Case Report ISSN 2835-6276

American Journal of Medical and Clinical Research & Reviews

Gallbladder Cancer: Epidemiological, Clinical, Therapeutic and Prognostic Aspects - A Case Series

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Received:20April 2026; Accepted:25April 2026; Published:05 May 2026

Citation: Zalarh Fadoua. Gallbladder Cancer: Epidemiological, Clinical, Therapeutic and Prognostic Aspects - A Case Series. AJMCRR. 2026; 5(5): 1-11.

Abstract

Gallbladder cancer is a rare malignancy with a poor prognosis, often diagnosed at an advanced stage. This retrospective study included 49 cases managed at Ibn Rochd University Hospital in Casablanca between 2012 and 2020, with a female predominance and a mean age of 61 years.

The most common clinical features were right upper quadrant pain, weight loss, and vomiting. Diagnosis was based on imaging and histopathological examination, sometimes incidentally after cholecystectomy.

Curative surgery was possible in only a minority of patients, while most received palliative treatment. The median survival was 8 months.

Gallbladder cancer remains a highly aggressive disease, highlighting the need for early diagnosis and multidisciplinary management.

Introduction:

Gallbladder cancer (GBC) is a rare, highly-lethal malignant neoplasm of the biliary system (1). It shows striking variation in incidence across world regions (2) Worldwide, gallbladder cancer is noted to disproportionately affect females more than males, perhaps due to the higher propensity of females to having gallstone disease (1).Gallbladder cancer usually presents in one of the following three ways: diagnosed malignancy (commonly advanced disease), malignancy detected intraoperatively for cholecystectomy done for an apparently benign disease, and malignancy diagnosed incidentally on pathologic examination following routine cholecystectomy (3). Surgery is the only curative treatment, however, most gallbladder cancer patients are diagnosed with advanced-stage disease and have an extremely poor prognosis, with reported 5-year overall survival rates <5% (4), not exceeding 10% even after curative treatment

Material and methods

We report in this retrospective study 49 observations of gallbladder cancer collected at the depart-

ment of Digestive oncologic surgery and liver transplantation of the Ibn Rochd University Hospital of Casablanca (wing3) over a period of 9 years, from January 2012 to December 2020. Among our 49 patients, we collected, according to an operating sheet, the following data: age, sex, antecedents, the symptomatology motivating the hospitalization, clinical examination data, paraclinical data, the treatment administered, the anatomopathological study of the operating room and the follow-up of the patients. The therapeutic attitude was always discussed in multidisciplinary consultation meetings of digestive oncology.

Results

A total of 49 patients with gallbladder carcinoma were included. Age ranged from 34 to 80 years, with a mean age of 61 years. Twenty-eight patients (58%) were older than 60 years. There were 35 women and 14 men, corresponding to a male-to-female sex ratio of 0.40. A history of diabetes mellitus was present in 9 patients (18.4%) and arterial hypertension in 7 patients (14.3%). Six patients (12.2%) had known gallbladder lithiasis diagnosed on ultrasound 2 to 4 years before presentation. The most observed clinical signs are broken down in the following table (Table 1).

Table 1: Distribution of patients by clinical signs observed

Clinical symptoms	Number of patients	Percentage
Right hypochondrium pain	44	90%
Slimness	40	81.6%
Vomiting	29	59%
Retentional jaundice	16	32.5%
Abdominal tenderness	9	18%
Abdominal distension	7	14%
Constipation	6	12%
Fever	6	12%
Pruritus	5	10,2%
Occlusive syndrome	2	4%

The main clinical signs found in the series under examination were : sensitivity to right hypochondrium in 28,5% of cases, hepatomegaly in 18% of cases, a mass of right hypochondrium in 18% of cases and ascites in 10% of cases.

Abdominal ultrasonography was performed as the initial imaging modality in all patients. A suspicion of gallbladder carcinoma was raised in 20 patients (40.8%), with gallbladder wall thickening in 19 patients and liver parenchymal invasion in 6 patients (12.2%). A lithiasic gallbladder without wall abnormality was observed in 7 patients (14.3%). Dilatation of the intrahepatic bile ducts and of the main bile duct was found in 4 patients each (8.2%). Ultrasonography showed peritoneal carcinomatosis in 6 patients (12.2%).

