



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

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. Author AEK designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AEK and MO managed the analyses of the study. Author AEW managed the literature searches. All authors read and approved the final manuscript.*

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## **ABSTRACT**

Gallbladder cancer is the most common biliary tract cancer. It is most often diagnosed late at a stage of unresectable. We report in this retrospective study 43 cases of gallbladder cancer collected at the visceral surgery department of the Ibn Rochd University Hospital of Casablanca (wing3) over a period of 6 years, from January 2012 to December 2017. The aim of this work is to clarify the various epidemiological, clinical, paraclinical, therapeutic and prognostic aspects of this neoplasm, as well as its short and long-term evolution.

**Keywords:** *Gallbladder; cancer; therapy; surgery; prognosis.*

## **1. INTRODUCTION**

Gallbladder cancer is relatively a rare disease, which ranks fifth among gastrointestinal cancers. It is the most common biliary tract cancer [1]. It is

a tumor of aging subjects with a predominance of females. Approximately 90% of vesicular carcinomas are adenocarcinomas. The main risk factors are vesicular lithiasis and the existence of chronic cholecystitis lesions. The

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symptomatology presented by patients is not very specific and differs a little from the one observed in benign biliary tract diseases. Furthermore, there is no evident sign of early neoplasia. Its diagnosis, often late, is generally made at the stage when resectability is impossible [2,3]. The aim of this work is to clarify the various epidemiological, clinical, paraclinical, therapeutic and prognostic aspects of this neoplasm, as well as its short and long-term evolution.

## **2. MATERIALS AND METHODS**

We report in this retrospective study 43 observations of gallbladder cancer collected at the visceral surgery department of the Ibn Rochd University Hospital of Casablanca (wing3) over a period of 6 years, from January 2012 to December 2017. Among our 43 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 anatomo-pathological study of the operating room and the follow-up of the patients. The patients were divided as follows: 32 women and 11 men. With an average age of 57 years with extreme ages of 34 and 80 years. The therapeutic attitude was always discussed in multidisciplinary consultation meetings of digestive oncology.

## **3. RESULTS**

The age of our patients ranged from 34 to 80 years, with a mean age of 57 years. Among the patients 49% were older than 60 years. The patients were divided into 32 women and 11 men with a sex ratio of 0.34. The medical history of the patients was: diabetes in 8 patients (18.6%) and hypertension in 7 patients (16.3%). Six patients were known to have vesicular lithiasis diagnosed on ultrasound with a progression time of 2 to 4 years. The most observed clinical signs are broken down in the following table (Table 1).

The main clinical signs found in the series under examination were: sensitivity to right hypochondrium in 24% of cases, hepatomegaly in 21% of cases, a mass of right hypochondrium in 17% of cases and ascites in 10% of cases.

Abdominal ultrasonography was the first-line examination performed in all patients, and led to the suspicion of gallbladder cancer in 20 (46.5%) of the cases, with evidence of thickening of the vesicular wall in 14 patients and invasion of the

liver parenchyma in 6 patients. A lithiasic vesicle without wall anomaly was seen in 7 patients (16%), dilatation of the intrahepatic bile ducts in 4 patients (9%), dilatation of the main bile duct in 4 cases (9%) and peritoneal carcinosis in 6 patients (14%). The CT scan showed irregular parietal thickening of the gallbladder in 3 cases (6.97%), hepatic invasion in 22 cases (51%), dilatation of the intrahepatic bile duct in 5 cases (11%), dilatation of the main bile duct in 3 cases (9%) and peritoneal carcinosis in 10 cases (23.25%) (Table 2, Figs. 1-2).

