallbladder. Staging, treatment and prognosis. *Cancer* 1976;37:141-8.
31. Tsukada K, Yoshida K, Aono T, et al. Major hepatectomy and pancreatoduodenectomy for advanced carcinoma of the biliary tract. *Br J Surg* 1994;81:108-10.
32. Miyazaki K, Tsutsumi N, Kitahara K, et al. Hepatopancreatoduodenectomy for squamous and adenosquamous carcinoma of the gallbladder. *Hepato-Gastroenterology* 1995;42:47-50.
33. Ishibashi T, Nagai H, Yasuda T, et al. Two cases of early gallbladder cancer incidentally discovered by laparoscopic cholecystectomy. *Surg Laparosc Endosc* 1995;5:21-6.
34. Fong Y, Brennan MF, Turnbull A, Colt DG, Blumgart LH. Gallbladder cancer discovered during laparoscopic surgery: potential for iatrogenic tumor dissemination. *Arch Surg* 1993;128:1054-6.
35. Johnstone PA, Rohde DC, Swartz SE, et al. Port site recurrences after laparoscopic and thoracoscopic procedures in malignancy. *J Clin Oncol* 1996;14:1950-6.
36. Yamaguchi K, Chijiwa K, Ichimiya H, et al. Gallbladder carcinoma in the era of laparoscopic cholecystectomy. *Arch Surg* 1996;131:981-4.
37. Hanna SS, Rider WB. Carcinoma of the gallbladder or extrahepatic bile ducts. The role of radiotherapy. *Can Med Assoc J* 1978;118:59-61.

Correspondence address:

Mustafa ŞAHİN, MD
İnönü University School of Medicine,
Department of Surgery
44300, MALATYA
Tel: 422 3410660/1114
Fax: 422 324 4403