Chapter

Gall Bladder Carcinoma: Clinical Presentations and Different Modalities of Treatment

Wala Ben Kridis, Nabil Toumi, Jamel Daoud, Afef Khanfir and Mounir Frikha

Abstract

Gallbladder cancer (GBC) is the most common cancer of the biliary tract and has a particularly high incidence in Chile, Japan and northern India. The clinical presentation of GBC is often vague or delayed relative to pathologic progression, contributing to advanced staging and dismal prognosis at the time of diagnosis. In the diagnosis of GBC, differential diagnosis and determination of the local extension of tumor are important. For these purposes, imaging modalities such as endoscopic ultrasonography (EUS), CT, MRI and magnetic resonance cholangiopancreatography (MRCP) are useful. The treatment of localized GBC is based on surgery. Chemotherapy has been used extensively in advanced GBC, and we have gained some experience with gemcitabine-based combination (with cisplatin and oxaliplatin or with capecitabine) regimens.

Keywords: gallbladder carcinoma, clinical presentation, treatment

1. Introduction

Biliary tract cancers (BTCs) are invasive adenocarcinomas that arise from the epithelial lining of the gallbladder and intrahepatic and extrahepatic (hilar and distal common bile duct) bile ducts. Gallbladder cancer (GBC) is one of the most common malignant tumors of the extrahepatic bile ducts with high incidence in Japan, Chile and northern India [1]. The incidence of GBC steadily increases with age. Women are affected two to six times more often than men, with predominance in whites. Several risk factors are incriminated in the occurrence of this malignant tumor, and the main one is gallstone disease. The symptomatology is varied and nonspecific, dominated mainly by the pain of the right hypochondrium, which poses a problem of early diagnosis and management. The circumstances of discovery are multiple: preoperative, intraoperative and postoperative. GBC is characterized by local extension, regional lymph node metastases and distant metastases. Usually, GBC is the most aggressive of the biliary cancers with the shortest overall survival [1]. Complete surgical resection is the only chance for cure. However, only 10% of patients are considered surgical candidates [1]. Among patients who undergo curative resection, recurrence rates are high. Patients with unresectable or metastatic GBC have a very poor prognosis.

2. Epidemiology

Gallbladder cancer is the most common cancer of the bile ducts. It accounts for 3% of all malignant tumors and ranks fifth among digestive cancers after cancer of the colon, rectum, stomach and pancreas [2].

The incidence rates are high in Asia and Latin America, relatively high in some countries in eastern and central Europe, yet low in the United States and most Western and Mediterranean European countries [3]. Gallbladder cancer tends to afflict indigenous populations, according to a vast global cancer registry on five continents (representing 704.4 million people or 11% of the world population) [4]. Mapuche Indians from Valdivia, Chile and South America exhibit the highest rate of gallbladder cancer: 12.3/100,000 for males and 27.3/100,000 for females. American Indians in New Mexico, USA, follow with an average annual rate of 8.9/100,000. For these native people, GBC mortality rates exceed those for breast (8.7/100,000), cervical (8.0/100,000), pancreatic (7.4/100,000) and ovarian cancers (7.3/100,000) [5]. According to the literature, the sex ratio women-men ranges from 2:1 to 3:1. In India and South America, the sex ratio is particularly very high: 5/1 to 6/1. However, this difference between the two sexes is less pronounced in East Asia, where the sex ratio between men and women [6]. Gallbladder cancer rates tend to increase with advancing age. The median age was 67 years in a Memorial Sloan-Kettering report of 435 gallbladder cancer patients [7]. Gallbladder cancer is found in 1–2% of cholecystectomized patients. It is suggested that the presence of vesicular calculus may cause dysplasia of the vesicular mucosa after chronic irritation.

Usually, gallbladder cancer develops over 5–15 years, when metaplasia progresses to dysplasia, carcinoma in situ and, then, invasive cancer. Only 10% of patients are resectable at the time of surgery [6] with high recurrence rates [8].