Abdominal magnetic resonance imaging were performed to 25 patients, i.e. 58% of the cases, with extension to the liver hilum in 5 out of 25 (20%) of the patients, and extension to the main biliary tract in 1 out of 25 (4%) of the patients and the tumour size was specified in 5 patients. Dilatation of the bile ducts was observed in 10 patients (40%). A vesicular lithiasis was existing in 4 patients (16%). Hepatic evaluation was performed for all of the patients. It was normal in 35% of the cases, but disturbed in 65% of the patients. An isolated cholestasis was noted in 23% of the cases, and it was associated with cytolytic in 42% of the cases. A blood count was normal in 54% of the cases, while a normocytic normochromic anemia was found in 30% of the individuals. Tumour marker assays (ACE, CA 19-9) were performed for 35 patients. Their levels were elevated in 32 patients and normal in the other 3. The diagnosis of gallbladder cancer was strongly suspected pre-operatively based on clinical and paraclinical criteria in 17 out of patients. Discovery of this cancer during the operation happened in 8 patients. Its discovery after the operation occurred in 3 patients, in which it occurred in the first two following an anatomo-pathological examination of the operating specimen after simple cholecystectomy for lithiasic pathology, and surgical operation for bisegmentectomy IV and V was performed later. Whereas the third patient had a cholecystectomy for lithiasis but the anatomo-pathological examination was not performed. One month later, the patient showed retentive jaundice with a mass on the operation scar whose biopsy had allowed the post-operative diagnosis of gallbladder cancer. The computed tomography scan had shown an unresectable tumour. Twenty-six (60.5%) of the patients had an unresectable tumour on morphological examination. Observations were discussed with the multidisciplinary staff for a therapeutic decision. Six patients, or 14% of the cases, had a very altered general state or a very disturbed

biological assessment, which contraindicated any surgical procedure. The approach was a right sub-costal laparotomy in 13 patients (30%). Laparoscopy was performed in 30 patients (69.8%). The per-operative exploration had revealed a tumourous gall bladder in 25 cases, hepatic metastases in 7 cases, peritoneal carcinosis in 6 cases and invasion of neighbouring organs in 20 cases. Among the 43 patients, 28 (65%) of the cases were operated on, 7 of which had only benefited from biopsy samples. Surgery was considered curative in 11 out of 28 patients (39%). Treatment was palliative in 8 out of 28 patients (29%). Surgery was limited to biopsies of the tumour or of hepatic or peritoneal nodules in 9 of the 28 patients (32%).

Twenty-six (60.5%) of the whole patients had unresectable tumours and received palliative chemotherapy. Fifteen patients received adjuvant chemotherapy and other 11 received chemotherapy alone. Four patients received symptomatic treatment (rehydration+/ascites

puncture+/analgesic treatment). None of the patient had received radiotherapy. Twenty-four anatomic-pathological changes were reported, including: 14 occurred in cholecystectomy specimens and 10 in biopsy specimens. All of these results came back in favour of adenocarcinoma. The degrees of differentiation found were as follows: well differentiated in 4 cases, moderately differentiated in 14 cases and poorly differentiated in 3 cases. Staging was specified in 14 patients. The tumours were classified as T2 in 4 cases, T3 in 6 cases and T4 in 4 cases. There was no surgical mortality, except for one non-operative patient who died during hospitalization because of cardiorespiratory arrest. Surgical morbidity was 11%, of which two patients had presented superinfection of the wall and one patient had presented a biloma that required echo-guided drainage on two occasions with good progression. We had a follow-up for 18 patients, while the other 25 persons were lost to follow-up. For the 18 patients, the evolution was marked by: death between 2 and 10 months

**Table 1. Distribution of patients by clinical signs observed**

Clinical symptoms	Number of patients	Percentage
Right hypochondrium pain	38	89%
Retentional jaundice	15	35%
Vomiting	26	61%
Abdominal distension	7	17%
Pruritus	5	12%
Constipation	6	14%
Occlusive Syndrome	2	5%
Slimness	35	82%
Fever	5	12%
Abdominal tenderness	5	12%



**Fig. 1. Abdominal CT scan showing macrolithiasic gallbladder with wall thickening and infiltration of adjacent liver parenchyma**

in 9 patients, of which 2 patients had presented liver metastases and another had a recurrence of the tumour at the cholecystectomy site. Two of the 18 patients had no tumour recurrence, and two had liver metastases, two had peritoneal carcinosis, two had locoregional

recurrences especially in the vesicular bed, and one had pulmonary metastases. For the 18 patients monitored, mortality could only be defined in 11 patients. The others were lost to follow-up. The median survival was 8 months.

