Gallbladder Cancer Presenting as Acute Cholecystitis

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Introduction

There are 8,500 new cases of carcinoma of the gallbladder diagnosed each year [1]. The majority of these cases (70 %) are found incidentally when the patient is receiving cholecystectomy. In these circumstances, the diagnosis either occurs when the surgeon intraoperatively examines the gallbladder at the time of cholecystectomy or when the pathologist postoperatively examines the gallbladder. The next highest numbers of patients (30 %) are diagnosed for symptoms related to advanced gallbladder cancer [1, 2].

Overall, gallbladder cancer widely portends a poor prognosis for the patient due to the advanced stage at which carcinoma of the gallbladder is often diagnosed. The cancer-specific mortality of patients with gallbladder carcinoma following simple cholecystectomy is directly correlated with the T and N stages of the tumor (Table 17.1) [3]. While nearly all patients obtain long-term survival with simple cholecystectomy for T1a tumors, the 5-year survival for T1b and greater tumors drops precipitously without further intervention. Those patients diagnosed with early stage have the greatest likelihood of long-term survival if provided with a complete R0 resection [1, 2].

Presentation

With incidental gallbladder cancer representing the majority of all gallbladder cancer in the USA, one must question why it is not discovered more often preoperatively [4]. Patients are often symptomatic with right upper quadrant pain that appears to be due to cholelithaisis or acute/chronic cholecystitis. Imaging usually notes the gallstones and may also suggest thickening of the gallbladder wall usually without peri-cholecystic edema. Gallstones represent the most prevalent risk factor with over 75 % of patients with gallbladder cancer having associated gallstones [3, 5]. This association leads to the lack of preoperative diagnosis since the incidence of gallbladder cancer in resected cholecystectomies is only 1 % [6]. Certainly, the presence of gallstones is a risk factor for gallbladder cancer. In another series, 90 % of cases of incidentally discovered GBCA had gallstones compared to only 13 % of non-incidental [4].

Incidentally found gallbladder cancer is much more likely to be early stage than cases diagnosed preoperatively using ultrasound, computed

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Table 17.1 AJCC TNM staging

Primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or muscular layer
T1a	Tumor invades lamina propria
T1b	Tumor invades muscular layer
T2	Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades main portal vein or hepatic artery or invades at least two extrahepatic organs or structures
Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein
N2	Metastases to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes

abdominal tomography, magnetic resonance imaging, or magnetic resonance cholangiopancreatography scans. Right upper quadrant ultrasound, routinely used for evaluation of symptomatic patients, might show a polypoidal gallbladder mass and potentially invasion of adjacent structures. The presence of gallbladder calcification, also known as "porcelain gallbladder," may also be noted preoperatively. Wall thickness greater than 3 mm and increased vascularity of the gallbladder are considered sonographic features that can also signify possible malignancy [7].

During open routine cholecystectomy, which was standard procedure decades ago, surgeons might have felt an area of abnormality in the gallbladder during the operation and send the tissue for frozen section examination. Laparoscopic cholecystectomy often misses the incidental cancer during cholecystectomy due to the inability of the operator to actually "feel" the gallbladder and note focal abnormalities during removal. The tactile feedback afforded by a surgeon's hands appreciating a thickened, infiltrated, incidentally malignant gallbladder is lost in the laparoscopic technique. Unless the surgeon, thoroughly exams the gallbladder upon its removal, the diagnosis is not made for several days when the histologic examination of the tissue is complete.

If gallbladder cancer is not detected while the gallbladder is in situ, the treatment may be compromised. Adenocarcinoma of the gallbladder, in its early focal growth pattern invades into the lamina propria, followed by invasion into the deeper submucosal area and then advances diffusely throughout the gallbladder in the subserosal plane. If the surgeon does not suspect the diagnosis intraoperatively and perform a deep, wide excision of the gallbladder, the subsequent dissection may occur in the subserosal plane and leave cancer cells behind upon separation of the gallbladder from the liver. When this event occurs, incidentally discovered gallbladder cancer patients should undergo careful evaluation to determine the margins and likelihood of recurrence to determine the next best form of management after they have undergone a potentially incomplete cancer operation. Having a high risk for residual disease in the gallbladder fossa and a major risk of cancer seeding of the abdomen at the time of cholecystectomy should be considerations when further extirpative surgery is contemplated.