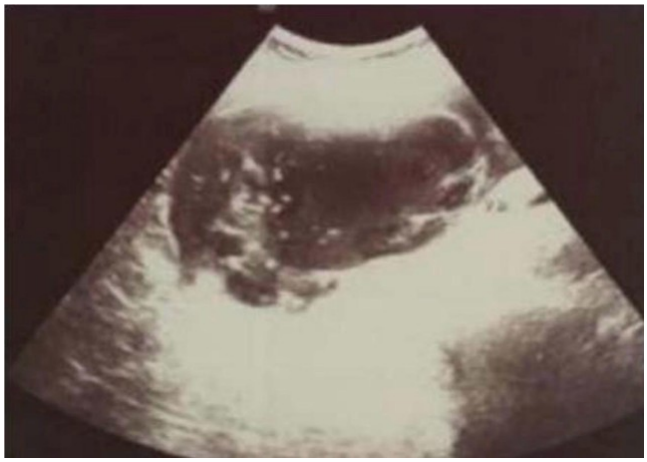

Figure 1: Ultrasound appearance of a distended gallbladder with identification of irregular wall thickening; the gallbladder content is heterogeneous with the presence of gallstones.

Computed tomography revealed irregular gallbladder wall thickening in 9 patients (18.4%) and liver invasion in 25 patients (51.0%). Dilatation of the intrahepatic bile ducts was observed in 7 patients (14.3%) and of the main bile duct in 6 patients (12.2%). Peritoneal carcinomatosis was detected in 10 patients (20.4%).

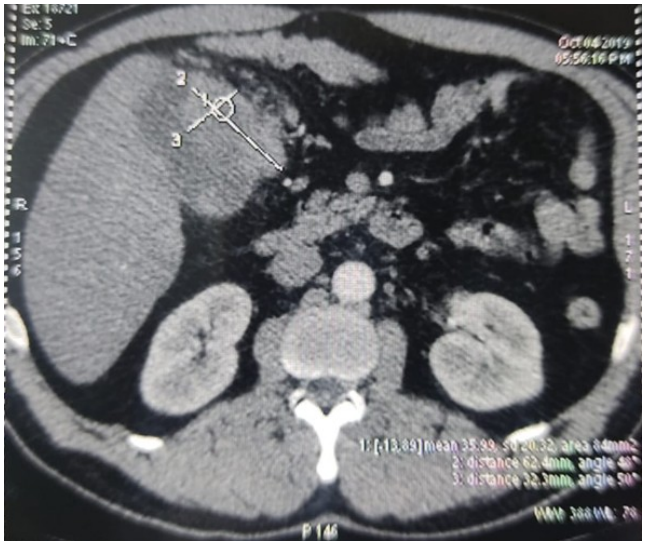

Figure 2: CT image of thickened gallbladder wall

Abdominal magnetic resonance imaging (MRI) was performed in 30 patients (61.2%). Extension of the tumour to the hepatic hilum was noted in 5/30 patients (16.7%), and to the main biliary tract in 2/30 patients (6.7%). Tumour size was specified in 8 patients. Dilatation of the bile ducts was observed in 12/30 patients (40.0%), and gallbladder lithiasis was present in 6/30 patients (20.0%).

