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Technical Aspects of Gallbladder Cancer Surgery

Motaz Qadan, MD PhD and T. Peter Kingham, MD FACS*

Keywords

Gallbladder cancer; incidental; non-incidental; laparoscopic; robotic; segment IVB/V; biliary tract cancer

Introduction

Gallbladder cancer is a rare disease, although it is the most common disease of the biliary tract. Its incidence has increased over the last 20 years. This may be a result of the increasing prevalence of laparoscopic cholecystectomy, which is responsible for incidentally-discovered gallbladder cancer.¹ Despite the increasing incidence of gallbladder cancer, laparoscopic cholecystectomy has permitted earlier detection and improved survival of what was once considered a disease associated with a dismal prognosis.²

In this review, we present an updated description of gallbladder cancer in 2 sections based on presentation: (1) disease that presents incidentally following laparoscopic cholecystectomy and (2) malignancy that is suspected pre-operatively. Elements pertaining to technical aspects of surgical resection provide the critical focus of this review, and are discussed in the context of evidence-based literature on gallbladder cancer today.

Epidemiology

The estimated incidence of gallbladder cancer is approximately 2 per 100,000 of the population in the United States (US).³ As of 2015, there are an estimated 10,910 cases in the US annually including other biliary tumors, compared with only approximately 9,250 cases in 2008.^{3,4} The incidence appears to be significantly higher in women (3:1) and more commonly occurs in patients older than 40.⁵ Incidence of gallbladder cancer is based on the central etiological factor of cholelithiasis, with variations in geography and race mirroring the incidence of gallstone disease. For example, the incidence of gallbladder cancer in Norway, where cholelithiasis rates are low, ranges from 0.2 to 0.4 per 100,000 people. Conversely, the incidence of gallbladder cancer ranges from 9.3 to 25.3 per 100,000 among Chilean Mapuche Indian women, where gallstone disease is more prevalent.⁶ Furthermore,

*Please address correspondence to Dr. Peter Kingham at the Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, (212) 639-5260, kinghamt@mskcc.org.

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mortality rates appear to also be higher in Andean populations within South America.⁷ Finally, even within the US, the incidence among Native Americans in the state of New Mexico is approximately 14.5 per 100,000, a rate that is dramatically higher than the national average.⁸

Etiology and Pathogenesis

Cholelithiasis is considered a primary etiological factor in gallbladder cancer, which results in chronic mucosal inflammation, dysplasia, and subsequent malignant transformation, with the development of porcelain features clinically.⁷ Only approximately 0.3% to 3% of patients with long-standing cholelithiasis will develop gallbladder cancer, highlighting the rarity of gallbladder cancer.⁹ Interestingly, in a case-control study that compared gallstones in patients with and without gallbladder cancer, there were significantly more stones and heavier stones in patients who developed gallbladder cancer.¹⁰ Despite this, the mechanistic association between gallstones and frank malignancy is not fully established. In a study by Jain and colleagues, the authors examined 350 gallbladder specimens from patients with gallstones, and found mucosal hyperplasia in 32%, metaplasia in 47.8%, dysplasia in 15.7%, and carcinoma in situ in 0.6% of specimens.¹¹ The authors were able to show loss of genetic heterozygosity in 2.1% to 47.8% of preneoplastic lesions at 8 different loci for several tumor suppressor genes associated with gallbladder cancer, but showed no loss of heterozygosity in normal gallbladders, thereby suggesting a possible mechanistic association between gallstones and gallbladder cancer beyond inflammation and neoplasia.

In keeping with other gastrointestinal malignancies, progression from adenoma to carcinoma has also been stipulated in gallbladder cancer, particularly in sessile adenomata greater than 1cm in size.¹² While adenomatous polyps exist in only about 1% of gallbladder specimens, up to 7% of lesions harbor malignancy.^{13,14} Cancer was more likely to exist in isolated, broad-based polyps, with increasing size. A size cutoff of 1cm is often considered relevant.