Detection of Incidentally Discovered Gallbladder Cancer

The surgeon's diagnosis of incidental carcinoma of the gallbladder intraoperatively is rare (0.1 %), especially when the procedure is performed laparoscopically. In a retrospective review of 3,050 patients undergoing laparoscopic cholecystectomy for cholelithiasis, carcinoma of the gallbladder was discovered during or after laparoscopic cholecystectomy in 10 patients. Interestingly, laparoscopy was converted to an open procedure in only three patients after pathologic diagnosis was confirmed using frozen section [6]. If signs of malignancy are encountered during laparoscopic cholecystectomy, the surgeon should convert to an open procedure [3, 6]. As noted above, the lack of tactile sensation during laparoscopic cholecystectomy makes

intraoperative assessment of malignancy quite difficult. A retrospective review of nearly 300 cases of laparoscopic cholecystectomy in which there was suspicion of gallbladder cancer, and frozen section was performed, the incidence of gallbladder cancer was only 1.3 %.

A thickened, infiltrated, or porcelain gallbladder should raise an index of suspicion for the surgeon. Preoperative imaging demonstrating porcelain gallbladder or polypoid lesions of the gallbladder are indications to examine the gallbladder closely intraoperatively for the possibility of malignancy. Among patients presenting with polypoid lesions of the gallbladder, the incidence of cancer is reported to range from 4 to 18 % [8]. Because of this association, patients with porcelain gallbladders should undergo frozen section examination of the gallbladder upon removal if a tumor is not detected intraoperatively by the surgeon.

If an early malignancy (pT1) is diagnosed intraoperatively, no additional resection is required if there has not been a perforation of the gallbladder. If inadvertent gallbladder perforation occurs during its removal, the peritoneal recurrence rate of gallbladder cancer is likely to be increased. In patients with pT2 (into perimuscular fibers) and beyond, hepatic resection of the gallbladder fossa, segmental hepatic resection, and complete dissection of the lymph nodes along the hepato-duodenal ligament (around the bile ducts, hepatic arteries, and portal vein from the hilus of the liver to behind the duodenum and pancreas) is indicated [6, 8, 9]. There are multiple issues to be considered in this situation such as obtaining operative consent for a much larger and unanticipated procedure, the patient's existing comorbidities and the skill required by the operating surgeon to perform this more complex procedure. Due to these issues, the operating surgeon should decide whether the better option is to perform an open radical resection or whether to close without attempts of resection. When faced with an unexpectedly malignant gallbladder, it is highly recommended that the operating surgeon obtain additional help from a specialty-trained surgeon if the original surgeon is not trained in the more complex surgery. The patient must then be referred for further oncologic work up and potential operative planning for resection (Fig. 17.1).