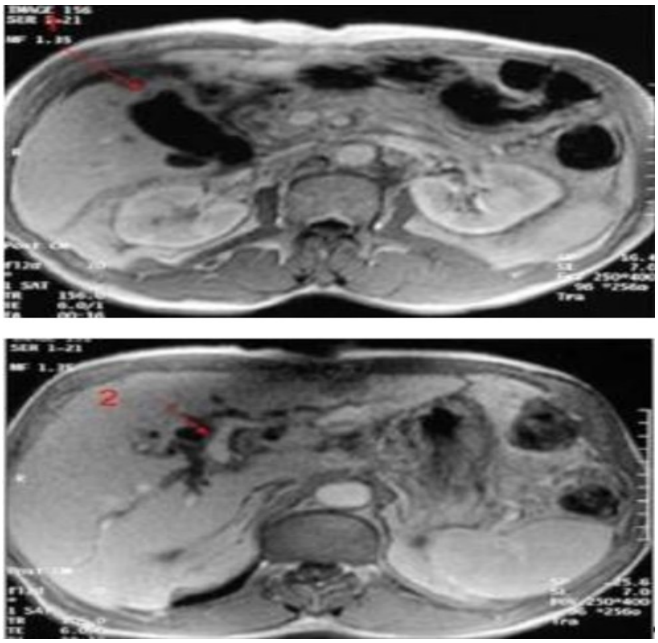

Figure 3: Axial MRI sections in FSE T2-weighted sequence after gadolinium injection show a thickened gallbladder, particularly at the fundus (1). A heterogeneous mass is noted in segment IV. The intrahepatic bile ducts are dilated (2)

Liver function tests were normal in 17 patients (34.7%) and abnormal in 32 patients (65.3%). Isolated cholestasis was observed in 24.4% of cases and was associated with cytolysis in 42% of cases. The complete blood count was normal in 57% of patients, whereas normocytic normochromic anaemia was present in 28.5% of patients.

Tumour markers (CEA and CA 19-9) were measured in 40 patients (81.6%). Serum levels were elevated in 35/40 patients (87.5%) and remained within the normal range in 5/40 patients (12.5%).

The diagnosis of gallbladder carcinoma was strongly suspected preoperatively, based on clinical and radiological findings, in 22 patients (44.9%). In 10 patients (20.4%), the diagnosis was made intraoperatively. In the remaining 17 patients (34.7%), carcinoma was diagnosed incidentally on histopathological examination of the cholecystectomy specimen. Twenty-seven patients (55.1%) had unresectable tumours on preoperative morphological imaging. Six patients (12.2%) had a markedly impaired general condition or severely altered biological parameters, precluding any surgical procedure.

An ultrasound-guided percutaneous biopsy was performed in one patient.

Among the 49 patients, 42 underwent surgery. A right subcostal laparotomy was used in 17 patients, and laparoscopy in 25 patients. Intraoperative exploration revealed liver metastases in 9 cases, peritoneal carcinomatosis in 7 cases and invasion of adjacent organs in 24 cases. Surgery was considered curative in 12 patients. Palliative procedures were performed in 10 patients, and surgery was limited to biopsy of the primary tumour or of hepatic or peritoneal nodules in 20 patients. Overall,

37 patients had unresectable tumours and received palliative chemotherapy. Eight patients received adjuvant chemotherapy. Four patients received exclusively symptomatic treatment (rehydration and/or paracentesis and/or analgesics). None of the patients received radiotherapy.

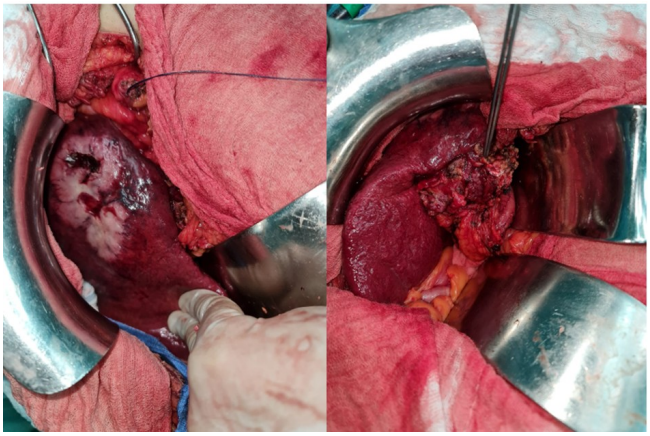

Figure 4 : per operative picture of unresecable tumor

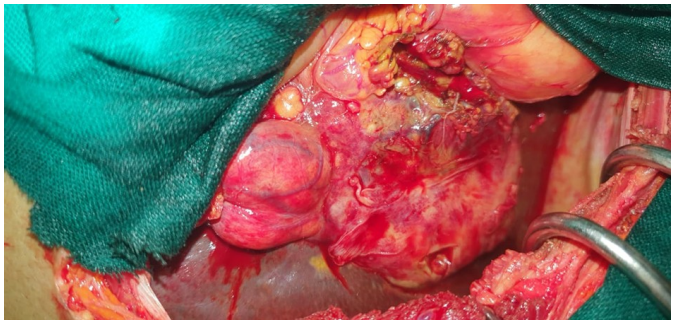

Figure 5 : Intraoperative image: locally advanced gallbladder tumor

Histopathological examination confirmed adenocarcinoma in all cases. The degree of differentiation was specified in 26 patients: 4 well-differentiated, 16 moderately differentiated and 6 poorly differentiated tumours. Pathological staging was specified in 12 patients: 4 tumours were classified as pT2, 6 as pT3 and 2 as pT4.

