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Gallbladder Cancer

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Gallbladder cancer is a highly aggressive malignancy that usually presents at an advanced, incurable stage.[1] It is the fifth most common gastrointestinal tumor and leads to approximately 2,800 deaths in the United States annually.[2] Gallbladder cancer has a propensity for early lymph node metastasis and for direct invasion into the liver, as well as a remarkable tendency to seed the peritoneal cavity, biopsy tracts, and laparoscopic-port sites. The median survival is less than 6 months after diagnosis. As is typical with solid gastrointestinal malignancies, chemotherapy has not had a significant impact on this tumor. Despite its aggressive nature, however, long-term cures have been reported after surgical resection, even with advanced locoregional disease. Therefore, it is important to understand the natural history of gallbladder cancer, its prognostic factors, and the appropriate management based on the stage of disease. Gallbladder cancer is occasionally diagnosed incidentally on pathologic review of cholecystectomy specimens, and it may be in this population that appropriate surgical management has the most impact on long-term survival. In this chapter, we will review the epidemiology, pathology, and staging of gallbladder cancer and describe the appropriate surgical management based on the stage of the disease.

EPIDEMIOLOGY

Careful epidemiologic studies have been performed in gallbladder cancer, and pronounced geographic and racial differences exist in the frequency of this tumor.[3] High rates of gallbladder cancer are seen in South American countries, intermediate rates are observed in many European countries, and lower rates are observed in the United States, and the United Kingdom. Within the United States, Native Americans have been found to have a high incidence of gallbladder cancer, and urban areas show higher incidences than rural regions. Lower socioeconomic status may lead to delayed access to cholecystectomy for gallstones, which may increase gallbladder cancer rates.[4]

Women are two to six times more commonly affected by gallbladder cancer than men, and the incidence steadily increases with age.[5,6] Other factors that increase the risk for gallbladder cancer include obesity, a high-carbohydrate diet, smoking, and alcohol use.[7] Clearly, the most significant risk factor for gallbladder cancer is the presence of a chronic inflammatory state of the gallbladder, usually as a result of gallstones. Most of the variance in geographic and racial gallbladder cancer rates can be explained by the varying incidence of gallstones in the populations. Nevertheless, only 0.3 to 3.0 percent of patients with gallstones develop gallbladder cancer. An appealing hypothesis is that chronic inflammation acts as a promoter for some mutational defects related to carcinogenic exposure. Kowalewski and Todd demonstrated that carcinoma of the gallbladder could be induced in 68 percent of hamsters that had cholesterol pellets inserted into their gallbladders to induce an inflammatory state, and that were then given the carcinogen dimethylnitrosamine.[8] The composition of bile from patients with gallbladder cancers has been studied for the presence of carcinogens. A higher concentration of secondary bile acids was found in patients with gall-

bladder cancer compared with controls having cholelithiasis alone.[9]

Because of the clear association of gallbladder cancer with cholelithiasis, it is often debated whether prophylactic cholecystectomy is indicated to prevent the development of gallbladder cancer. Because gallstones are common in the population and the incidence of gallbladder cancer in patients with gallstones is low, it is still recommended that cholecystectomy be performed only in patients with symptomatic cholelithiasis. The complication rate from cholecystectomy, although quite low, would still counter any potential benefit in the prevention of gallbladder cancer. The exception is in patients found to have a "porcelain" gallbladder, where the gallbladder wall is replaced by calcium as a result of chronic inflammation. In these patients, the gallbladder cancer incidence has been reported to be as high as 25 percent, and cholecystectomy is therefore indicated even in the asymptomatic setting.[10]

ANATOMY

Anatomic considerations are important in the management of gallbladder cancer. The gallbladder straddles the intersegmental plane between liver segments IVb and V. Tumors of the fundus and the body may invade liver segments IVb and V at an early stage. It is because of this that routine liver resection is recommended in the management of gallbladder cancer, as described below. Tumors that invade through the wall of the gallbladder away from the liver lead to peritoneal carcinomatosis at an early stage. Tumors of the infundibulum or cystic duct readily obstruct the common bile duct and/or portal vein and may become unresectable at an early time point. These often require extended liver resections (right trisegmentectomy) because of the proximity to the right portal pedicle.

The lymphatic drainage of the gallbladder has been mapped in detail[11] (Fig. 10–1). In general, the lymphatic drainage descends around the bile duct and involves cystic and pericholedochal lymph nodes first. From pericholedochal nodes, the drainage continues to nodes posterior to the pancreas, portal vein, and common hepatic artery. Finally, the lymphatic flow reaches the lymph nodes of the interaortocaval region, celiac artery, and superior mesenteric artery. There is evidence to suggest that some connections are made directly from pericholedochal nodes to interaortocaval nodes, which explains the difficulty in controlling this disease with a periportal lymph node dissection.

PATHOLOGY AND STAGING

Gallbladder cancer appears to develop from dysplastic mucosa that progresses to carcinoma in situ and then to invasive carcinoma.[12] Benign adenomas do appear in the gallbladder, but most cancers develop without a precursor adenoma. In one series, there was a 5-year difference between the mean age of the patients with dysplasia and those with carcinoma in situ, and a 10-year difference between the mean ages of patients with carcinoma in situ and those with invasive carcinoma.[12] Approximately 60 percent of tumors originate in the fundus of the gallbladder, 30 percent originate in the body, and 10 percent originate in the neck.[12] Gallbladder cancers can be categorized into infiltrative, nodular, combined nodular infiltrative, papillary, and combined papillary-infiltrative forms.[13] Infiltrated tumors cause thickening and induration of the gallbladder wall. They spread easily in a subserosal plane, which is the same plane used for routine cholecystectomy. Nodular types show early invasion through the gallbladder wall into the liver or neighboring structures and may be easier to surgically control than the infiltrative form. Papillary carcinomas have the best prognosis and exhibit a polypoid cauliflower-like appearance. These may completely fill the lumen of the gallbladder, with only minimal invasion of the gallbladder wall.