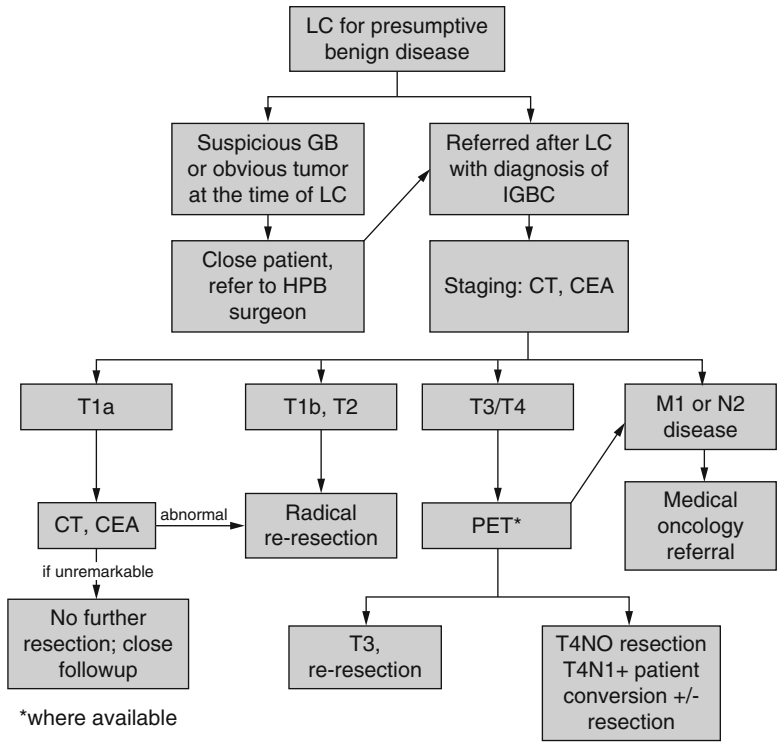

Fig. 17.1 Management algorithm for patients with incidental gallbladder carcinoma. *LC* laparoscopic cholecystectomy, *BG* gallbladder, *IGBC* incidentally discovered gallbladder cancer, *HPB* hepato-pancreatico-biliary, *CT* computed tomography, *CEA* carcinoembryonic antigen, *PET* positron emission tomography. Used with permission: Belin, Laurence J., Christina E. Lewis, and Yuman Fong. "Management of Incidental Gallbladder Carcinoma." Carcinoma of the Gallbladder: The Current Scenario. New Delhi: Elsevier, 2014. 54–66. Print. ECAB Clinical Update Surgical Gastroenterology and Liver Transplantation

Incidentally Discovered Gallbladder Cancer by Pathologic Review

Most commonly, incidental gallbladder cancer is diagnosed after histologic examination of the gallbladder by the pathologist postoperatively. In many cases, the patient has already been discharged from the hospital and has expected no further gallbladder treatment (see Fig. 17.2 and its description of what is a typical case). For the pathologist and the surgeon, the site of the malignancy in the gallbladder and the pathologic stage must be carefully determined to counsel the patient on appropriate further therapy. Review of the histology by another experienced pathologist or at a tumor board is critical because some stages of disease do not require further surgical therapy. For example, patients with pT1a tumors do not benefit from additional treatment as their prognosis is good. Additional operative resection in patients with stage pT1a incidental gallbladder cancer did not result in better survival when compared with patients who had the initial cholecystectomy performed without additional treatment. Patients with more advanced stages of disease (pT2 or greater), however, may well benefit from additional treatment such as re-resection [10].

Because of the rarity of this malignancy, there are no prospective, randomized trials available to provide Level 1 evidence as to the benefits of additional surgical resection as compared to observation or use of adjuvant chemoradiotherapy in those with incidental gallbladder cancer. However, multiple retrospective reports have recommended that patients undergo an additional resection if gallbladder cancer (>pT1) is diagnosed postoperatively after laparoscopic cholecystectomy [10]. In one report, less than a third of these patients diagnosed postoperatively received an additional resection as described above with segmental liver resection and hepatoduodenal nodal dissection with or without bile duct excision and hepatico-jejunostomy because of extensive disease [11]. If the invasion of the gallbladder cancer is limited to the mucosa or subserosa, the 5-year survival rate is over 95 % [12]. The 5-year survival for T1b and greater tumors drops precipitously without further intervention. Duffy et al. found that over half of the patients undergoing a second operation after incidental gallbladder cancer found initially were noted to have much more extensive disease in their liver, peritoneum, and hepatoduodenal nodes [10].

Due to a lack of prospective, randomized data regarding results of aggressive resection following incidentally discovered gallbladder cancer, no consensus surrounds the extent of necessary resection for this scenario. Importantly, no radical procedure is recommended after postoperative diagnosis of incidental pT1a (through lamina propria). T1a tumors with a normal CT and CEA may therefore be closely monitored without reexploration. If after the index laparoscopic or open cholecystectomy, pathology reveals tumor infiltration beyond the lamina propria and muscularis (>pT1a and pT1b), computed tomographic scans should be done to evaluate for residual and disseminated disease. For all T1 tumors with a positive cystic node and all tumors T1b or greater, reexploration and radical resection for accurate staging and potential cure are indicated [9]. If the patient has a normal carcinoembryonic antigen (CEA) level and CT scan showing no evidence of unresectable disease, additional resection in pT1b have been recommended based on retrospective series suggesting that further resection has been associated with improved survival compared with patients that did not undergo further surgery [13]. As described above, the recommended procedure is that of gallbladder fossa segmental hepatic resection (segments IVb and V) combined with hepato-duodenal lymph node dissection.