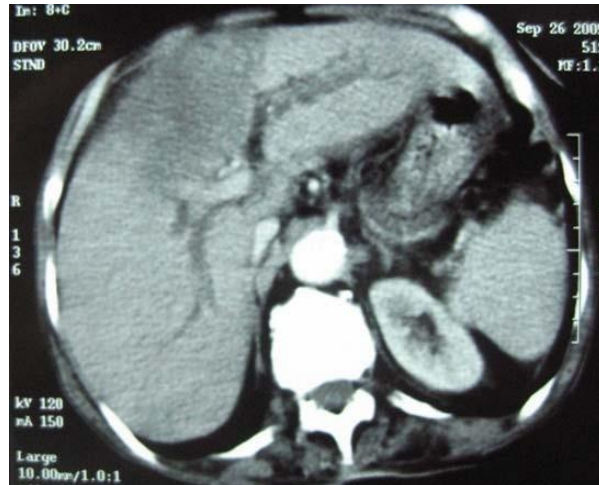


Fig. 2. Abdominal computed tomography scan showing tumour invasion to segments IV and V

Table 2. Distribution of patients according to surgical procedure

<b>Curative</b>	<b>11</b>	<b>39%</b>
Isolated cholecystectomy	3	11%
Cholecystectomy + lymph node dissection	4	14%
Cholecystectomy + bisegmentectomy IV and V + lymph node removal	3	11%
Cholecystectomy + bisegmentectomy IV and V+curing+right colectomy	1	3.5%
<b>Workaround</b>	<b>8</b>	<b>29%</b>
Cholecystectomy of cleanliness	3	11%
Cholecystectomy + hepatic-digestive diversion	1	3.5%
Hepatico-digestive derivation alone	4	14%
<b>Biopsy samples</b>	<b>9</b>	<b>32%</b>
Total	28	100%

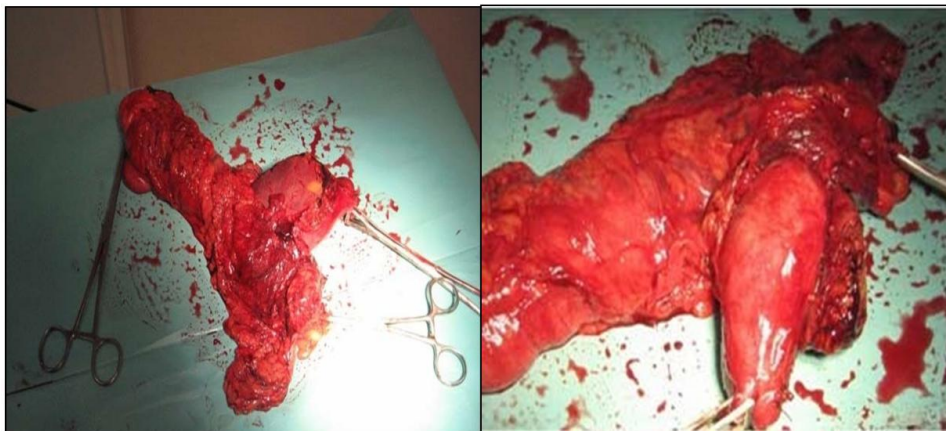


Fig. 3. A monoblock resection of bisegmentectomy IV and V, cholecystectomy, lymph node dissection and right hemicolectomy