Histologically, the most common type of gallbladder cancer is adenocarcinoma. Other types, such as adenosquamous carcinoma, oat cell carcinoma, and sarcomas, have also been described. Rare primary histologies such as carcinoid, lymphoma, and melanoma have been reported. Adenocarcinomas can be divided into multiple subtypes, including well-differentiated, papillary, intestinal type, pleomorphic giant cell, poorly differentiated small cell, signet ring cell, clear cell, colloid, and the choriocarcinoma-like cell subtype.[12] The papillary histologic subtype has the best prognosis whereas the poorly

differentiated small cell tumor has the worst prognosis.[2] Recently, gallbladder cancers have been divided into nonmetaplastic and metaplastic types on the basis of metaplastic changes in the tumor tissues. (This is similar to the classification of gastric carcinomas into intestinal and diffuse types.) The metaplastic type showed a significantly improved survival rate.[14] Gallbladder cancers should be histologically graded from G1 (well differentiated) to G4 (undifferentiated). It is not clear that this grading provides any improved prognostic information over histologic subtype. Papillary tumors are well differentiated and have an improved prognosis. The majority of patients present with grade 3 (poorly differentiated) tumors.

In 92 percent of invasive carcinomas, 86 percent of carcinomas in situ, and 28 percent of dysplastic epithelia, p53 protein is identifiable (and believed dysfunctional).[15] In 39 percent of gallbladder cancers, K-*ras* mutations are identified,[16] and it is felt that allele-specific deletions of the p53, deleted in colon cancer (DCC), and 9p genes play an important role in the pathogenesis of gallbladder cancer. Other important genetic abnormalities in gallbladder cancer include overexpression of the c-erbB-2 gene and decreased expression of the nm23 gene product.[17,18]

Gallbladder cancer can spread by direct invasion through the gallbladder wall into the liver or peritoneal cavity. The gallbladder has a narrow wall consisting of a thin lamina propria and a single muscle layer. Other viscera are composed of at least two muscle layers. Once a gallbladder cancer penetrates this muscle layer, it has access to major lymphatic and vascular channels as well as the liver or peritoneal cavity by penetration through the wall. This may be the reason that gallbladder cancer seems to present in such advanced stages. An autopsy study demonstrated a 94.4 percent incidence of lymphatic metastases and a 64.8 percent incidence of hematogenous dissemination.[19] Boerma and colleagues reviewed the literature and determined that only 10 percent of gallbladder cancers were confined to the gallbladder wall at presentation, 59 percent invaded the liver, 45 percent invaded regional lymph nodes, 34 percent had distant hepatic metastases, and 20 percent had extrahepatic hematogenous metastases.[20] Perpetuo and colleagues demonstrated that at

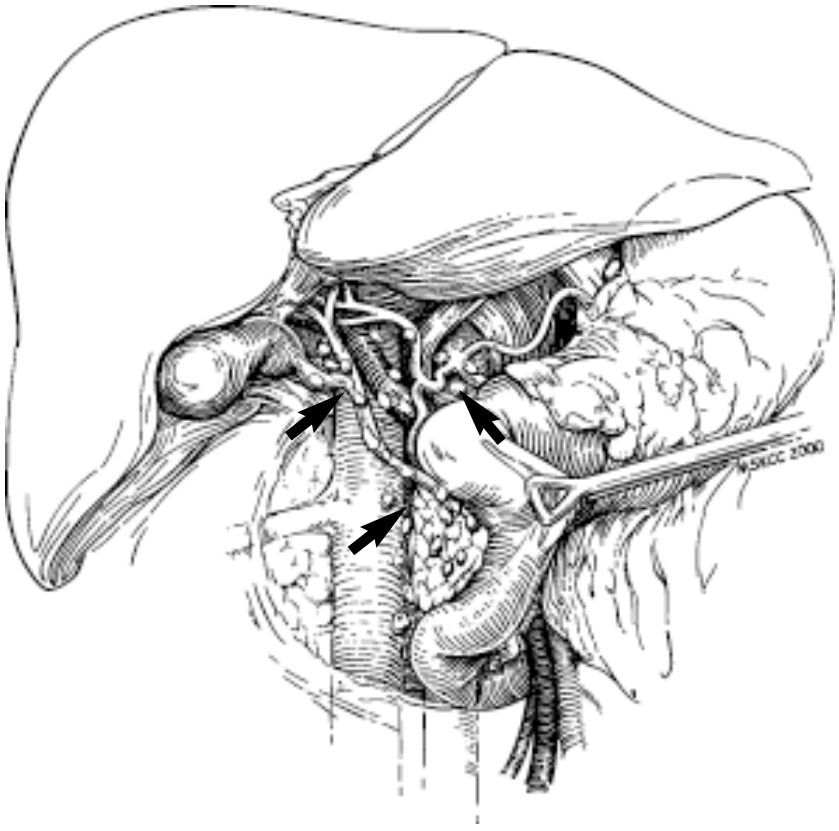

Figure 10–1. Lymph node metastases from primary gallbladder cancer spread in a nonuniform manner. The small arrow points to first-level involvement (N1), and the big arrows point to second-level involvement (N2). Some lymphatic connections are made directly from pericholedochal nodes to interaortocaval nodes. All of these regions should be dissected during an extended cholecystectomy for gallbladder cancer.

Table 10–1. SUMMARY OF THE TUMOR-NODE-METASTASIS (TNM) STAGING SYSTEM*

Stage	Description
1	Mucosal or muscular invasion (T1N0M0)
2	Perimuscular-tissue invasion (T2N0M0)
3	Transmural invasion, liver invasion < 2 cm; lymph node metastasis to hepatoduodenal ligament (T3N0M0, T1–3N1M0)
4A	Liver invasion > 2 cm (T4N0M0, T4N1M0)
4B	Distant nodal (outside porta hepatis) or hematogenous metastasis (TxN2M0, TxNxM1)

*Developed by the American Joint Commission on Cancer/UICC.

autopsy, 60 percent of patients had intraperitoneal metastases of gallbladder cancer.[1] The most common site of extra-abdominal metastases is the lung, but it is rare to have pulmonary metastases in the absence of advanced intra-abdominal disease.

