Gallbladder Cancer

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KEYWORDS

• Gallbladder cancer • Radical cholecystectomy • Port site recurrence
• Biliary tract malignancy • Incidental gallbladder cancer

KEY POINTS

- Gallbladder cancer remains a disease with poor overall prognosis.
- Chronic inflammatory conditions of the gallbladder are associated with gallbladder cancer.
- T stage translates into the likelihood of identifying residual disease at reoperation for incidental gallbladder cancer, and residual disease negatively impacts survival.
- In select patients with radical operative intervention, there is an improvement in survival if R0 (margin negative) resection is achieved.
- There is no difference in survival in patients undergoing staged curative resection versus single-stage radical operation.
- Port site involvement of disease is predictive of poor outcome, often correlating with the presence of carcinomatosis.
- Improved systemic therapy is paramount to improving the overall survival in patients with gallbladder cancer.

INTRODUCTION

Gallbladder cancer remains a relatively rare malignancy with a highly variable presentation. Gallbladder cancer is the most common biliary tract malignancy with the worst overall prognosis. With the advent of the laparoscope, in comparison with historical controls, this disease is now more commonly diagnosed incidentally and at an earlier stage.[1–4] However, when symptoms of jaundice and pain are present, the prognosis remains dismal.[5] From a surgical perspective, gallbladder cancer can be suspected preoperatively, identified intraoperatively, or discovered incidentally on final surgical pathology.

INCIDENCE AND EPIDEMIOLOGY

Biliary tract cancers include intrahepatic bile duct cancers, extrahepatic bile duct cancers, and gallbladder cancers. These adenocarcinomas all arise from the biliary

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epithelium, with gallbladder cancer being the most common.[6] There will be an estimated 10,310 new cases of gallbladder and extrahepatic biliary tract cancers diagnosed in 2013. This subset is the sixth most common gastrointestinal malignancy, with gallbladder carcinomas composing most of this group.[6]

Worldwide, there are regional variations in the incidence of gallbladder cancer. Central and Northern European, Indian, and Chilean populations have a higher incidence of gallbladder cancer when compared with the overall US population. The incidence rates of gallbladder cancer in Chile are more than 25 per 100,000 females and 9 per 100,000 males. These rates far exceed those that are found in the United States. The US incidence rates for gallbladder cancer are 0.9 and 0.5 per 100,000 females and males, respectively.[7] Racial discrepancies are also found with gallbladder cancer in the United States. American Indians, Alaskan natives, Asian Pacific/Islanders, blacks, and Hispanics all have a higher incidence when compared with non-Hispanic whites.[8–10]

As with most malignancies, the incidence of gallbladder cancer increases with age. The mean age at diagnosis is 65 years.[11] There is a strong predilection for gallbladder cancer among women, with female-to-male ratios varying from 1.3 to 3.5:1.0.[8,11–13] Sex and ethnicity are further discussed later as they relate to risk factors for this disease.

RISK FACTORS

Most gallbladder cancers are adenocarcinomas arising from the gallbladder mucosa. It is thought that chronic inflammation of the gallbladder mucosa may trigger progression from dysplasia to carcinoma in susceptible patients. Most of the known risk factors associated with gallbladder cancer are related to inflammation.[14]

Gallstones

The development of cholelithiasis is multifactorial in nature. Some of the risk factors for the development of cholelithiasis include age, sex, race, parity, and rapid weight loss.[15] Within the United States, cholesterol stones are the predominant stone type and are formed as a result of cholesterol supersaturation of bile, accelerated cholesterol crystal nucleation, and impaired gallbladder motility.[16] As discussed later, there is a potential genetic association that independently increases the risk of cholelithiasis and, thus, gallbladder cancer.[17,18]

There is clearly an association between benign gallstones and gallbladder cancer.[19–22] Piehler and Crichlow's[23] review of more than 2000 patients with gallbladder cancer found that 73.9% of patients had stones present. Other investigators have found similar results. Most patients (70%–88%) who present with gallbladder cancer have a history or presence of stones, but the incidence of gallbladder cancer among patients with stones is only 0.3% to 3.0%.[4,13,19,24] Diehl[24] showed that there is an increased association with gallbladder cancer as the size of gallstone increases. Although this is a graded phenomenon, stone size greater than 3 cm is thought to confer an up to 10 times increased risk of gallbladder cancer.[24] Roa and colleagues[25] showed that patients with gallbladder cancer will have an increased volume, weight, and density of their gallstones. Gallstone volume is associated with increased relative risk (RR) for developing gallbladder carcinoma, with volumes of 6 mL and 10 mL having RRs of 4.92 and 11.0, respectively.[25]

Gallbladder Polyps

Most polyps are not adenomatous, and most gallbladder cancers do not arise from polyps; however, removal of gallbladders containing polyps greater than 10 mm is recommended for cancer risk reduction.[26,27]