While porcelain gallbladder does not automatically imply malignancy, gallbladder cancer may occur in approximately 1 in 13 patients with a porcelain appearance.¹⁵ These data are still debated, as demonstrated by a recent case series evaluating the risk of gallbladder cancer in patients with a porcelain gallbladder. This series found 13 patients with porcelain gallbladder identified among 1200 cholecystectomy patients. None of the 13 patients had evidence of carcinoma.¹⁶ Systematic reviews including 60,665 cholecystectomies reported 0.2% of patients had porcelain gallbladders. Only 15% of those patients (i.e., 0.03% of total cohort) were diagnosed with gallbladder carcinomas. The issue of cholecystectomy for porcelain gallbladder remains unsettled, but given the possibility of an elevated relative risk of cancer in porcelain gallbladder compared with non-porcelain gallbladder and the potential for cure in patients treated with early cholecystectomy, it is reasonable to consider cholecystectomy.¹⁷

TNM Staging System

The American Joint Commission for Cancer (AJCC) gallbladder cancer TNM staging system is described in Table 1. Most cases of gallbladder cancer are adenocarcinomas,

although variants including papillary, mucinous, squamous, and adenosquamous subtypes are well described. Importantly, and while describing the T-stage (depth of tumor invasion), emphasis should be placed on where the gallbladder cancer is in the gallbladder, given that the gallbladder hepatic interface lacks serosa and consists only of the peri-muscular connective tissue that is continuous with hepatic connective tissue (cystic plate). This has implications in the surgical management of resectable disease as described below. Nodal drainage patterns are shown in Figure 1.

Incidental Gallbladder Carcinoma

Incidental gallbladder cancer following cholecystectomy is found in approximately 0.2% to 1.1% of all laparoscopic cholecystectomies.¹⁸ When discovered intra-operatively, the procedure should be aborted and the patient should be transferred to a hepatobiliary center. Outcomes of patients with an incidental finding of gallbladder cancer have a better prognosis than non-incidentally-discovered disease, provided the patient is staged and managed appropriately with R0 resection.¹⁹ Critically, however, the presence of any residual disease following attempted resection dramatically reduces disease-free interval and disease-specific survival, with survival comparable to stage 4 gallbladder cancer. In a report by Butte and colleagues, disease-free survival in patients with residual disease was 11.2 months, compared with 93.4 months in patients without residual disease.²⁰

Pre-Operative Workup

Following referral of cases with incidentally-discovered gallbladder cancer within the gallbladder specimen post-cholecystectomy, high-resolution imaging is uniformly utilized to evaluate for residual disease, nodal metastases, and identification of distant metastatic disease. Given associated post-operative changes, the role of ultrasound imaging is limited. However, review of pre-cholecystectomy ultrasound findings in order to determine the location of the tumor are often helpful, in addition to discussing intra-operative findings with the referring surgeon of record.

Whereas computed tomography (CT) or magnetic resonance imaging (MRI) provide critical information in restaging patients following laparoscopic cholecystectomy, the role of fluorodeoxyglucose positron emission tomography (FDG-PET) in this setting is not established. FDG-PET scans have shown a 78% sensitivity and 80% specificity in detecting residual disease.²¹ In addition, FDG-PET helped detect metastatic disease in 29% to 55% of patients who had undergone cholecystectomy.²² A complementary role with CT in detecting extrahepatic metastases has been demonstrated.²³ Significant false-positivity associated with non-specific FDG-avidity in the post-cholecystectomy gallbladder fossa has also been elucidated in these studies. A recent report from our institution correlated CT and MRI findings with FDG-PET scans in patients with gallbladder cancer.²⁴ Of 100 total patients included in the study, there were 63 patients with incidental gallbladder cancer. Three of the 100 patients had additional disease on FDG-PET which prevented unnecessary operation, 2 patients had suspicious CT findings refuted by FDG-PET that permitted operation, 12 patients had equivocal CT findings confirmed by FDG-PET, and 3 patients had additional invasive procedures performed owing to FDG-PET avidity in other sites. The findings

confirmed a modest impact on management of patients with gallbladder cancer, particularly in patients with suspicious nodal disease and those without a prior cholecystectomy (non-incidental gallbladder cancer). FDG-PET caused a change in management, however, in only 13% of patients with incidental gallbladder cancer, compared to 31% in patients with in-situ gallbladder cancer ($p=0.035$).