The stage of disease is the most reliable predictor of outcome and ultimately outweighs histology, grade, or other biologic parameters. Multiple staging systems have been described for gallbladder cancer, and this creates confusion when attempting to compare the treatment results of different series in the literature. The main staging systems over the past 5 years include the modified Nevin system,[21,22] the Japanese Biliary Surgical Society system,[23] and the American Joint Commission on Cancer (AJCC)/Union Internationale Centre le Cancer (UICC) tumor-node-metastasis (TNM) staging system[24] (Table 10–1). In the AJCC/UICC TNM staging system, stage 1 (T1, N0) represents tumors confined to the mucosa or muscularis level of the gallbladder. It is important to realize that tumors can arise in Rokitansky-Aschoff sinuses and be included in stage 1 even though they are in a subserosal position. Stage 2 (T2, N0) represents tumors that invade the perimuscular connective tissue without extension beyond the serosa or into the liver and without lymph node metastases. Stage 3 (T3, N0, Tx, N1) represents (a) tumors that invade through the serosa and less than 2 cm into the liver and (b) tumors involving first-level lymph nodes in the hepatoduodenal ligament. Stage 4A (T4, N0.1) represents liver invasion greater than 2 cm into the liver, and stage 4B (Tx, N2) represents metastases to second-level lymph nodes or distant metastases including any lymph node basins beyond the hepatoduodenal ligament. We have previously reported that curative resection is possible in patients with liver invasion greater than 2 cm (T4). Such liver invasion represents a better prognosis than that of distant nodal metastases or hematogenous metastases, and it should therefore be included in stage 3 disease.[25]

WORK-UP

The clinical presentation of gallbladder cancer is difficult to separate from that of biliary colic. Advanced symptoms such as persistent pain, weight loss, and jaundice are often signs of unresectability. Elderly patients with a history of biliary colic that changes to a persistent, unrelenting, dull pain should be suspected of having gallbladder cancer, especially in the presence of weight loss or a right-upper-quadrant mass. Any new right-upper-quadrant symptoms should prompt a work-up.

The work-up for right-upper-quadrant pain or biliary colic generally starts with an ultrasound examination of the gallbladder. Any suspicion of a mass in or near the gallbladder should be considered for further preoperative work-up. Other signs of malignant disease on ultrasound examination include discontinuous mucosa, echogenic mucosa, and submucosal echolucency.[26] Diffuse thickening of the gallbladder is also common in gallbladder cancer but is also found in benign conditions. Many patients who are found incidentally at the time of cholecystectomy to have gallbladder cancer are found retrospectively to have had suspicious lesions on ultrasound examination that were not appropriately worked up.

Laboratory tests should include liver function tests and hematocrit. Advanced cases may demonstrate anemia and elevated alkaline phosphatase and bilirubin. Gallbladder cancer may obstruct the right hepatic bile duct at an early stage and may present with elevated alkaline phosphatase and normal bilirubin. Tumor markers may be of help and should be considered if gallbladder cancer is suspected. Serum carcinoembryonic antigen (CEA) greater than 4 ng/mL is 93 percent specific and 50 percent sensitive for detecting gallbladder cancer in the presence of appropriate symptoms,[27] and a CA 19-9 serum level greater than 20 U/mL is 79.4 percent sensitive and 79.2 percent specific.[28]

Further radiologic work-up is indicated if the diagnosis of gallbladder cancer is suspected. A helical computed tomography (CT) scan with fine cuts through the liver may provide improved imaging over ultrasonography and should be examined carefully for evidence of liver metastases and enlarged celiac, perihepatic, and interaortocaval lymph nodes. A magnetic resonance (MR) scan with MR cholangiography is an ideal study, and we find it to be sensitive for small hepatic metastases as well as common bile duct involvement. Magnetic resonance angiography may help eliminate the option of resection if the portal vein or common hepatic artery is involved. Positron emission tomography (PET) has not been described as a diagnostic tool for primary gallbladder cancer (ie, for differentiating gallbladder cancer from chronic cholecystitis), but it may have a role in staging. Endoscopic ultrasonography is a sensitive study for peripancreatic and periportal adenopathy and may be helpful as an adjunct to other imaging modalities. Unfortunately, enlarged inflammatory lymph nodes are common in this area and are difficult to differentiate from metastatic tumor. In some cases, a needle biopsy is possible through the endoscope and may help avoid a laparotomy. Endoscopic retrograde cholangiography or percutaneous cholangiography may be required to help define resectability or palliative options. Bile cytology has been shown to be as high as 73 percent sensitive for the diagnosis of gallbladder cancer.[29]

In cases where gallbladder cancer is suspected, a needle biopsy can be considered. In general, if curative resection is contemplated, the needle biopsy should be performed at the time of the procedure, with the plan of proceeding to an extended operation if cytology or frozen-section biopsy confirms the diagnosis of gallbladder cancer. Because of a high propensity for gallbladder cancer to seed biopsy tracks and the peritoneal cavity, it is best to avoid preoperative biopsy if possible. For stage 4 disease, a needle biopsy can be diagnostic and can help avoid an operative exploration.

SURGICAL TREATMENT

Benign polyps of the gallbladder are common and are often picked up on screening ultrasonography. The risk of gallbladder cancer in patients with these polyps depends on the size and number of the polyps. A large solitary polyp has a higher likelihood of being malignant than numerous small polyps. Yang and colleagues described malignant lesions as more common in patients over 50 years old with solitary lesions greater than 1 cm.[30] Shinkai and colleagues recommend cholecystectomy in patients with fewer than three polyps, regardless of size.[31] Kuboto and colleagues[32] recommend that polyps larger than 18 mm should be managed with open cholecystectomy (rather than a laparoscopic approach) to avoid the potential for peritoneal and port-site seeding.