There was no surgery-related mortality. One non-operated patient died during hospitalization from cardiorespiratory arrest. Postoperative morbidity was observed in 4 patients, consisting of 2 cases of wound infection, 1 anastomotic fistula and 1 biloma requiring two ultrasound-guided drainages, with favourable outcome.

Follow-up data were available for 19 patients; 30 were lost to follow-up. Among the 19 patients with follow-up, 10 died between 2 and 10 months after diagnosis. Two patients were alive without evidence of tumour recurrence, whereas 2 had liver metastases, 2 peritoneal carcinomatosis, 2 locoregional recurrence in the gallbladder bed and 1 pulmonary metastases at last follow-up. Overall, survival status could be determined in 12 patients, and the median survival was 8 months.

Discussion

Gallbladder cancer (GBC) is a rare, highly-lethal malignant neoplasm of the biliary system . It ranks sixth among gastrointestinal cancers. However, the global rates for gallbladder cancer exhibit striking variability, reaching epidemic levels for some regions and ethnicities (5). A wide range of conditions, environmental exposures and lifestyle behaviors have been linked to a higher risk of developing GBC. Predisposing conditions affecting the gallbladder and bile ducts are associated with a higher incidence of gallbladder cancer, specifically those that cause chronic irritation and or inflammation of the gallbladder (1).

Gallbladder cancer rates tend to increase with advancing age (1). Women are affected two to six times more often than men.

Gallstones represent an important risk factor for this malignancy, being present in most (~85%) patients with gallbladder cancer (5). In our study, it was present in 20% of the cases. The exact mechanism by which cholelithiasis predisposes an indi-

vidual to gallbladder carcinoma is incompletely understood, though chronic epithelial irritation and mucosal damage is presumed to be involved (1). Gallstone characteristics further influence the frequency at which gallbladder cancer develops. Increasing stone size augments the risk of gallbladder cancer; stones of 3 cm carry a tenfold increased risk when compared with smaller stones (1; 5). Persistent low grade inflammation within the gallbladder appears to contribute to the development of gallbladder wall calcification; diffuse calcification results in a porcelain gallbladder, which is associated with an extremely high risk of cancer development, in most but not all reports (1; 5)

The clinical presentation often is with nonspecific symptoms like abdominal pain, discomfort, anorexia and weight loss which delays the clinical diagnosis, reason for which most of the patients present in an advanced stage with metastasis. (5).

Weight loss is often associated with asthenia and anorexia. The finding of weight loss in a patient with gallbladder lithiasis should suggest cancer. In our series, the alteration of the general state was found in 81,6% of the cases. Fever is a fickle sign whose frequency varies between 10 and 51.5% of the cases (6). It is often attributed to tumour necrosis or superinfection. In our series, fever was noted in 12% of the cases. Right upper quadrant pain is the most common symptom (3), frequently resulting in hepatic colic, sometimes diffuse abdominal pain or epigastralgia resistant to the usual analgesics. Sometimes the patient presents in a painless picture but with other signs suggestive of biliary pathology. Roughly 90% of the patients in our series had pain in the right hypochondrium. Jaundice along with the pain of right hypochondrium are the two main symptoms of cancer. Jaundice may be discrete, often progressive and inconsistently associated with pruritus. Its presence may correspond to direct invasion of the hepatic pedicle or hilum by the tumor process, extrinsic compression by metastatic adenopathy in the hepatic or retro-pancreatic pedicle, non-tumoral inflammatory pediculitis, or could be lithiasis of the main bile duct. More rarely, it is related to obstruction of the bile duct by calculi or mucinous secretions, or endo-biliary neoplastic thrombus. Weight loss and jaundice, when present, generally indicate advanced disease with a low likelihood of long-term survival, even after R0 resection (2; 7). Icterus was observed in 32,5% of cases in our series. Vomiting and nausea were found in 59% of the cases in our series often worsening the nutritional status of patients. In case of adjacent duodenal involvement, vomiting can be o sign of duodenal obstruction.