#### 4. DISCUSSION

Gallbladder cancer, at all stages combined, is one of the rarest digestive cancers. Its incidence increases with age, and it is rarely seen before the age of 50. Female prevalence is higher in Europe and South America (sex ratio close to 3) than in Asian countries (sex ratio of 1.5) [4]. Its distribution by sex is similar to that of vesicular lithiasis [5,6]. Its incidence in women versus men varies in the literature between 2:1 and 4.4:1, respectively [7]. In our series, women account for approximately 75% of all patients, with a sex ratio of 2.9, which is perfectly consistent with the data reported in the literature. Gallbladder cancer occurs mainly in the elder. Its incidence increases with age in both sexes, peaking in the sixth and seventh decades [8]. In our series, the mean age was 57 years with extremes of 34 and 80 years. Pathophysiologically, chronic inflammation of the vesicular mucosa is the most common implicated condition [9]. It is observed in chronic lithiasis cholecystitis, primary sclerosing cholangitis, chronic carriage of germs in the bile and/or chronic biliopancreatic reflux [10]. This chronic aggressive inflammation of the inner wall of the gallbladder is the cause of metaplastic and then dysplastic mucosal lesions promoting degeneration of the biliary mucosa [11]. At the molecular level, chronic inflammation of the gallbladder associated with genetic susceptibility, such as loss of P53 heterozygosity, or mutations/alterations in the expression of *k-ras*, *P-glycoprotein*, *COX2* and *EGFR* have been suggested as degeneration for certain populations at risk or in a dangerous situation [12]. In approximately 75% of cases, gallbladder cancer is associated with vesicular lithiasis with evidence of cholecystitis [13]. In less than 1% of cases, gallbladder cancer is discovered on definitive histological examination of a cholecystectomy specimen for symptomatic gallbladder stones [14]. Experts agree that there is a strong epidemiological link between chronic vesicular lithiasis and gallbladder cancer [15]. In most countries, mortality from gallbladder cancer is inversely related to the rate of cholecystectomies. It is estimated that patients with vesicular lithiasis (chronic carriage) have 4 to 7 times higher relative risk for developing gallbladder cancer [16]. The relative risk for developing gallbladder cancer in patients with chronic vesicular lithiasis is roughly  $\times 2.4$  if the stones are between 2 and 3 cm in diameter, and more than  $\times 10$  if the stones are more than 3 cm in diameter [17]. The same observation was reported with the weight of the stones [18].

During degeneration to adenocarcinoma and in almost 50% of cases, epithelial changes such as the appearance of "Goblet" or "Paneth" cells, mucus hypersecretion with unusual expression of lysozyme, the appearance of endocrine cells (argyrophils) and dysplastic lesions are observed [19]. Genetic factors, including the existence of "dominant lithogenic genes" associated with bacterial bile infection, may explain the disparity in incidence between different ethnic populations [20]. Despite conflicting results in the literature, it can be noted that: the age of patients ( $> 60$  years), the duration of vesicular lithiasis carriage, especially if symptomatic ( $> 15$ -20 years), and the size of the stones ( $> 3$  cm) are the three factors favouring, or associated with, cancer of the gallbladder. Polypoid lesions of the gallbladder are visible in 3-6% of cases on ultrasound scans of the hepatobiliary region. Cholesterolemic polyps, which represent about half of these cases, are generally small ( $< 10$  mm), always benign, and do not require removal, except when associated with symptomatic vesicular lithiasis [21]. Less than 10 mm polyps have a rate of degeneration between 0 and 5%, while this rate increases to 50-70% for polyps  $> 15$  mm. In practice, nearly 20% of single polyps with pedicles larger than 10 mm are dysplastic, and this rate reaches 30% when the polyp is sessile. Different situations can also lead to degeneration and to the indication for a preventive cholecystectomy for polyp, when there is a rapid increase in the size of a polyp over two morphological examinations, or when the infracentimetric polyp is associated with vesicular lithiasis. The recent Freeman Hospital (New-Castle, UK) study confirmed that cut-off of polyp size greater than 1 cm measured on ultrasound had a 50% predictive value of malignancy with a sensitivity of 100% and a specificity of 86% [47]. Vesicular adenomyomatosis (or adenomyosis) is a lesion characterized by hyperplasia of the vesicular epithelium and muscle layer responsible for thickening of the vesicular wall [22]. The epithelium protrudes through the muscle and forms pockets (Rokitansky-Aschoff sinus). It is often asymptomatic. The lesions are visible on ultrasonography or even endoscopy [23]. The scannographic aspect may be characteristic. Vesicular adenomyomatosis may be associated with vesicular lithiasis or an abnormality of the biliopancreatic junction and may be observed from childhood [24]. Despite the existence of isolated cases of degeneration, they are considered as benign and should not be mistakenly considered as a precancerous