With the adoption of laparoscopic cholecystectomy as the standard of care for less morbidity and improved recovery time, prophylactic cholecystectomy in the setting of asymptomatic cholelithiasis has been considered and discussed. The incidence of gallbladder cancer is quite low compared to the incidence of gallstones in the population, and the prevention of cancer should not be taken into consideration in this decision. Nevertheless, any abnormality in the wall of the gallbladder on ultrasound examination as discussed above should be taken seriously and worked up further. Because of the high reported incidence of gallbladder cancer in some series, a calcified or "porcelain" gallbladder is an indication for open cholecystectomy.[10]

Significant variations in the management of gallbladder cancer exist at different institutions across the United States and the world. Surgeons' recommendations range from simple cholecystectomy alone to combined extended hepatectomy, resection of the common bile duct, and pancreaticoduodenectomy[33] for the same stage of disease. The accumulated retrospective data describing outcomes after surgical resection help define the appropriate surgical management for gallbladder cancer. The stage of the disease is the most important determinant of the outcome and extent of resection. Other considerations include the location of the tumor and whether it is a reresection after simple cholecystectomy or an initial resection for suspected disease.

In 1954, Glenn and Hayes originally described the radical cholecystectomy for treatment of gallbladder cancer. Their description included a wedge resection

of the gallbladder bed and regional lymphadenectomy of the hepatoduodenal ligament.[34] The recommended procedure today is similar to this but may vary, depending on the stage of disease as well as on the circumstances under which the resection is being performed. The procedure is referred to as an extended cholecystectomy (Fig. 10–2). We believe that the extended cholecystectomy should include segments IVb and V of the liver en bloc with the gallbladder, as well as a complete clearance of the periportal lymph nodes (Fig. 10–3), the posterior pancreaticoduodenal lymph nodes, and interaortocaval lymph nodes in this region. A simple wedge resection of the gallbladder bed may be as effective as a formal segmental resection, but it is difficult to maintain a reliable margin of tissue. A formal segmentectomy, especially when preceded by inflow segmental occlusion with demarcation of the intersegmental plane, is a safe, uniform, and reliable procedure.

Numerous studies have demonstrated that a simple cholecystectomy is curative for stage 1 disease (T1, N0)[35–37] (Table 10–2). For accurate pathologic T1 staging, no extended cholecystectomy is indicated, and a simple cholecystectomy should result in a 100 percent 5-year survival. If the lesion is recognized intraoperatively, then a cystic duct lymph node and periportal lymph node should be sampled to rule out stage 2 disease. This is especially important if the frozen section does not clearly delineate the thickness of the lesion. If a T1 gallbladder cancer is recognized only incidentally on pathologic examination, then no further surgery is indicated. The incidence of lymph node metastasis is almost nonexistent in the setting of T1 disease.[38] It is essential that the cystic duct margin is not involved with tumor. A positive margin dictates the need for reresection. Shirai reported recurrences in only 2 of 89 patients with stage 1 gallbladder cancer.[39] Both patients had tumor involving the cystic duct margin, and both went on to die of their disease. Also, if there is any doubt that the pathologic staging is not accurate, a more extensive reresection is justified.

Patients with stage 2 disease (N2, N0) are best treated with an extended cholecystectomy. The cancer should ideally be recognized and diagnosed prior to disrupting the subserosal plane (which may be invaded with tumor) during simple cholecystecomy, thus avoiding tumor spillage. Unfortunately, since most of these cases will initially be addressed

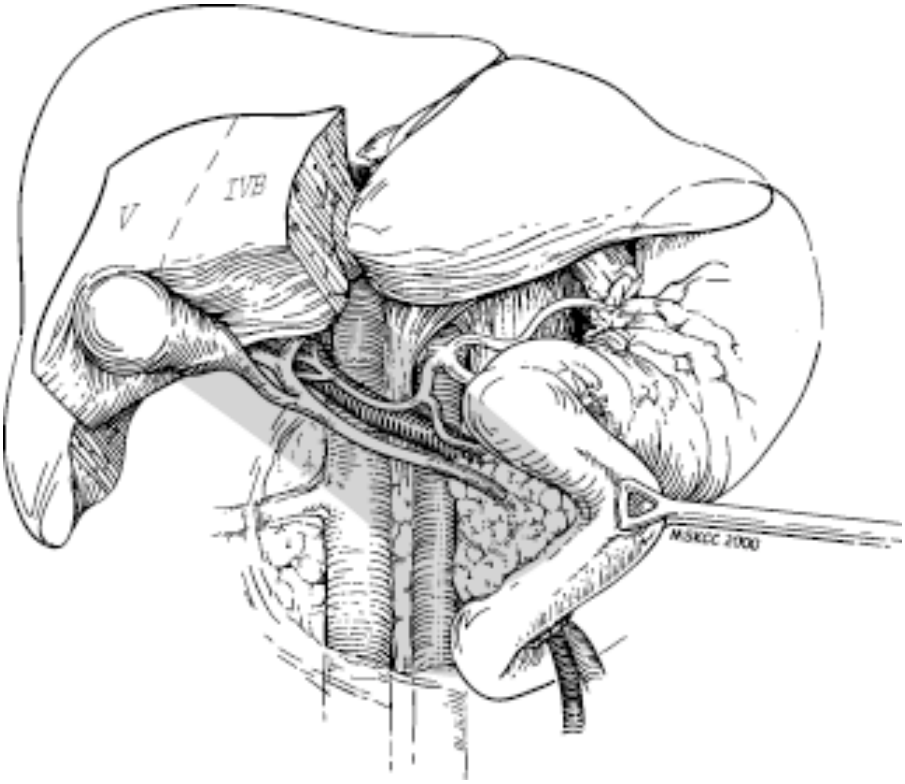

Figure 10–2. An extended cholecystectomy includes the gallbladder en bloc with segments IV and V of the liver. Lymph nodes should be dissected completely from the shaded region.