Other authors give guidelines for further workup and aggressive tissue resection after diagnosis of advanced stage gallbladder cancer. Certain authors from Asia have recommended complete bile duct resection, hepatic-jejunostomy to proximal hepatic ducts along with caudate lobe resection [12]. For patients with T2 and T3 tumors, a staging computed tomographic scan with and without contrast is recommended to evaluate for residual disease in the liver and peritoneum as well as suspicious lymphadenopathy. In accordance with the >50 % probability of lymph node involvement in T3+ tumors, PET-CT scan may offer additional information for staging purposes. Magnetic resonance imaging with

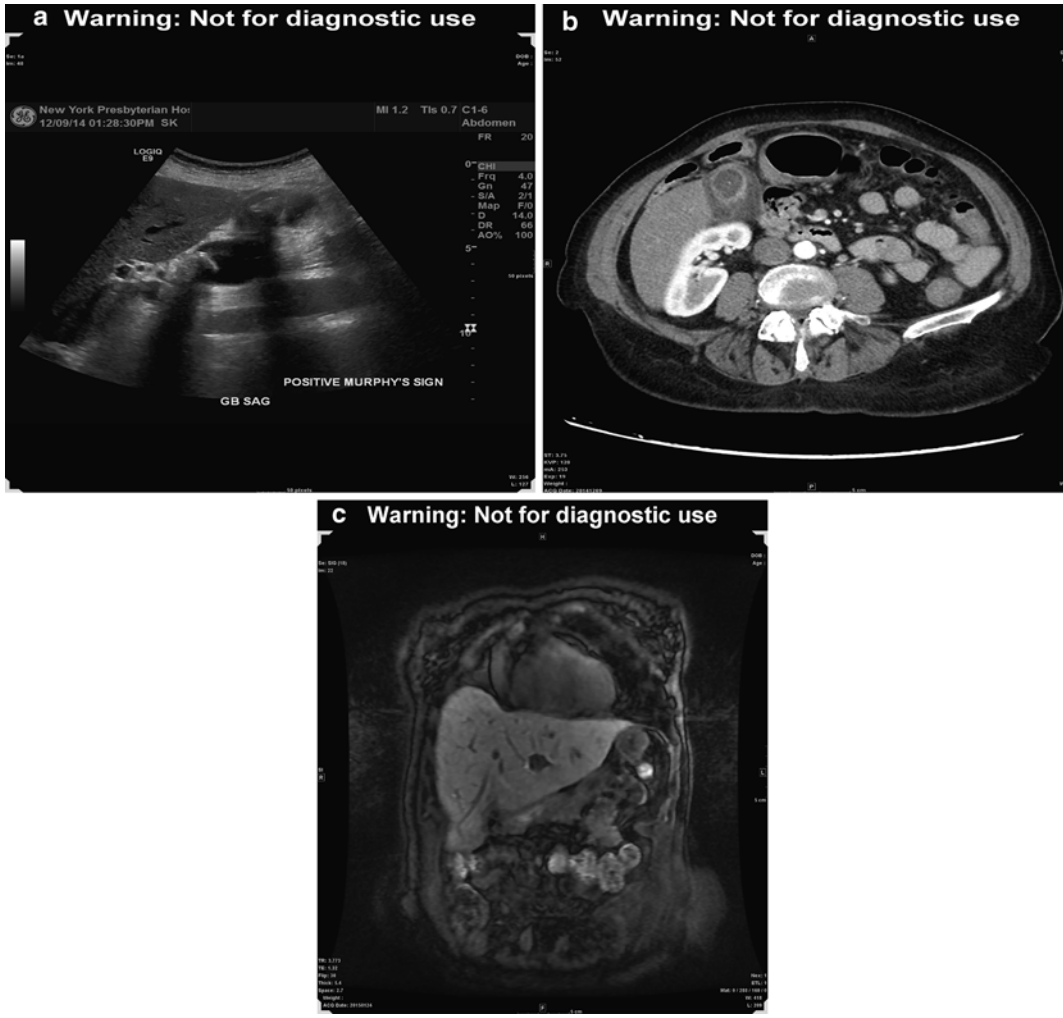

Fig. 17.2 Seventy-three-year-old female presenting with right upper quadrant pain initially thought to be acute cholecystitis. Patient underwent laparoscopic cholecystectomy. Pathology revealed invasive adenocarcinoma of the gallbladder with high-grade dysplasia and invasion of perimuscular connective tissue (T2, Nx). (**a**) Preoperative right upper quadrant ultrasound image showing thickened gallbladder wall (9 mm), multiple gallstones, and sludge with normal intraheptatic ducts. Impression read as acute cholecystitis. (**b**) Preoperative axial CT-scan of abdomen showing 2.0 cm gallstone within the gallbladder neck. This is associated with gallbladder wall thickening/edema and pericholecystic fluid. Mild enhancement of the hepatic parenchyma adjacent to the gallbladder was also noted. No intra- or extra-biliary ductal dilatation was seen. (**c**) Postoperative coronal MRCP image after the patient was found to have incidental gallbladder cancer with acute cholecystitis. Slightly abnormal signal in the subcapsular portion of hepatic segment 5 in the gallbladder fossa, possible tumor invasion. No clear residual tumor at the level of the cystic duct remnant. No tumor involvement of the common hepatic or common bile duct was noted on pathology

magnetic resonance cholangiopancreatography and serum CEA and CA19-9 levels, which are 93 % and 79.4 % sensitive for gallbladder cancer when elevated, respectively, may also be obtained [9]. The presence of T4 disease is often regarded as widely disseminated through vascular invasion and/or metastasis, thus rendering the disease unresectable. No reexploration is recommended in those patients if there is any evidence of metastatic disease and the patient should be referred to medical oncology for therapies. Some of these advanced stage patients may require palliative surgery or interventional radiologic drainage for certain conditions such as jaundice or bowel