Surgical Restaging of Incidental Post-Cholecystectomy Gallbladder Cancer

Selection for re-operation is based on surgical staging, as evaluated by the AJCC staging system above. In general, M1 disease is considered unresectable, with no role for surgical intervention. Approximately one-quarter of patients with gallbladder cancer have metastatic disease.²⁵ Since there is limited role for palliative surgical intervention in this disease process, unnecessary laparotomy should be avoided, and starting with staging laparoscopy provides a logical approach in the treatment of incidentally-discovered post-cholecystectomy gallbladder cancer. In a review performed at our institution, Butte and colleagues evaluated the role of staging laparoscopy in patients with incidental gallbladder carcinoma.²⁶ In 136 consecutive patients, staging laparoscopy was carried out in 46 patients, of whom 10 had disseminated disease. Only 2 of these patients, however, had disease detected during laparoscopy, prior to conversion to laparotomy (yield 4.3% and accuracy 20%). While disseminated disease was a relatively infrequent event, the likelihood of disseminated disease correlated with increasing T-stage, positive margin at initial cholecystectomy, and increasing tumor grade. Given the low risks associated with the procedure, high yield, and significant benefit associated with avoidance of unnecessary laparotomy in this population, we perform staging laparoscopy in all patients undergoing resection of incidental gallbladder cancer at our institution.

Timing of Radical Re-Resection

There are now data that delaying re-resection of patients with incidental gallbladder cancer may improve patient selection. Ausania and colleagues reported results using a treatment algorithm with intentional delayed staging of incidental T2 and T3 gallbladder cancer following cholecystectomy by 3 months. This permitted careful evaluation for residual disease and extrahepatic spread, as well as observation of the biologic behavior of the tumor.²⁷ Importantly, the authors were able to show that this strategy permitted the avoidance of unnecessary laparotomy in patients who, arguably, may not have benefited from surgical resection. This was done without adversely affecting survival in patients who remained candidates for resection. Median overall survival among the 24 patients who underwent radical resection was 54.8 months. There were 24 patients who were found to be unresectable on pre-operative imaging and 1 found to be unresectable at operation, in whom median survival was 9.7 months.

Surgical Treatment Early (T1 and T2) Incidental Gallbladder Cancer

Since T1a gallbladder cancer only extends into the lamina propria, a simple cholecystectomy is often considered sufficient for the treatment of these tumors. With negative margins, cure rate after simple cholecystectomy has ranged from 85% to 100%.²⁸ Therefore, no additional resection is warranted in this group of patients.

With T1b tumors, survival data did not similarly support the concept that simple cholecystectomy would suffice. For example, in a report by Principe, the authors reported a 1-year survival rate of 50% only following margin negative simple cholecystectomy, despite lack of invasion of the tumor into the peri-muscular connective tissue.²⁹ The reduced survival rate and importance of radical resection in this setting arises due to a residual disease incidence of up to 10% and lymph node metastatic incidence of 10% to 20% described in the literature, with potential locoregional recurrence rates of up to 20% to 50%.^{1,30} Radical resection, including re-resection of the hepatic bed (segments IVB and V) and portal nodal lymphadenectomy, is recommended for T1b tumors detected incidentally post-cholecystectomy.

With T2 tumors, early studies showed 5-year survival rates of 20% to 40% after cholecystectomy, compared with 70% to 80% in patients who underwent radical resection.^{1,30-33} While residual disease rates are, once again, increased with increasing T-stage, nodal involvement is thought to occur in approximately one-third of cases, although other studies have reported involvement in over 60% of cases.³⁴ Radical resection, including re-resection of the hepatic bed in an operation that includes segments IVB and V, with portal nodal lymphadenectomy, is recommended for T2 tumors detected incidentally post-cholecystectomy. Re-resection additionally provides accurate staging information, which allows patients to be referred for appropriate adjuvant therapy.