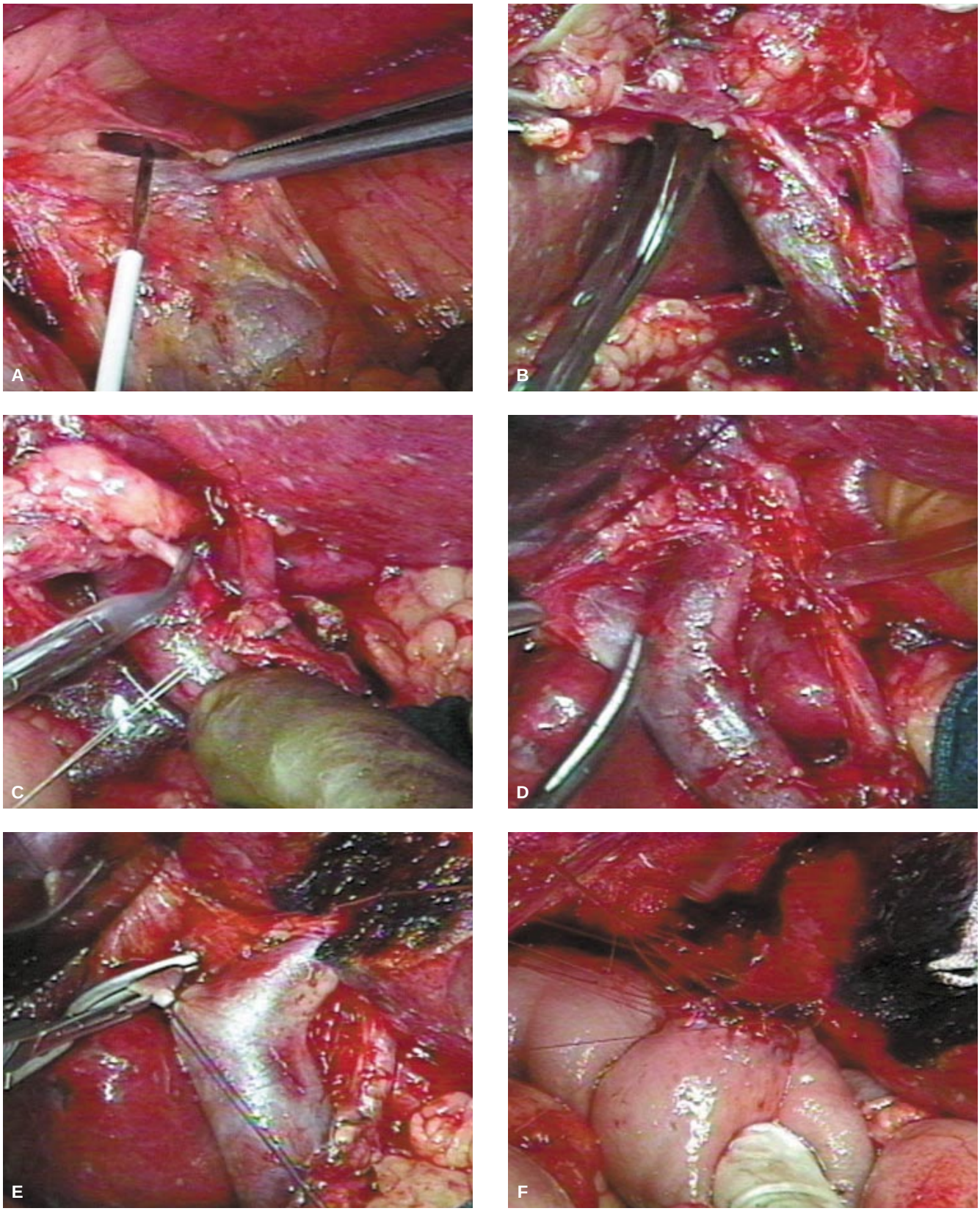

Figure 10–3. A complete periportal lymph node dissection, including bile duct resection in conjunction with a right trisegmentectomy, for a patient with gallbladder cancer. *A,* Beginning the dissection of periportal adipose tissue. *B,* The bile duct is swept superiorly with the specimen, leaving the skeletonized portal vein and hepatic artery. *C,* The right hepatic artery is divided at its origin. *D,* Dissection of the portal vein into the liver. *E,* The right portal vein is divided at its confluence. *F,* An end-to-side left hepaticojejunostomy.

Table 10–2. RETROSPECTIVE REVIEWS: ACTUARIAL SURVIVAL AFTER RESECTION OF STAGE 1 GALLBLADDER CANCERS

Lead Author	Reference	Year	N	Procedure	5-yr Survival (%)
Shirai	42	1992	39	Simple cholecystectomy	100
Yamaguchi	35	1992	6	Simple cholecystectomy	100
Matsumoto	40	1992	4	Extended cholecystectomy	100
Oertli	55	1993	6	Simple cholecystectomy	100
de Aretxabala	37	1997	32	69% simple cholecystectomy	94

N = number of patients.

laparoscopically, intraoperative diagnosis is uncommon for T2 disease. It is perhaps in these patients that radical reresection creates the best chance of a long-term cure. When an extended cholecystectomy is performed for stage 2 disease, the 5-year survival has been reported to be as high as 100 percent,[40] but it probably falls in the range of 70 to 90 percent[36,37,41] (Table 10–3). In one study by Shirai and colleagues, 35 patients underwent simple cholecystectomy for stage 2 disease and had a 5-year survival of 40.5 percent.[36] Ten patients in that series underwent extended cholecystectomy for stage 2 disease and had a 5-year survival of 90 percent, suggesting that extended cholecystectomy is a better operation in this setting.