On the whole, the vague symptoms associated with primary cancer of the gallbladder make the early diagnosis of the disease difficult. GC is largely asymptomatic until the advanced stages of the disease. In patients with symptoms of acute cholecystitis, generally long-term survival is possible because such patients may be diagnosed at an early stage of the disease. Patients with chronic cholecystitis may present with chronic unspecified upper epigastric pain or tenderness, food intolerance, and a sense of fullness. Patients with symptoms of biliary tract disease and those with clinical features of malignancy have extensive disease. Once a patient develops symptoms related to GC, the disease has often progressed beyond the curable state (8).

Clinical examination is of limited value in gallbladder cancers it is very often normal. On the other hand, it can show a mass of right hypochondrium,

which is the most specific sign, in our series this sign was present in 18% of cases. A hard mass of right hypochondrium is palpable under the lower edge of the liver, and mobile with respiration. It is a poor prognosis factor in favour of advanced pathology. Patients with a palpable right-upper quadrant mass reflected unresectability in 23 of 25 patients in one study (9). Irregularly hard and tumor-like hepatomegaly or regular, firm and cholestatic can be observed. In our series it was found in 18% of cases .Concerning sensitivity of right hypochodrium, which is an inconstant sign it occurred in 28,5% of cases in our series. Furthermore, ascites, which is a late sign, is related to the invasion of the cancer to the peritoneum. It happened in 10% of the patients of this study.

Unlike certain other cancers, there are no tests or procedures that are used routinely for early detection or prevention of gallbladder cancer. Carcinoembryonic antigen (CEA) and carbohydrate antigen (CA 19-9) are traditionally used tumor markers for GC. Their increased presence should raise suspicions of malignancy. CEA concentrations greater than 4 µg/L are 93% specific, but only 50% sensitive, while a CA 19-9 concentration higher than 20 U/mL has 79.4% sensitivity and 79.2% specificity (8). In our series, 35 patients had a high level of CEA and CA 19-9. Chaube et al suggested that CA 125 is one of the important markers of GC: CA 125 concentrations higher than 11U/mL have 64% sensitivity and 90% specificity (10).

Imaging has a key role in the diagnosis and staging of GBC. Optimal imaging evaluation help avoid unnecessary laparotomies. Diferentiation of the cause of gallbladder wall thickening remains a challenging task even with advances in imaging modalities (11). Investigation of suspected GBC usually begins with sonography as it is cost-efective and easily available. USG is sensitive for evaluation of the gallbladder mural thickening or mass and local extension into liver. However, its role in staging is limited as it is less reliable for detection of lymph nodes and peritoneal metastasis (11).It is the most widely used technique in the preoperative study of GC and the standard initial study in patients with upper quadrant pain. Early cancer can be identified as a hypo- or iso-echogenic irregularly shaped lesion, appearing as a subhepatic mass that usually masks the gallbladder. The presence of gallstones trapped within the tumor during its growth is a very useful sign of possible GC. The thickness of the vesicular wall does not normally exceed 3 mm, and the tumor may present as a partial thickening of more than 1 cm, usually irregular and often asymmetric.This finding requires a differential diagnosis with other diseases that may also produce this thickening, such as acute or chronic cholecystitis and hyperplastic cholecystoses. The presence of a mass or polyp with intraluminal growth appears as an intraluminal mass, usually with a diameter of greater than 10 mm, which is not displaced by patient's movements and has a nodular or smooth shape. If the tumor is advanced, US shows a loss of the interface between the gallbladder and the liver. US has a sensitivity of 85% and accuracy of 80% for the diagnosis of GC (8). In our series, ultrasonography was performed for all of the patients and it led to suspicious diagnosis in 40.8% of the cases.