obstruction but these procedures should be individualized based on the symptoms, prognosis, disease state, and the wishes of the patient or health care agent.

Reexploration for Incidentally Discovered Gallbladder Cancer Identified After Simple Cholecystectomy?

The fundamental basis of reexploration surrounds the observation that gallbladder cancer carries a poor prognosis, with the only chance for cure lying in early detection and complete surgical resection. Additionally, as many as 50 % of patients reexplored for incidental gallbladder cancer had residual disease following laparoscopic cholecystectomy [13]. As noted, re-resection of patients with early stage incidental gallbladder cancer may result in long-term survival, but workup of these patients must be thorough to avoid unnecessary reexploration as there is a risk of peritoneal or port-site seeding leading to metastatic disease. After diagnosis of gallbladder cancer, a high theoretical risk of residual disease exists after the initial operation. Also, the staging is usually incomplete as the original surgery rarely has complete nodal dissection performed.

As T stage increases, the likelihood of residual disease on reexploration increases.

In another large, multicenter retrospective review, the incidence of residual disease at the second operation was 61 % which correlated directly with T stage and indirectly with long-term outcome [13]. Bartlett et al. reported a 5-year survival rate is 69 % for T2 disease after radical resection as compared to the best results for simple cholecystectomy, a 5-year survival rate of 40 % being reported [14]. In the same report, Bartlett et al. went on to describe a 5-year survival rate of 67 % for T3 disease after complete resection.

Prognosis After Re-resection

As is common with most carcinomas of the gastrointestinal tract, the incidence of regional lymph node metastases increases with the T stage of the primary tumor, increasing from 12 to 45 % for patients with T1 to T3 primary tumors. Similarly, as is found with other gastrointestinal malignancies, the presence and extent of positive regional nodes adversely affects 5-year survival (26 % with nodal metastasis vs. 73 % in patients with no nodal involvement) [13]. Any planned secondary surgery should be done in an attempt to remove remaining cancer either in regional nodes or at adjacent primary sites. Thus, the underlying rationale for re-resection is to excise residual tumor and nodal tissue and thereby obtain a possibility of long-term survival or cure.