3. Diagnosis

3.1 Symptoms and signs of gallbladder carcinoma

The clinical presentation of GBC is often vague or delayed relative to pathologic progression, contributing to advanced staging and dismal prognosis at the time of diagnosis. The clinical presentation is nonspecific. Pain is the most constant symptom. It is present in 72–77% of patients [9]. Frequently, it is an intense paroxysmal pain with respiratory inhibition, sitting in the right hypochondrium, and with posterior irradiation to the tip of the right shoulder blade and anterior to the right shoulder, realizing the classic pain in sling. It could be atypical such as epigastralgia and diffuse abdominal pain [9].

Jaundice is observed in 58% of cases. It may be secondary to either tumor invasion or extrinsic compression of the bile ducts by lymphadenopathy or tumor or by the presence of liver metastases [10]. Nausea and vomiting are found in 20–49% of cases. Clinical examination may be strictly normal at the early stages. The most common signs are evidence of a very advanced disease. GBC is manifested in 15–50% of cases by a mass of the right hypochondrium [11]. Abdominal palpation shows a sensitivity of the right hypochondrium in 50–80% of cases [11]. A defense of the right hypochondrium or even a positive sign of Murphy can be found on the examination, but they remain an unspecific signs [11].

3.2 Diagnosis

Imaging modalities such as ultrasonography (US), endoscopic ultrasonography (EUS), computed tomography (CT), *magnetic resonance imaging* (MRI) and

magnetic resonance cholangiopancreatography (MRCP) are useful. EUS has good sensitivity in differentiating benign gallbladder diseases from GBC [12]. CT and MRI examinations are useful for local and metastatic staging [13].

Ultrasonography is the first examination to be carried out in the diagnostic approach in front of a patient presenting a biliary symptomatology or for the preoperative study of a vesicular tumor (**Figure 1**, [14, 15]). It has a sensitivity of 85% and a specificity of 80% in the diagnosis of tumors of the gallbladder. Budding image is the most common image [15]. It is a vegetative lesion projecting into the vesicular lumen. It can be single or multiple and is manifested by a hypo or iso-echoic image without shadow cone, irregular edge and implantation base. EUS allows directly visualizing the tumor and evaluating its deep extension in the vesicular wall, in the hepatic parenchyma and the bile ducts [14]. It also makes it possible to differentiate an early tumor from an advanced tumor. It has a significant sensitivity for the etiological diagnosis of neoplastic icterus.

If US suggest a resectable GBC, CT, MRI with magnetic resonance cholangiography (MRC) and/or traditional cholangiography often provide additional information [16]. These modalities allowed specific staging [17].

CT is to be done in second intension after the ultrasound. It allows the diagnosis of GBC in 60–74% of cases. However, its main interest lies in the establishment of the tumor extension report. The CT scan aspects are similar to those detected by ultrasound. A parietal thickening (**Figure 2**) or a budding tumor presenting as a hypodense, heterogeneous lesion containing hypodense zones and other hyperdense secondary to tumor necrosis may be found. The enhancement by the tumor may be diffuse or partial, preferentially, peripheral in case of avascular central necrosis [18, 19]. Although CT is inferior to ultrasound in depicting mucosal irregularity, mural thickening and cholelithiasis, it is superior for evaluating the thickness of portions of the gallbladder wall that are obscured by gallstones or mural calcification on ultrasound. In unclear cases, hybrid PET-CT systems may provide structural and functional information simultaneously and may offer early and accurate staging with high specificity [20].