Colour Doppler ultrasonography is another approach to improve the specificity of US, enhanced vascularity is sonographic feature that can signify potential malignancy. Measurement of the flow rate is also important, with a higher rate for malignant tumors than for benign tumors (8; 5).The use of

High- resolution ultrasound (HRUS), may be useful for differentiating GBC from benign conditions like adenomyomatosis and xanthogranulomatous cholecystitis (5; 12).

Endoscopic ultrasound (EUS) is currently the definitive modality for staging gallbladder cancer. EUS also offers sampling via fine needle aspiration (13). EUS may improve diagnosis of GC by predicting the depth of tumor involvement with accuracy, but its usefulness for making a differential diagnosis between benign and malignant lesions remains controversial (8). In some cases, endoscopic ultrasound (EUS) is used to obtain a biopsy for diagnosis.

CT scan is the imaging modality of choice for detecting and staging GBC, quantifying the volume of future liver remnant (FLR) and identifying any anatomical variations of the vessels. It helps identify any extension to lymph nodes, liver involvement, or distant metastases., performed preoperatively, determines gallbladder resectability with a high accuracy (up to 93%) (12; 5; 3). High resolution cross-sectional imaging is essential for adequate staging. A good imaging would avoid un-necessary laparotomies in patients with advanced disease who would otherwise not be candidates for curative resection (14).CT scan is inferior to USG in depicting mucosal irregularity, mural thickening, and cholelithiasis, but is superior for evaluating the areas of the GB wall that are obscured by gallstones or mural calcification. However, local spread of the disease and involvement of the peritoneum and the omentum are frequently underestimated on CT scan, compared to intraoperative extent (12). In our series CT scan was performed in 41 patients and led to a diagnosis in 59% of the cases

Standard magnetic resonance imaging (MRI) is generally less valuable, it is less frequently used for the staging of GBC. However, MRI is particularly useful for visualizing invasion of the hepatoduodenal ligament, portal vein encasement, and lymph node involvement. Magnetic resonance (MR) cholangiography and MR angiography quite accurately detects bile duct or vascular invasion, with sensitivity and specificity approaching 100% (13; 8).

The use of magnetic resonance cholangiopancreatography (MRCP) in the evaluation of malignant biliary obstruction has also been reported, providing more detailed information than US or CT, it helps in a better definition of the level and extent of hilar involvement by GBC (12; 8). Kim et al, in their retrospective study on 86 operated and histologically proven patients of GBC, showed that a combination of MRI with MRCP and dynamic contrast- enhanced sequences has an accuracy of 84% for determining the T stage (15). In another retrospective study, Schwartz and colleagues demonstrated that a combination of conventional MRI with MRCP achieved a sensitivity of 100% for liver invasion and 92% for nodal involvement in staging GBC (16)

There is no role for preoperative biopsy of a primary tumor that appears resectable on imaging. In unresectable patients planned for neoadjuvant or definitive chemotherapy, percutaneous biopsy is a reliable method of diagnosis with a sensitivity of approximately 88% .In addition to providing prognostic information, biopsy can also facilitate genetic testing to guide chemotherapy (7; 14).

The diagnosis of GBC can be established by percu-

taneous fine needle aspiration cytology (FNAC) or biopsy, mostly under USG guidance and occasionally under CT guidance, depending on the Institutional protocol. Sampling of the primary mass, as well as any distant suspected metastatic lesions, should be done for deciding management. USG- guided FNAC is shown to have a diagnostic sensitivity of 90%. Percutaneous FNAC is safe and is associated with minor abdominal pain in 4.5% of cases and biliary peritonitis in 1–6%. EUS- guided FNAC is an option for lesions which are small, particularly the ones located in the neck of the GB. Studies have shown that EUS- guided FNAC is safe and provides definitive diagnosis (12; 17; 18)

Treatment options usually focus on curative resection, which can be compromised by the extent of tumor invasion. Unfortunately, the population falling into this operational course is largely limited, as a large number of patients (>70–90%) can only accept non-surgical treatment. Such unfavorable outcome is because of the atypical clinical symptoms at earlier stages, contrary to the noticeable symptoms that emerge in most cases with advanced disease. Indeed, primary tumor invasion (T) is the most important subset of the American Joint Committee on Cancer staging criteria; it determines the surgical approach (5; 19; 11).