Of recent interest in the treatment and selection of patients for resection with T2 disease is tumor location. In a recent multi-institutional study by Shindoh and colleagues, the authors examined 437 patients with gallbladder cancer who were analyzed with tumor location defined as “hepatic side” or “peritoneal side”, given the anatomic discrepancy described above between the 2 locations.³⁵ The authors showed that in patients with tumors on the hepatic side, patients had higher rates of vascular invasion, neural invasion, and nodal metastases when compared with tumors located on the peritoneal side (51% vs. 19%, 33% vs. 8%, and 40% vs. 17%, respectively). Five-year survival rates were 64.7% versus 42.6% ($p=0.0006$) for peritoneal and hepatic tumors, respectively, with tumor location serving as a predictor of liver and distant nodal recurrence despite radical resection. Additional studies have confirmed the importance of tumor location in T2 disease, and even recommended reservation of radical resection for T2 cancers located on the hepatic side.³⁶

Surgical Treatment of Advanced (T3 and T4) Gallbladder Cancer

Treatment of T3 incidental gallbladder cancers is similar to T2 cancers, and includes a radical resection of the gallbladder fossa with portal nodal lymphadenectomy. Outcomes following radical resection of T3 disease, while historically poor, now range widely from 21% to 63% in some studies, with an operative mortality below 5%.^{37,38} The incidence of residual disease and lymph node metastases is higher again, estimated at 36% and 46%, respectively.²⁵ With advanced disease stage, the need for more extensive hepatic and bile duct resections are often indicated in the attainment of negative surgical margins.³⁹ These are discussed further below.

In the case of T4 disease, the role of extensive vascular reconstructions in the treatment of gallbladder cancer has not been shown to provide a durable survival benefit. The peri-

operative morbidity and mortality associated with extensive reconstructions generally outweigh any survival benefit, and extensive resection and vascular reconstruction is generally not recommended. The role of neoadjuvant therapy in the treatment of advanced gallbladder cancers (T3 and T4) is discussed below.

Surgical Treatment of the Extrahepatic Bile Duct

Routine resection of the extrahepatic bile duct has not been uniformly associated with improved outcomes.⁴⁰ Rather, resection of the common bile duct has been shown to increase peri-operative morbidity, with little additional benefit when performed empirically.^{41,42} Unless there is a positive cystic duct margin to warrant additional re-excision, bile duct resection can be avoided. In cases where there is concern, intra-operative frozen section of the cystic duct stump margin can help determine the need for extended duct resection. If detected, a positive duct margin warrants bile duct excision in order to ensure negative margins. In this setting, bile duct resection may be performed following adequate exposure with a Kocher maneuver and division of the duct at the level of the duodenum. Reconstruction is then carried out with a Roux-en-Y hepaticojejunostomy. In the case of jaundice arising from malignant infiltration of the bile duct, the prognosis is often poor, so a biliary stent and neoadjuvant chemotherapy is warranted.⁴³ Finally, resection of the extrahepatic bile duct has not been associated with a more effective portal nodal lymphadenectomy.

Surgical Treatment of the Hepatic Margin and Extended Liver Resections

In terms of radical re-resection, recommendations for liver resection have varied from limited 2cm wedge resections of the gallbladder fossa to routine extended right hepatectomy. In reality, the size of the wedge liver resection will depend on the pathologic depth of the tumor and stage of disease, ranging from limited segment IVB and V wedge resections, to formal anatomic resections (Figure 2). With the aid of intra-operative ultrasound, vascular anatomy should be delineated to guide the resection margin, ensuring full tumor clearance and identifying branches of the middle hepatic vein to allow for a controlled transection. Pedicles to segment 4b can be dissected in the umbilical fissure and divided before parenchymal transection begins. The main right anterior sectoral branches must be carefully preserved, although the pedicle to segment V is often also divided. In larger tumors, dividing the entire right anterior pedicle may be necessary. Pringle occlusion of the hepatic vascular inflow is helpful during parenchymal transection.

With respect to extended hepatic resections, if the tumor invades hepatic inflow vascular structures, particularly the right portal vein with larger tumors, a right hepatectomy may be required in order to ensure adequate tumor clearance and an R0 resection. The importance of meticulous pre-operative planning must not be underestimated in this setting. If clearly visualized, right inflow involvement may be used as justification for administration of neoadjuvant chemotherapy. This provides an opportunity for response to therapy to be determined, with potential avoidance of an unnecessary extensive operation. In cases where extended hepatectomy is necessary, bile duct resection is often also necessary, due to the size of the tumor. In a study by D'Angelica and colleagues, empiric resections of liver (15 of 36 patients) and bile duct (32 of 68 patients) did not predict outcome after resection for

gallbladder cancer.⁴² Instead, there was an increased rate of peri-operative morbidity among patients who underwent major hepatectomy and common bile duct excision, with outcome correlating only with tumor biology and disease stage. These data are used to justify our approach of using extensive resection only as needed to clear disease.