The GBC appears hypo- or isosignal in T1 and hypersignal in T2 at MRI, the perilesional inflammation in hypersignal T2 and the calculations are hyposignal. Intravenous gadolinium injection increases sensitivity and provides additional data

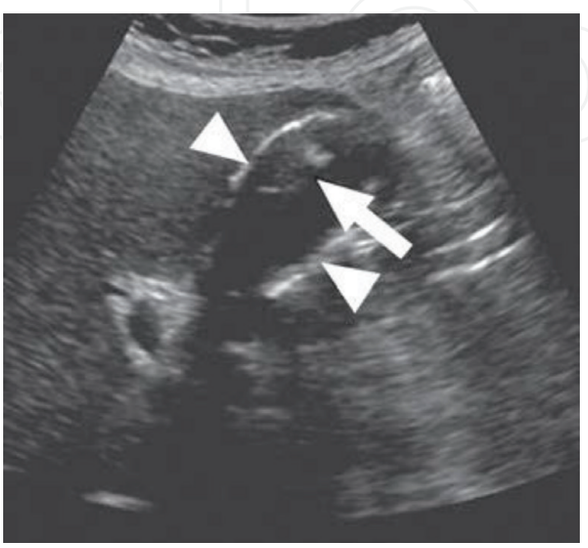

Figure 1.
Ultrasonography shows hyperechoic shadowing portions of gallbladder wall (arrowheads) consistent with porcelain gallbladder and hypoechoic, polypoid mass (arrow) suggestive of malignant degeneration into gallbladder carcinoma.

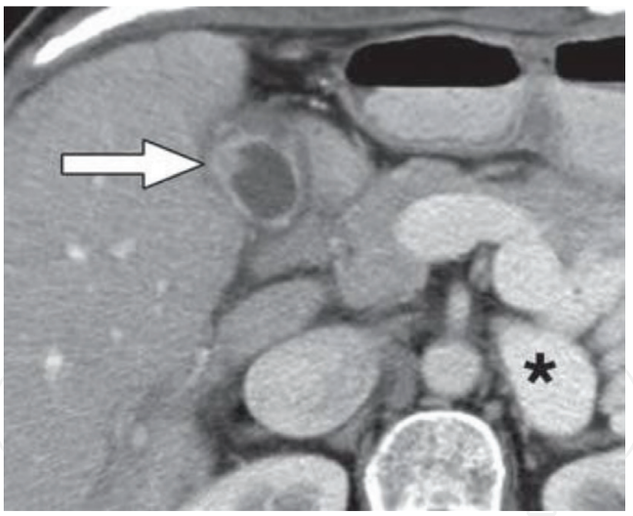

Figure 2.
Contrast-enhanced CT scan during portal venous phase shows focal nodular thickening (arrow) and diffuse gallbladder wall thickening.

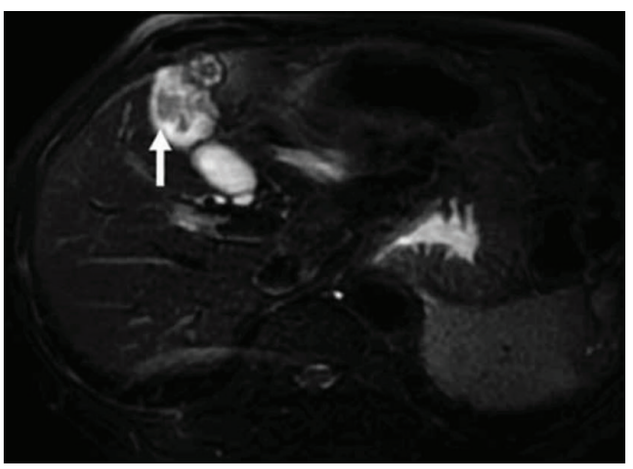

Figure 3.
Axial fat-saturated T2 fast spin image shows a mildly hyperintense, polypoidal and intraluminal gallbladder mass (arrow).