The overall 5-year survival for patients with gallbladder cancer who underwent R0 curative resection was reported to range from 21% to 69%, and 0% for patients who did not get R0 resection. So the R0 curative resection is objective of surgical management for gallbader cancer (20).

Although laparoscopic cholecystectomy has been contraindicated in patients with GBC for some time, many recent reports have shown that laparoscopic surgery does not adversely affect the perioperative and survival outcomes of patients with GBC (21; 22).One recent report showed that laparoscopic extended cholecystectomy for GBC achieved an outcome comparable with that of open surgery over long-term follow-up (23). Port-site recurrences can follow laparoscopic cholecystectomies in up to 17% of cases where unsuspected gallbladder cancer is discovered. Here, accidental bile spillage implants tumor cells at the trocar or incision site, leading to recurrence. Surgical planning for suspected gallbladder cancer thus requires an “open” surgical approach (5) (13).

Incidental gallbladder cancers are detected histologically after the fact in 0.3-3% of laparoscopic cholecystectomies performed for cholelithiasis. For these patients a second radical resection is indicated after adequate diagnostic and treatment preparation, except for Tis and T1a disease (13). Most IGBC are diagnosed on pathologic review. However, if cancer is diagnosed by frozen section at the time of initial operation, the surgeon should carefully inspect the peritoneal cavity for signs of distant spread and consider biopsy of any suspicious LNs before closure (7).

After the diagnosis of GBC has been confirmed on pathologic examination of the resection specimen from the previous cholecystectomy, appropriate staging must be performed prior to initiating treatment. Patients should undergo high quality cross-sectional imaging (24). The role of re-resection after an incidental GBC is diagnosed is to remove residual microscopic local-regional disease from the surgical bed in an effort to achieve an R0 resection, as well as to perform a complete staging lymphadenectomy. Re-resection is indicated in patients

with pathologically confirmed T1b (invasion in the muscularis layer), T2 (invades perimuscular connective tissue without extension beyond serosa or into liver), or T3 (perforation of serosa/liver invasion) disease without evidence of metastatic disease and appropriate performance status to undergo the potential morbidity of a larger operation (25). Re-resection should be performed optimally 4 to 8 weeks after initial cholecystectomy as re-resection within 4 weeks of initial cholecystectomy or greater than 8 weeks afterwards was associated with worse outcomes, even when accounting for tumor stage (26). The excision of port sites from the original laparoscopic cholecystectomy is not indicated routinely, though previous groups have argued for the routine excision of port sites during re-resection (27).

There is no increase in the proportion of GBC patients who received adjuvant therapy for GBC over time, despite findings that both chemotherapy and chemoradiotherapy (CRT) improve OS in patients with T2 tumors or greater. Currently, less than one-third of patients receive adjuvant therapy (28).A retrospective cohort of 74 patients with locally advanced or node-positive GBC was treated with neo-adjuvant chemotherapy and then reevaluated for resection. Thirty percent of patients were eligible for surgical attempt, with 14% undergoing R0 resection (29). This finding suggests that patients who are initially unresectable but who respond to chemotherapy should be reevaluated by a surgeon.

The latest NCCN guidelines recommend consideration of chemotherapy or CRT after resection of GBC. However, the data are limited, and no regimen has emerged as superior (no high-quality randomized controlled trials). There are numerous single-center studies, but several large studies offer valuable insight. Decisions for adjuvant therapy should take into account individual risks and benefits (30).

After R0 resection, there have been some data that suggest a survival benefit with the use of adjuvant radiotherapy (31; 32). Patients with pT2 disease or R1 resection for GC are at highest risk for locoregional recurrence and thus would benefit the most from adjuvant CRT before progression (33). Node-positive patients revealed the best OS with R0 resection combined with adjuvant CRT (34).

Chemotherapy is the traditional therapy for unresectable GBC and no RCTs have been conducted to examine the role of locoregional radiation therapy for unresectable cancer (35).

Conclusion

Gallbladder cancer is a highly malignant and rarely curable disease because of late diagnosis due to unspecific symptoms. Earlier detection, a better understanding of the mechanisms of carcinogenesis should make it possible to significantly improve the prognosis in future years. Surgery associated to chemotherapy treatment can provide survival benefits for patients with advanced GBC.

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