Incidentally discovered cases of gallbladder cancer have a significantly longer median survival (16 months) than those with a diagnosis established preoperatively (5 months) [15]. Patients with incidentally discovered gallbladder cancer who undergo reexploration and resection have a significantly improved median survival compared with those who are reexplored and cannot undergo resection and those who never have a re-laparotomy. This observation derives from retrospective studies and parallels similar findings to those examining results of re-resection for other areas of the gastrointestinal tract. In all retrospective series, re-resection for cancer occurs at the judgment of the attending surgeon and is dependent on factors such as initial tumor staging, patient age and comorbidities and other factors suggestive a high degree of patient selection bias. Outcomes of re-resection are dependent on the T stage of the tumor with an excellent chance of long-term survival possible in early-stage tumors. Important prognostic variables associated with prognosis after re-resection includes T, N, and M stages, tumor differentiation, and re-resection margin status. As patient selection has improved due to more extensive radiologic evaluation, there has been an increase in R0 resections from 14 to 40 %, a decrease in operative mortality from 24 to 5 %, and an improvement in overall median survival from 3 to 12 months [10]. Thus, it is critically important to thoroughly assess the patient's performance status, comorbidities, and initial tumor biology to make the correct choices regarding reoperation.

In patients with T3 or T4 tumors, counseling must be provided noting lack of intervention essentially precludes any chance of long-term survival.

Stage for stage, re-resection for incidentally discovered gallbladder cancer is safe and equivalent to initial definitive resection. In one retrospective study from Memorial Sloan Kettering, no significant differences were noted in regards to mortality, postoperative complication rate, or long-term outcomes between patients with incidental gallbladder cancer and preoperatively diagnosed cases undergoing definitive re-resection. In addition, prior surgical resection was not statistically associated with a decreased likelihood of obtaining an R0 resection and, in fact, was less likely to be associated with metastatic disease [16].

Extent of Re-resection

At the time of reexploration for patients with initial T1b, T2, and T3 tumors, thorough examination of the abdomen for peritoneal disease should occur. As has been done for patients with gastric and pancreatic cancers, peritoneal lavage for cytology should be performed with cytologic results reported by immediate analysis if possible. The planned operation should include resection of the gallbladder fossa (liver segments IVb and V) along with a complete lymphadenectomy of the hepatoduodenal ligament. Some have suggested that major hepatectomy, common bile duct (CBD) excision, and resection of adjacent organs improves patient survival, but only small retrospective studies support this concept. Tumor biology often trumps the extent of surgical resection especially when dealing with secondary surgery. Major hepatic and CBD resections should not be performed routinely, and are only necessary when these structures are directly involved with residual tumor. A microscopically positive cystic duct margin, however, is an indication for common duct resection as greater than one-third patients have residual disease in the resected common duct compared to <5 % of those with a negative cystic duct margin [13].

Tumor Seeding and Port Site Metastases

Retrospective reviews have described the potential risk of tumor seeding during the laparoscopic cholecystectomy prior to the cancer diagnosis. Peritoneal carcinomatosis is observed during follow-up of patients with gallbladder carcinoma, suggesting that tumor seeding of the peritoneum, port sites, and subcutaneous tissues occurs as a result of gallbladder perforation, bile and stone spillage, and perhaps seeding of laparoscopic instruments. Perforation may occur at the time of dissection of the gallbladder initially or during removal from the umbilical port site.

Port site recurrence rates after laparoscopic cholecystectomy can occur in up to 40 % of patients, but most reports put the number in single digits, as higher incidences are associated with known gallbladder perforation. Some clinicians have suggested that port-site resection be done routinely since doing so removes a potential site of tumor seeding or peritoneal disease [16]. At present, conflicting evidence makes it difficult to determine whether to routinely remove all port sites at the secondary laparotomy. A retrospective study out of the Memorial Sloan Kettering Cancer Center examined their incidence of port site metastasis [17]. In their study, 113 incidentally discovered gallbladder cancer patients who presented after laparoscopic cholecystectomy for definitive oncologic resection over a 17-year period were reviewed. Of the 69 patients who had undergone port-site resection, 13 (19 %) patients had port-site metastases. These patients all had T2 or T3 primary tumors. These findings significantly correlated with the development of peritoneal metastasis. After adjustment for T and N stage, however, port-site resection was not associated with overall or recurrence-free survival when compared to patients who did not undergo port-site resection. However, median survival of T2/T3 patients in whom port-site metastases were confirmed was 17 months compared to 42 months in patients with negative port sites. Thus, port-site resection may be useful for accurate staging of metastatic disease and have implications for prognosis and adjuvant therapies.