Extension		M0			M1
		N0	N1*	N2**	
Tis	Carcinoma in situ	0	—	—	—
T1a	Tumor invades the lamina propria	I	IIIB		IVB
T1b	Tumor invades the muscular layer				
T2	Tumor invades the perimuscular connective tissue; no extension beyond the serosa or into the liver	II			
T3	Tumor perforates the serosa and/or invades the liver and/or other adjacent organ or extrahepatic bile ducts	IIIA			
T4	Tumor invades the main portal vein or the hepatic artery or two or more extrahepatic organs	IVA			

**Along the cystic duct, the common hepatic duct, the common hepatic artery and the portal vein.*
***Peri-aortic, peri-cellar, celiac trunk and superior mesenteric artery.*

Table 1.
TNM classification (7th edition).

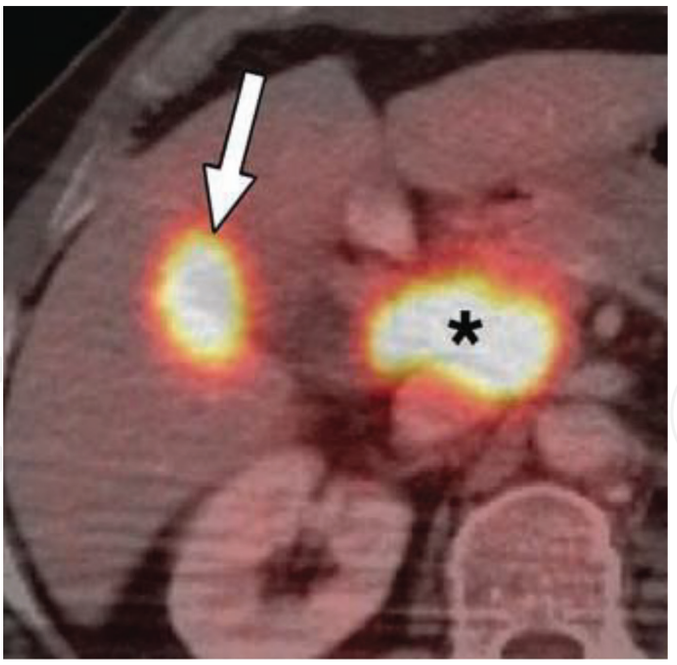

Figure 4.
PET/CT image: gallbladder carcinoma (arrow) with lymph nodes (asterisk).

on vascular involvement (**Figure 3**). The section thickness should be 5 mm or less, with a 1–2 mm gap between sections.

Cholangio-MRI is a very useful test for jaundice. It allows to specify the tumor extension. It may be the only examination to be performed after ultrasound in patients with jaundice. Dynamic MRI with MRCP is an accurate and a reliable method of showing GBC and in assessing its local and regional extent as part of preoperative assessment [13]. However, only the pathological study could confirm the diagnosis of gallbladder carcinoma.

In unclear cases, fluorodeoxyglucose-positron emission tomography (FDG-PET) can be considered to establish the benign or the malignant nature of the lesion and to obtain a primary staging study (**Figure 4**).

Table 1 showed TNM classification (7th edition)—UICC—AJCC (2010) cancers of gall bladder.

4. Treatment

4.1 Localized GCC

4.1.1 Surgery

4.1.1.1 Tis, T1a, T1b and T2 cancers discovered incidentally on the cholecystectomy

The reference is IVb-V bisegmentectomy with lymph node dissection and possibly resection of the bile duct. Bisegmentectomy can be discussed in favor of resection of the vesicular bed for these "small cancers," especially if the cancer is located on the free side of the gallbladder. Similarly, resection of the bile duct is recommended only in cases of cystic involvement or patent nodal invasion (**Figure 5**) [21].

Systematic secondary resection of trocar orifices is currently controversial.