As discussed above, a simple cholecystectomy uses the subserosal plane of the gallbladder as the plane of dissection. By definition, this plane is violated with tumor cells in patients with T2 tumors, and a positive margin is almost unavoidable. In a review by Yamaguchi and Tsuneyoshi of 25 patients with T2 tumors, 11 had positive microscopic margins after simple cholecystectomy.[35] No patients in this review survived 5 years after having a positive resection margin without reresection. Lymph node metastases are common with T2 primary tumors, providing another reason in favor of radical reresection after simple cholecystectomy. In our own series, 6 of 13 patients with T2 disease had metastatic disease to regional lymph nodes.[25] De Aretxabala and colleagues compared 20 patients undergoing curative reresection for T2 tumors incidentally found at the time of cholecystectomy to 18 patients who did not undergo reresection and demonstrated a 50 percent improved 5-year survival rate (70% vs 20%).[37]

For patients with stage 3 disease (T3, N1), an extended cholecystectomy is the recommended treatment approach. This may include en bloc resection of the common bile duct for grossly positive periportal lymph nodes to improve periportal lymph node clearance. Patients with metastases to N1 nodes (cystic duct or periportal lymph nodes) can be cured, thus further justifying reresection for all tumors with transmural invasion. Onoyama and colleagues reported a 5-year survival of 60 percent for patients having metastatic disease to N1 nodes.[23] Shirai and colleagues reported a 45 percent 5-year survival for patients with metastases to lymph nodes.[42] Overall for stage 3 disease, the 5-year survival has been reported to be as high as 63 percent after extended resection.[25] The 3-year survival has ranged from 38 to 80 percent in various trials[21,40,41]

Table 10–3. RETROSPECTIVE REVIEWS: ACTUARIAL SURVIVAL AFTER RESECTION OF STAGE 2 GALLBLADDER CANCERS

Lead Author	Reference	Year	N	Procedure	3-yr Survival (%)
Shirai	42	1992	35	Simple cholecystectomy	57
			10	Extended cholecystectomy	90
Yamaguchi	35	1992	25	Simple cholecystectomy	36
Matsumoto	40	1992	9	Extended cholecystectomy	100
Oertli	55	1993	17	Simple cholecystectomy	29
Bartlett	25	1996	8	Extended cholecystectomy	100
Paquet*	—	1998	5	Extended cholecystectomy	100

N = number of patients.
*Data from Paquet KJ. Appraisal of surgical resection of gallbladder carcinoma with special reference to hepatic resection. J Hepatobiliary Pancreat Surg 1998;5:200–6.

Table 10–4. RETROSPECTIVE REVIEWS: ACTUARIAL SURVIVAL AFTER EXTENDED RESECTION OF STAGE 3 AND 4 GALLBLADDER CANCERS

Lead Author	Reference	Year	N	Stage	3-yr Survival (%)
Matsumoto	40	1992	8	3	38
Chijiiwa	41	1995	12	3	80
Onoyama	23	1995	12	3	44
Bartlett	25	1996	8	3	63
Todoroki	52	1991	27	4	7
Nimura	33	1991	14	4	10
Matsumoto	40	1992	27	4	25
Chijiiwa	41	1995	11	4	11
Onoyama	23	1995	14	4	8
Bartlett	25	1996	7	4	25

N = number of patients.

(Table 10–4). For these patients, it is clear that simple cholecystectomy or a lesser operation would not result in long-term survival.

In general, stage 4 gallbladder cancer represents an aggressive malignancy that is beyond surgical treatment. Some investigators, however, have recommended aggressive resections of stage 4 disease under certain circumstances.[43] Patients with stage 4A (T4, N0,1) tumors may achieve long-term survival after an extended resection[25] (Fig. 10–4). Data from Memorial Sloan-Kettering Cancer Center revealed a 33 percent 5-year survival for patients with completely resected stage 4 tumors.[25] The only long-term survivors were those with T4N0 disease, which suggests that these patients had a different biology from those with distant lymph node metastases. Patients with N2 disease seem to have a very poor prognosis; for this patient population as well as those with distant hematogenous metastases, we advocate palliative care alone. Some investigators have reported anecdotal cases of long-term cures in patients with N2 disease,[40,42] but most have reported a poor outcome that does not justify the morbidity of the extended resection.

Many patients will have gallbladder cancer identified incidentally at the time of cholecystectomy and probably after laparoscopic cholecystectomy. Since nodal metastases cannot be assessed for these patients, the T stage of the primary tumor dictates subsequent management. As mentioned earlier, patients with T1 disease do not require reoperation. There is little to no chance of lymph node metastases, and a simple cholecystectomy is considered curative.[38] Patients with T2 disease are recommended to undergo a reoperation because 40 to 50 percent will have a positive margin on the primary and 40 to 50 percent will have regional lymph node metastases.[38] The recommended operation is an extended cholecystectomy, and it is recommended that laparoscopic port sites be excised to minimize the risk of recurrences of tumor at the port sites.[44] It is important to accept the possibility of an extrahepatic bile duct resection during the extended procedure because scar tissue in this region may be difficult to differentiate from tumor and may prevent a good lymph node clearance. If scarring is minimal and if lymph node dissection can be performed while leaving the bile duct intact, then lymph node dissection is preferable as the complication rate of the procedure is increased in patients undergoing resection of the bile duct.

Stage T3 and T4 tumors will most likely be recognized preoperatively or at the time of initial surgery, and the appropriate operation is usually extended cholecystectomy, as discussed earlier. It is important for all surgeons and pathologists to closely examine all gallbladder specimens at the time of resection. Any suspicious areas should be examined histologically by frozen section for evidence of tumor cells. If a suspicious area is recognized prior to cholecystectomy, a limited biopsy (ideally by needle aspiration) should be performed prior to cholecystectomy to avoid dissection in the subserosal plane and spreading tumor cells into the peritoneal cavity. Gallbladder cancer has a remarkable propensity to seed the peritoneal cavity, needle biopsy tracts, and abdominal incisions. Care should be taken to minimize tumor cell spread during biopsies and resection if a curative potential exists. If a positive intraoperative biopsy specimen is obtained, then en bloc extended cholecystectomy should be performed at the initial operation. Appropriate initial management provides the best chance of long-term survival.

Radical operations, including trisegmentectomy of the liver, extrahepatic bile duct resection, and en bloc pancreaticoduodenectomy, have been described for advanced cases of gallbladder cancer.[39] These types of radical procedures should not be recommended in most cases but may be beneficial under certain circumstances. Hepatic trisegmentectomy for large primary tumors without distant nodal or

hematogenous metastases may lead to long-term survival. Smaller tumors at the infundibulum may require a trisegmentectomy because of early tumor involvement of the right portal pedicle. As discussed above, scarring in the porta hepatis can sometimes be difficult to differentiate from tumor tissue. In these circumstances, it may also be necessary to perform extended hepatectomy and resection of the extrahepatic bile duct. While pancreaticoduodenectomy has been advocated for patients with bulky lymph node involvement in the peripancreatic nodal group, this represents stage 4B disease and has such a poor prognosis that this should not be generally recommended.