Finally, in well-selected patients, the resection of other organs, including stomach, colon, and duodenum, in the absence of distant metastatic disease, may be resected to ensure an R0 resection. Combined pancreaticoduodenectomy with hepatectomy can be performed after treating with chemotherapy.⁴⁴

Surgical Treatment of Lymph Nodes

Lymph node dissections have historically ranged from excision of the cystic duct lymph node to a complete portal lymphadenectomy with pancreaticoduodenectomy in the Japanese literature.^{45,46} In our experience, the addition of hepatic and pancreatic resections contributes to additional morbidity without significant improvement in long-term survival, and is not recommended.⁵

The presence of N1 nodal disease is not considered an absolute contraindication to surgical resection. Long-term survival with the presence of nodal metastatic disease, however, remains rare.⁵ Given these poor outcomes, we usually treat patients with positive lymph nodes with neoadjuvant chemotherapy. More extensive nodal involvement that extends outside the hepatoduodenal ligament (N2) is considered unresectable, given the major post-operative morbidity and mortality associated with resection without any significant survival benefit.⁴⁷ Additional celiac and para-aortic lymph node metastases are considered M1 disease, and surgical resection is contraindicated. The highest peri-pancreatic lymph node marks the transition between the N1 and N2 fields, and has been found to be prognostic of disease-specific and recurrence-free survival in biliary tract adenocarcinoma in a retrospective study performed at our institution.⁴⁸

At laparotomy, every effort should be made to carefully examine lymph nodes outside the radical resection field. As such, the exploration should begin with a Kocher maneuver to evaluate aortocaval and retropancreatic nodes, with careful examination of celiac nodes. Any suspicious nodes should be evaluated intra-operatively with frozen pathologic assessment, and, if positive, the procedure should be aborted at that time.

A standard portal lymphadenectomy for gallbladder cancer beyond T1a includes nodes in the porta hepatis, gastrohepatic ligament, and retroduodenal space (N1 nodes). While resection of those nodes has never been evaluated in a prospective setting to determine whether there is any positive effect on survival, lymph node evaluation in this setting provides accurate staging and prognostic information at the very least. Indeed, the detection of lymph node disease, particularly in early stage gallbladder cancer, may influence the decision to administer adjuvant systemic therapy, which is discussed below.

Surgical Resection of Previous Port Sites

In a recent study from our institution, patients who underwent port-site resection (69 patients) were compared with patients who underwent operation without port-site removal

(44 patients).⁴⁹ Thirteen patients were noted to have port-site metastases, which occurred in T2 and T3 patients only, and correlated significantly with the development of peritoneal metastases. Survival was reduced from 42 months to 17 months when port-site disease was detected. However, port-site resection was not associated with overall survival or recurrence-free survival when R0-resected patients were compared and adjusted for T and N-stage. Instead, port-site metastases were considered a harbinger of generalized peritoneal recurrence that would not be prevented with resection of these sites.⁵⁰ This finding was confirmed in a separate study by Fuks and colleagues.⁵¹ As a result of these combined findings, we do not routinely resect previous port-sites during radical resection.

Gallbladder Perforation During Cases of Incidental Gallbladder Cancer

In a recent German retrospective study by Goetze and colleagues, the authors examined the rate of intra-operative perforation combined with the use of retrieval bags, and showed that the rate of overall gallbladder cancer recurrence in perforated patients was significantly higher at 38.4%, compared with 27.2% in non-perforated patients.⁵² Once perforated, however, the use of retrieval bags did not reduce the recurrence rate, as evidenced by a non-statistically significant difference in recurrence between cases with and without use of retrieval bags (32.5% vs. 27%, respectively). Similarly, a recent study by Lee and colleagues showed that bile spillage compared with no spillage was associated with a profound decline on disease-free survival (71.4% vs. 20.9%, respectively) and overall survival (72.6% vs. 25.8%, respectively).⁵³ Although the diagnosis of incidental gallbladder cancer is only available following operation, we advocate for resection of the cystic plate in cases where clinical suspicion for malignancy arises during routine cholecystectomy, in order to significantly reduce the incidence of detrimental gallbladder perforation.