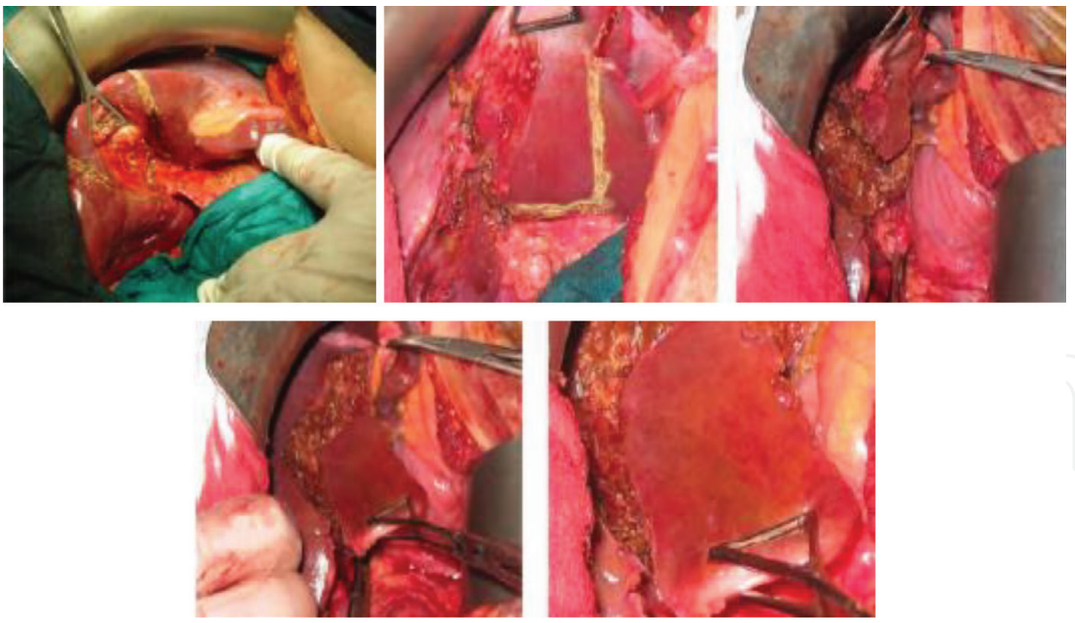

Figure 5.
Photos d'une bi-segmentectomy IVb-V.

4.1.1.2 Locally advanced tumors >T2

The extent of liver resection remains controversial. Thus, an IVb-V bisegmentectomy or a more extensive hepatic resection of the trisegmentectomy type may be proposed, and for tumors invading the hepatic pedicle, an enlarged right hepatectomy or a central hepatectomy (IV, V, VIII) associated with a segment I resection. Segment I resection is especially useful for tumors invading the hepatic hilum. Direct invasion of the colon, duodenum or liver is not an absolute contraindication to resection, but the morbidity and mortality of these combined resections are high. Ganglion dissection should include extensive resection of the hepatic pedicle ganglia, anterior and posterior pancreatic ganglia and peeling of the hepatic artery until birth in the celiac trunk. Some authors recommend extensive curling, extended to the celiac trunk, to the trunk of the superior mesenteric artery down the anterior aspect of the aorta (para-aortic ganglia). Involvement of the hepatic pedicle and the main bile duct is early in gallbladder cancer without necessarily having a clinical impact (jaundice) or contact with the tumor [22]. In addition, removal of the main bile duct facilitates nodal dissection of the hepatic pedicle. It is therefore recommended for tumors >T2.

4.1.1.3 Palliative surgery

Surgical biliary shunts (and trans-tumor intubations) have not been demonstrated superior to prosthetic drainage in terms of quality of life or survival time. Their mortality (>25% in several series) and their morbidity are not negligible. However, the surgical biliary drainage usually allows prolonged palliation to the entire survival patients [22].

4.1.2 Adjuvant treatment

The role of adjuvant chemoradiotherapy is not well defined because of a lack of randomized trials. Most of the published studies are retrospective with small numbers of patients and a mix of gallbladder and bile duct tumors.