Of note, the management of bile spillage during the initial operation and the entity of free gallstones found within the peritoneal cavity at reoperation for incidental gallbladder carcinoma is unclear. Most would advocate removal of the residual stones and careful localized washout of the abdomen when possible but there is little evidence that doing so improves long-term outcome or prognosis of the patient.

Conclusion

In summary, incidentally discovered gallbladder carcinoma often leads to an early stage presentation of the cancer and treatment has the potential for cure. Patients with the earliest stages (pT1a) do not require further reoperation. For patients with Stage T1b, controversy exists as to the benefits of reoperation, but many surgeons would recommend reoperation in the young, fit, healthy patient without serious comorbidities. In patients with Stage T2 and T3 tumors discovered incidentally at the time of their initial operation, complete radiologic work-up should proceed including obtaining serum CEA and Ca 19-9 levels. In the absence of known metastatic disease, reoperation should be done unless patient factors preclude a more extensive procedure. The true benefits of adjuvant therapies such as chemotherapy and radiotherapy are unclear from the current data.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. CA Cancer J Clin. 2006;56:106–30.
2. Varshney S, Butturini G, Gupta R. Incidental carcinoma of the gallbladder. Eur J Surg Oncol. 2002;28:4–10.
3. http://www.cancer.gov/cancertopics/pdq/treatment/gallbladder/HealthProfessional/page3
4. Pitt S, Jin L, Hall B, et al. Incidental gallbladder cancer at cholecystectomy when should the surgeon be suspicious? Ann Surg. 2014;260:128–33.
5. Shih SP, Schulick RD, Cameron JL, et al. Gallbladder cancer: the role of laparoscopy and radical resection. Ann Surg. 2007;245:893–901.
6. Steinert R, Nestler G, Sagynaliev E, et al. Laparoscopic cholecystectomy and gallbladder cancer. J Surg Oncol. 2006;93:682–89.
7. Joo I, Lee JY, Kim SJ, et al. Differentiation of adenomyomatosis of the gallbladder from early-stage, wall-thickening-type gallbladder cancer using high-resolution ultrasound. Eur Radiol. 2012;23(3):730–38.
8. Kwon AH, Imamura A, Kitade H, Kamiyama Y. Unsuspected gallbladder cancer diagnosed during or after laparoscopic cholecystectomy. J Surg Oncol. 2008;97:241–45.
9. Belin LJ, Lewis CE, Fong Y. Management of incidental gallbladder carcinoma. In: Carcinoma of the gallbladder: the current scenario. New Delhi: Elsevier; 2014. p. 54–66. ECAB clinical update surgical gastroenterology and liver transplantation.
10. Duffy A, Capanu M, Abou-Alfa GK, et al. Gallbladder cancer (GBC): 10=year experience at Memorial Sloan-Kettering Caner Centre (MSKCC). J Surg Oncol. 2008;98:485–9.
11. Lundberg O, Kristofferson A. Wound recurrence from gallbladder cancer after open cholecystectomy. Surgery. 2000;127:296–300.
12. Ouchi K, Mikuni J, Kakugawa Y, Organizing Committee, The 30th Annual Congress of the Japanese Society of Biliary Surgery. Laparoscopic cholecystectomy for gallbladder carcinoma: results of a Japanese of 498 patients. J Hepatobiliary Pancreat Surg. 2002;9:256–60.
13. Pawlik TM, Gleisner AL, Bigano L, et al. Incidence of finding residual disease for incidental gallbladder carcinoma: implications for re-resection. J Gastrointest Surg. 2007;11(11):1478–86.
14. Bartlett DL, Fong Y, Fortner JG, et al. Long-term results after resection for gallbladder cancer: implications for staging and management. Ann Surg. 1996;224:639–46.
15. Konstantinidis IT, Deshpande V, Genevay M, et al. Trends in presentation and survival for gallbladder cancer during a period of more than 4 decades: a single-institution experience. Arch Surg. 2009;144:441–7.
16. Fong Y, Jarnagin W, Blumgart LH. Gallbladder cancer: a comparison of patients presenting initially for definitive operation with those presenting after prior noncurative intervention. Ann Surg. 2000;232:557–69.
17. Maker AV, Butte JM, Oxenberg J, et al. Is port site resection necessary in the surgical management of gallbladder cancer? Ann Surg Oncol. 2012;19:409–17.