Non-Incidental Gallbladder Carcinoma

Early diagnosis of gallbladder cancer is uncommon in patients presenting with non-incidental gallbladder cancer. Interestingly, outcomes are significantly worse compared with incidentally-discovered disease, even when matched for disease stage.^{1,25} Given frequently advanced stage on diagnosis, presenting signs and symptoms are wide-ranging, and include local signs and symptoms such as jaundice, abdominal pain, abnormal stools, vomiting, and presence of a palpable mass, as well as non-specific symptoms such as weight-loss, lethargy, and loss of appetite.

In addition, patients may present with generalized phenomena that are related to underlying malignancy, such as venous thromboembolism (VTE), including migratory thrombophlebitis (Trousseau's sign), or with signs and symptoms that may be secondary to metastatic disease at presentation, such as shortness of breath in the case of pulmonary metastases or pathologic bone pain and/or fracture in osseous metastases.

Jaundice as a Presenting Sign

In cases of non-incidentally-diagnosed gallbladder cancer, patients may present with jaundice as their initial presenting sign, which suggests malignant invasion of the biliary tree. In a study by Hawkins and colleagues from our institution, the authors retrospectively

reviewed the significance of jaundice in patients with gallbladder cancer.⁵⁴ The authors identified 82 jaundiced patients among 240 patients with gallbladder cancer, who were more likely to have advanced stage disease. A mere total of 6 patients were resected with curative intent, and only 4 underwent resection with negative margins. The median disease-specific survival among jaundiced patients was 6 months, compared with 16 months in non-jaundiced patients. There were no disease-free survivors at 2 years among jaundiced patients, compared with 21% in non-jaundiced patients.

Conversely, in a later study by Varma and colleagues, resection with negative margins was possible among 50% of patients with gallbladder cancer who presented with jaundice.⁵⁵ The authors showed that while disease was significantly advanced among jaundiced patients, jaundice per se was not associated with disease unresectability in their patient cohort.

While we do not recommend preclusion of resectability based on presentation with jaundice, meticulous evaluation of resectability is warranted, given that only 4 of 82 patients were resected with negative margins among patients reviewed at our institution. Jaundice is considered to be an ominous sign in our opinion, and usually provides grounds for consideration of neoadjuvant therapy in the initial setting, in addition to endoscopic or percutaneous decompression of the biliary tree.

Workup

In cases of pre-operative diagnosis of malignancy, disease is often locally advanced as described earlier. Radiologic staging is often carried out using CT or MRI to evaluate the extent of tumor invasion and depth, nodal metastases, and distant disease, with an ability to accurately delineate anatomic anomalies and detect vascular involvement, invasion into the biliary tree, hepatic parenchymal invasion, and nodal metastases. It is estimated that 75% of cases are already considered unsuitable for resection in non-incidentally-diagnosed patients. FDG-PET, which is associated with lower false-positive rates than in incidentally-diagnosed post-cholecystectomy disease, has been utilized with over 80% sensitivity and specificity in differentiating between malignant and non-malignant pathology in this setting.⁵⁶

Pre-operative Tissue Diagnosis

Whereas in incidental gallbladder cancer a diagnosis is already available, by definition, pathologic diagnosis in non-incidental disease is considered unnecessary for patients who are potentially resectable. Gallbladder cancer is characterized by an ability to seed the peritoneum, biopsy tracts, and surgical wounds, and, as such, unnecessary biopsy may increase the risk of tumor dissemination.^{57,58} In unresectable patients, percutaneous biopsy offers a reliable diagnosis with a documented sensitivity of approximately 88%.⁵⁹ Attempts to provide a pathologic diagnosis by removing the gallbladder are ill-advised, given the significant risk of tumor spillage.