A systematic review and meta-analysis of published data from 20 studies between 1960 and 2010 (6712 patients) showed a nonsignificant improvement in overall survival with any adjuvant therapy (chemotherapy (CT), radiotherapy (RT) or radiochemotherapy (RCT)) compared to curative surgery alone (HR 0.74, $p = 0.06$). There was no difference between gall bladder tumors and bile duct tumors ($p = 0.68$). The association became significant when both cancer registries were excluded, with a significantly higher benefit of CT or RCT than RT alone (OR: 0.39, 0.61 and 0.98, respectively, $p = 0.02$). The greatest benefit of adjuvant treatments was observed with N+ status (OR: 0.49, $p = 0.004$) or R1 (OR: 0.36, $p = 0.002$) [23]. There is no randomized trial of adjuvant RT or RCT. However, there are only heterogeneous retrospective series, addressing the issue of adjuvant radiation therapy. In these small series, differences in patient selection criteria, staging systems, extent of resections, radiation therapy techniques and doses and chemotherapy schedules, it is difficult to pinpoint the exact role of adjuvant therapy in GBC [24, 25]. Bilcap study is a phase III study that included patients with completely resected cholangiocarcinoma (CCA) or gallbladder cancer (including liver and pancreatic resection, as appropriate), with adequate biliary drainage, no ongoing infection, adequate renal, hematological and liver function and ECOG PS ≤ 2. It demonstrated that capecitabine improved overall survival when used as adjuvant and should become standard of care [26].

4.2 Metastatic GCC

A small Scandinavian randomized controlled trial showed that a chemotherapy by 5Fluorouracil and (more etoposide so good general condition) increased the quality of life and survival compared exclusive supportive care in patients with advanced pancreatic or biliary cancer (6.0 vs. 2.5 months, $p < 0.01$), however not significantly in the patient subgroup with biliary cancer, and at the cost of considerable toxicity (grade 3–4, 41%) [27]. A single-center Indian randomized controlled trial in 81 patients with carcinoma of the gallbladder has shown a global survival benefit of chemotherapy by gemcitabine and oxaliplatin not only compared to exclusive supportive care but also compared to a chemotherapy with 5FU and folinic acid (9.5, 4.5 and 4.6 months respectively, $p = 0.039$) [28]. Collectively, these two trials show that first-line chemotherapy is legitimate in patients with advanced biliary cancer whose general condition is not too impaired (PS 0–2).

The British randomized controlled trial ABC-02 demonstrated, in 410 patients with PS ECOG 0–2 (ECOG 0–1: 88%) and controlled biliary obstruction (total bilirubinemia <1.5 N), superiority of gemcitabine-cisplatin combination (GEMCIS regimen) on gemcitabine alone (survival overall: 11.7 vs. 8.1 months, hazard ratio [HR]: 0.64 [95% CI, 0.52–0.80], $p < 0.001$) [29]. The benefit of survival with the GEMCIS regimen was independent not only of tumor stage (locally advanced or metastatic) but also of the primary tumor site (intra- or extrahepatic bile ducts, hile, gallbladder, vater bulb). These results were supported by those of the randomized trial Phase II Japanese BT-22 in 84 patients (ECOG 0-1: 100%) [30]. These results make the GEMCIS regimen the first standard of first-line chemotherapy in patients with advanced biliary cancer. The GEMOX scheme [31] is an alternative, despite the lack of a randomized controlled trial comparing these two regimens. The treatment of metastatic forms is to be discussed according to the general condition (PS, age). In case of PS > 2, it is recommended to do exclusive support care. In case of PS between 0 and 2, it is the indication of a palliative CT by gemcitabine-cisplatin. The GEMOX scheme is an alternative.

5. Conclusion

GBC represents a major challenge in oncology. The only curative treatment for this disease is surgical resection. The roles of radiation and chemoradiation in the neoadjuvant and adjuvant settings remain to be defined in prospective studies. Bilcap study demonstrated that capecitabine improved overall survival in adjuvant situation. The treatment of metastatic forms is to be discussed according to the general condition (PS, age). In case of PS > 2, it is recommended to do exclusive support care. For patients with PS between 0 and 2, it is the indication of a palliative CT by gemcitabine-cisplatin. The GEMOX scheme represents an alternative.

Conflict of interest

None.

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