In series of extended cholecystectomies, operative morbidity ranges from 5 to 46 percent and mortality from 0 to 21 percent.[21,45,46] The morbidity and mortality rates of major liver resections have decreased in recent reports even in the elderly population; with careful patient selection, the extended cholecystectomy should thus be a very safe procedure. In a multi-institution review from Japan of 1,686 gallbladder cancer resections, the authors

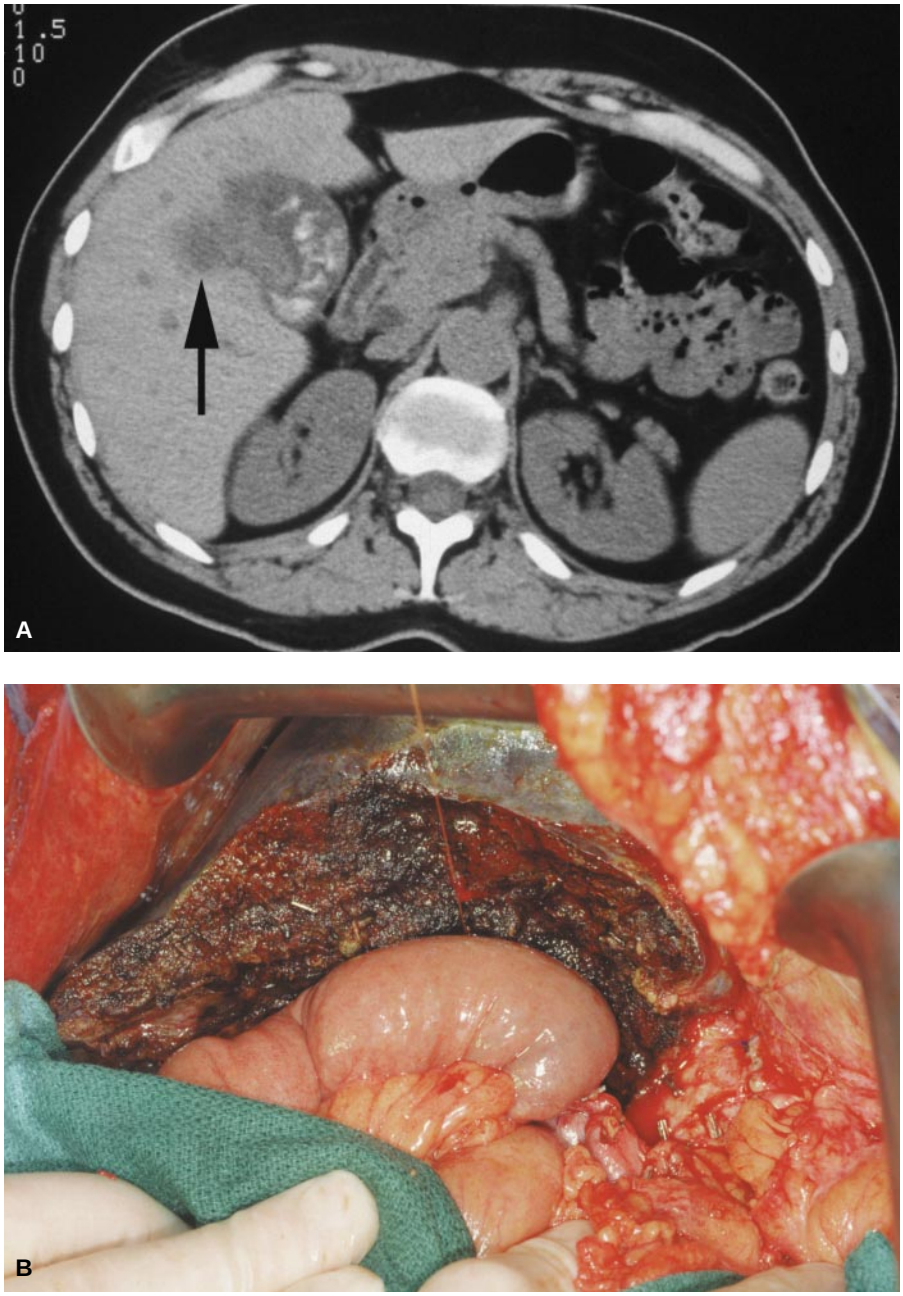

Figure 10–4. Stage 4 gallbladder cancer. *A,* A computed tomography scan demonstrating an obvious T4 gallbladder cancer, with tumor invasion into liver segment V (*arrow*). *B,* An operative photograph taken after a right trisegmentectomy and lymph node dissection with a left hepaticojejunostomy. The region of the bile duct anastomosis is indicated (*arrow*).

reported morbidity of 12.8 percent for simple cholecystectomy, 21.9 percent for extended cholecystectomy, and 48.3 percent for hepatic lobectomy.[47] The mortality rates were 2.9, 2.3, and 18 percent, respectively. They reported 150 hepatopancreaticoduodenectomies for gallbladder cancer, with a 54 percent morbidity rate and a 15.3 percent mortality rate. The risk of resection for each patient and for each type of resection needs to be weighed against the patient's chance of benefiting from the procedure, based on the tumor stage. In our series, the complication rate was highest for those undergoing bile duct resection.