Extent of Surgical Resection of Non-Incidental Gallbladder Cancer

In cases of non-incidental gallbladder cancer, many of the principles discussed following incidental diagnosis of gallbladder cancer apply, with the principle objective being attainment of negative surgical margins, including wedge, anatomic, or more extensive

hepatic resections, with portal lymphadenectomy, and extrahepatic bile duct resection only in the attainment of negative duct margins.³⁹ Simple cholecystectomy is almost never the treatment of choice in cases of non-incidental gallbladder cancer, given that T1a tumors, by definition, are unlikely to present or be detected radiologically in non-incidental disease.

Minimally-Invasive Resection of Gallbladder Cancer

Traditionally, laparoscopic surgery has not been routinely recommended in the surgical management of suspected gallbladder cancer in the non-incidental setting. Several studies have pointed towards an increased incidence of port-site recurrence due to the manipulation of instruments through ports, but also due to the chimney effect associated with carbon dioxide insufflation within the abdominal cavity.^{7,60-63} However, more recent studies have failed to demonstrate any detrimental effect from purely laparoscopic approaches in the management of gallbladder cancer, with recent studies suggesting equivalent outcomes between laparoscopic and open approaches (Table 2).⁶⁴⁻⁶⁹ Robotic-assisted procedures have also been described, and are carried out at our institution.⁷⁰

When performing minimally-invasive radical cholecystectomy, we begin by placing the patient in low lithotomy position, with the surgeon standing between the patient's legs. Robotic port placement is shown in Figure 3. The procedure commences with staging intraoperative ultrasound. Use of laparoscopic energy devices is required and we recommend use of a laparoscopic bipolar device for hemostasis during parenchymal transection (Figure 4a-c). Given inevitable blood loss during hepatic transection, we perform portal lymphadenectomy prior to parenchymal transection, in order to ensure optimal visualization during portal triad dissection. Performing a Kocher maneuver is essential for adequate lymph node dissection. Retrieval bags should be used when extracting all specimens through port sites. Principles of resection, including lymphadenectomy, cystic duct margin analysis, and extrahepatic bile duct resections are similar to open radical cholecystectomy.

Systemic Therapy

Despite conflicting data on use of adjuvant regimens in the treatment of gallbladder cancer, there are only limited level I data to support use, with most data being based on empiric therapies, phase II studies, or retrospective analyses. Phase III trials are emerging, and now include gemcitabine-based therapies, which have shown improved efficacy over 5-fluorouracil (5-FU) regimens. In a recent 3-arm trial by Sharma and colleagues, gemcitabine was compared to best supportive care and 5-FU in patients with unresectable disease.⁷¹ Gemcitabine was shown to improve median overall survival compared to both best supportive care and 5-FU, which exhibited similar survival (9.5 months vs. 4.6 months, vs. 4.5 months, respectively). In an earlier landmark Japanese phase III multi-institutional trial that included 140 patients with gallbladder cancer, patients were randomized to undergo resection followed by adjuvant mitomycin and 5-fluorouracil versus resection alone.⁷² The study showed actuarial 5-year survivals of 20.3% versus 11.6% in favor of adjuvant therapy in patients with gallbladder cancer. Additional prospective trials have shown benefit from combining gemcitabine-based regimens with platinum agents, such as oxaliplatin and cisplatin, providing the rationale for current therapies in practice today.^{73,74}

In a review of the published literature examining the role of radiation therapy in the treatment of gallbladder cancer, Houry and colleagues demonstrated a slight improvement in survival in patients who received some form of radiation treatment.⁷⁵ Most recently, a phase II trial combining gemcitabine, capecitabine, and radiation therapy in patients with extrahepatic biliary tract and gallbladder cancers showed promising efficacy and limited toxicity from use of this regimen, thereby allowing for future phase III trials incorporating gemcitabine-based radiation regimens to be investigated.⁷⁶

As described earlier, neoadjuvant chemotherapy is thought to provide an opportunity for response to therapy to be determined, during which time patients with biologically aggressive tumors who, arguably, may not benefit from extensive operations may declare themselves. Data investigating the regimens and outcomes related to neoadjuvant therapies are limited, and have produced disappointing results in general. In a recent study from MD Anderson Cancer Center, the authors performed a retrospective review of their gallbladder cancers who were resected with wide 1cm negative margins, and had received either neoadjuvant or adjuvant therapy.⁷⁷ Five-year survival was 50.6%. A total of 17.8% of patients received neoadjuvant therapy, 48.7% received adjuvant chemotherapy, and 15.8% received adjuvant chemoradiation. Adjuvant therapy showed no improvement in survival, and neoadjuvant treatment had only served to significantly delay time to operation in their study, with immediate resection increasing survival from 42.3 months to 53.5 months. The authors concluded the neither neoadjuvant treatment nor adjuvant therapies affected outcomes in patients who were resected with clear negative margins. Small case series have suggested possible efficacy associated with gemcitabine-platinum based combinations used in the neoadjuvant setting in the treatment of gallbladder and biliary tract cancers.⁷⁸⁻⁸¹

Long-Term Outcomes

Many patients with gallbladder cancer will recur, with increased recurrence rates in non-incidental gallbladder cancer compared with incidental disease.¹ In a report published from our institution by Jarnagin and colleagues, 97 patients who underwent curative-intent resection were analyzed for long-term survival and outcomes.⁸² Overall, the median time to recurrence was 11.5 months, with 66% experiencing a recurrence at 24 months from their index procedure. Isolated locoregional recurrence occurred in only 15% of patients, compared with 85% presenting with distant disease that most commonly recurred in the peritoneum, and was unrelated to initial disease stage on multivariate analysis. The systemic nature of gallbladder cancer was apparent. Positive resection margin was the only factor associated with distant recurrence on multivariate analysis, highlighting the importance of the above surgical principles in the definitive treatment of gallbladder cancer.

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Key Points

- 1- Gallbladder cancer is a rare disease that may be diagnosed incidentally following cholecystectomy or non-incidentally, often with more advanced disease.
- 2- The principle aim of surgical resection is attainment of negative margins.
- 3- Jaundice is considered an ominous sign in the presentation of gallbladder cancer.
- 4- Minimally-invasive resection techniques are well described in the surgical treatment of gallbladder cancer
- 5- The roles of adjuvant and neoadjuvant therapies in the treatment of gallbladder cancer remain poorly elucidated.

Figure 1.
Lymph node drainage basins in gallbladder cancer.

Figure 2.
A schematic of radical cholecystectomy including cholecystectomy, segment IVB and V resection, and portal lymphadenectomy.

Figure 3. Robotic port configuration in minimally-invasive radical cholecystectomy. One or 2 accessory ports are used depending on the body habitus of the patient.

Figure 4a.
Intraoperative image of portal lymphadenectomy during robotic radical cholecystectomy.

Figure 4b.
Intraoperative image of preparation for segment IVB and V wedge resection during robotic radical cholecystectomy.

Figure 4c.
Intraoperative image of the completed radical cholecystectomy.

Table 1AJCC 7th edition TNM staging system for gallbladder cancer

Primary Tumor	
T_x	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T_{is}	Carcinoma <i>in situ</i>
T1a	Tumor invades lamina propria
T1b	Tumor invades muscular layer
T2	Tumor invades peri-muscular connective tissue without extension into serosa
T3	Tumor perforates serosa (visceral peritoneum) and/or directly invades liver or an adjacent organ
T4	Tumor invades main portal vein or hepatic artery, or invades 2 or more organs
Regional Lymph Nodes	
N_x	Regional 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 para-aortic, para-caval, superior mesenteric artery, and/or celiac artery lymph nodes
Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis

From AJCC: Gallbladder. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 211-7; with permission.

Table 2

Laparoscopic radical cholecystectomy series to date

	Cho et al. 2010 ⁶⁷	Gumbs et al. 2010 ⁶⁹	Agarwal et al. 2015 ⁶⁸
Study Period	2004-2007	2005-2011	2011-2013
Patient Number	18	15	24
Inclusion of Primary Gallbladder Cancer	Primary T1-T2	Primary T1-T3	Primary T1-3
Inclusion of Incidental Gallbladder Cancer	No	Yes	Yes
Aortocaval Node Sampling	No	No	Yes
Extent of Liver Resection	2mm wedge	Segment IVB/V	Segment IVB/V
Lymph Node Yield	8 (4-21)	4 (1-11)	10 (4-31)

Data from Refs 67-69.