OTHER THERAPY

In general, gallbladder cancer does not respond to systemic chemotherapy, and its mode of spread through the peritoneal cavity does not lend itself to radiation therapy. Nevertheless, because of the poor prognosis in patients with regionally confined disease, a combination of adjuvant chemotherapy (5-fluorouracil [5-FU], mitomycin-C) and radiation therapy has been studied.[48] Chow and Greager reported 15 patients who received some form of chemotherapy and/or radiation therapy after resection for gallbladder cancer. There was no significant improvement in survival for these patients, compared to 7 patients who did not receive adjuvant therapy.[49] Oswalt and Cruz reported a median survival of 20 weeks in patients treated with adjuvant chemotherapy, compared to 8 weeks in patients treated with surgery alone.[50] Morrow and colleagues reported a median survival of 4.5 months for patients receiving adjuvant chemotherapy and/or radiation therapy versus 3 months in patients treated with surgery alone.[51] All of these trials compared treated patients to control patients in a nonrandomized fashion. It may be that the patients with better performance status received adjuvant therapy, and it is, therefore, difficult to say whether their treatment had an effect on their survival. Todoroki and colleagues examined intraoperative radiation therapy after complete resection for stage 4 gallbladder cancer and reported a 10 percent 3-year survival versus 0 percent survival for patients treated by surgery alone.[52] In a retrospective study from Finland, patients who received postoperative radiation survived a median of 63 months, compared to 29 months for patients treated by surgery alone.[53] It is difficult to perform randomized trials in such a rare disorder with varying prognoses based on stage, but until a better controlled study is performed, adjuvant therapy should be considered experimental.

Advanced gallbladder cancer may be an ideal setting for regional chemotherapy either for primary treatment or as an adjuvant to resection. Makela and Kairaluoma described the use of intra-arterial mitomycin-C for gallbladder cancer and reported a prolongation of median survival from 5 months to 14 months compared to historical controls.[54] Because of the propensity for intraperitoneal spread, an intraperitoneal chemotherapeutic approach may be ideal in an adjuvant setting, especially where prior simple cholecystectomy may have resulted in tumor cell spillage.

Because the majority of patients present with unresectable tumors, the issue of palliative management is important. The median survival for patients presenting with unresectable disease is 2 to 4 months, with a 1-year survival rate of less than 5 percent.[55,56] This is a very aggressive disease; therefore, any palliative efforts should be associated with minimal time in the hospital. The goal of palliation is to relieve pain, jaundice, and bowel obstruction. Percutaneous biliary decompression may be adequate for patients with extensive disease. In cases in which the patient is explored and an operative biliary drainage is required, a segment III bypass is ideal.[57] By approaching the segment III duct from the anterior surface of the liver, the porta hepatis can be avoided completely. A dilated segment III duct is relatively easy to find and use for an anastomosis. The biliary drainage will then be well out of the way of the primary tumor, lessening the chance of recurrent obstruction. Kapoor and colleagues described 41 patients who underwent segment III bypass for gallbladder cancer with an 87 percent success rate but a 12 percent 30-day mortality rate.[58] Chemotherapy and radiation therapy are other options for regional palliation. Systemic chemotherapy trials have included 5-FU, Adriamycin, mitomycin-C, and nitrosoureas, but responses are not high enough to justify chemotherapy as standard care. Radiation

therapy has shown minimal benefit, with a reported median survival of 6 to 8 months.[59] A combination of new chemotherapy agents and better radiation schemes may achieve improved results; thus, chemotherapy and radiation therapy should continue to be explored in this patient population.

SUMMARY

Gallbladder cancer is an aggressive tumor that is highly lethal. While reasonably good results have been described from single institutions in early-stage disease, the overall 5-year survival reported in large reviews and surveillance programs is consistently less than 5 percent, with a median survival of 5 to 8 months.[1,60,61] In a large multi-institutional review from Japan, 984 patients who underwent radical resection had a 5-year survival of 50.7 percent, compared to 6.2 percent for 702 patients who underwent more conservative management.[46] These results suggest that a fatalistic attitude toward gallbladder cancer is not warranted and that with appropriate staging, careful patient selection, and appropriate surgical management, long-term survival is possible. Despite the association with gallstones, prophylactic cholecystectomy is not recommended. The radiologist should be attentive to ultrasonographic abnormalities in the gallbladder wall that would suggest cancer. The clinician should be attentive to atypical pain, a history of weight loss, or atypical laboratory values. The surgeon performing cholecystectomy for symptomatic cholelithiasis should always carefully examine the specimen for any evidence of gallbladder cancer and be prepared to perform an immediate extended cholecystectomy if the diagnosis is confirmed on frozen-section analysis. This is much safer and potentially more successful than a reoperation after the final pathologic diagnosis.

An algorithm for the management of gallbladder cancer should separate those patients who are noted on preoperative ultrasound examination or at operative exploration to have a suspicious mass from those patients who are incidentally found to have gallbladder cancer on pathologic examination of a cholecystectomy specimen. In the former situation, an open exploration should be performed, and a fine-needle aspiration or frozen-section biopsy should be performed intraoperatively. If the diagnosis is confirmed, then a thorough exploration for peritoneal metastases, liver metastases, and peripancreatic and interaortocaval lymph node metastases should be performed. Patients with distant metastases should not undergo radical resection. Patients with T2 or T3 disease can undergo a resection of segments IVb and V en bloc with the gallbladder, including a periportal and peripancreatic lymph node dissection. Patients with T4 tumors and significant hepatic invasion will require extended hepatic resection and lymph node dissection. Advanced N1 disease or tumors invading the hilum may necessitate an extrahepatic common bile duct resection. Of patients with an incidental pathologic finding of gallbladder cancer, those with T1 disease and a negative cystic duct margin require no further therapy. Patients with a positive cystic duct margin require reresection of the duct to a tumor-free margin. Patients with T2 disease should undergo a radical reresection, and this may require an extended lobectomy, a common bile duct resection, and a resection of laparoscopic-port sites. Any documentation of peritoneal spread or N2 disease should eliminate the option of radical resection.

Patients with advanced and unresectable disease have a poor prognosis and should be palliated in a minimally invasive manner. Innovative approaches to adjuvant therapy, such as intraperitoneal chemotherapy and regional intrahepatic arterial therapy, should be considered. New chemotherapy and biologic therapy should be studied in patients with advanced gallbladder cancer to help improve the dismal prognosis.

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