lesions. abnormality of the biliopancreatic junction are a rare congenital anomalies (< 3% of endoscopic retrograde cholangiopancreatograms) characterized by an abnormal junction between the bile duct and the Wirsung duct forming an abnormally long common duct (> 10-15 mm) outside the duodenal wall without a clean sphincter [25]. It facilitates the chronic reflux of pancreatic juice to the bile ducts, thus promoting metaplasia, dysplasia and degeneration of the vesicular wall (or the wall of the main bile duct if associated with a bile duct cyst) [26]. Approximately 15% of patients with gallbladder cancer have PBCA. If an abnormal of biliopancreatic junction is associated with a bile duct cyst, the risk of degeneration is about 17% [27]. This risk increases with age and if there is a history of cysto-digestive bypass, which should be avoided [28]. The risk of degeneration justify a systematic complete excision of the biliary tract with hepatic-jejunal anastomosis [29]. More recent studies show that among patients with proven PJPA, the risk of gallbladder cancer is higher when the diameter of the gallbladder tract is less than 20-30 mm, whereas when this diameter is larger, the risk of degeneration is greater in all portions of the gallbladder tract that are dilated [30]. The porcelain vesicle, described in France in 1831, is characterized by calcification of the vesicular wall (sclerotic shell). It is more frequently observed in women around 60 years of age. Calcifications may be complete or partial, affecting the mucosa or the entire vesicular wall [31]. Porcelain gallbladder is associated with gallbladder cancer in a highly variable proportion ranging from 12 to 60% of cases [32]. Depending on the location and extent of the calcifications, there are three types: type I: Complete diffuse and intramural calcification; type II: Complete calcifications of the mucosa; and type III: incomplete calcifications of the mucosa. Type I appears to be associated with a lower incidence of vesicular cancer than types II and III [33]. Despite the conflicting results regarding the incidence of porcelain vesicle degeneration, it is recommended to offer preventive cholecystectomy to these patients with porcelain vesicle.

Weight loss has been found in 28.1% to 58.6% of the patients [34]. It 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 82% of the cases. Fever is a fickle sign whose frequency varies between 10 and 51.5% of the cases [35]. It is

often attributed to tumour necrosis or superinfection. In our series, fever was noted in 12% of the cases. Pain most often occurs at the level of the HCDt [36], 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 89% of the patients in our series had pain in the CTHD. Jaundice along with the pain of tCdH are the two main symptoms of cancer [37]. Icterus was observed in 33 to 58.6% of cases [6], which is in line with our results (35% in our series). 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. This jaundice may be discrete, often progressive and inconsistently associated with pruritus. Vomiting and nausea were found in 20 to 49% of cases [38], often worsening the nutritional status of patients. In our series, vomiting was found in 61% of the cases. Clinical examination is of limited value in gallbladder cancer as it is very often normal. On the other hand, it can show a mass of right hypochondrium, which is the most specific sign. It is present in 15 to 50% of cases [39], and in our series this sign was present in 17% 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 prognostic factor in favour of advanced pathology. A hepatomegaly: irregularly hard and tumor-like or regular firm and cholestatic [20]. It is observed in 37.5 to 46% of cases (21% in our series). Concerning sensitivity of tCdH, which is an inconstant sign it occurred in 29% of cases (24% in our series). Furthermore, ascites, which is a late sign, is related to the invasion of the cancer to the periton. It happened in 10% of the patients of this study. In total gallbladder cancer has no specific symptomatology and can take on several misleading clinical aspects. However, this cancer should be suspected in any elderly person, especially females who are known carriers of a vesicular lithiasis with unexplained weight loss and exacerbation of pain from right hypochondrium. The most frequently cited tumor markers are carcino-embryonic antigen (CEA), CA 19-9 and alpha-fetoprotein. The marker that seems to be the most specific is CA 19-9, as it is most frequently and early positive, even in early

stage. It can also help to assess the progression of neoplasia. In our series, 4 patients had a high level of CEA and CA 19-9.

Ultrasonography is the first examination to be performed in a patient with suspected biliary pathology [40]. In 20-30% of cases, ultrasound finds vesicular parietal thickening. Budding polypoid forms are presented in about 30% of cases. In our series, ultrasonography was performed for all of the patients and it led to suspicious diagnosis in 46.5% of the cases. Echoendoscopy made it possible to describe 4 morphological types of cancer, including: type A that is characterised by a polyposis lesion with a nodular surface, which does not alter the architecture of the wall; type B corresponding to a lesion of wide implantation with the presence of parietal irregularities, but without affecting the architecture of the wall, and type C and type D with lesions characterised by the presence of simple irregularities or a rupture of the wall architecture, respectively. The CT scan makes it possible to establish a resectability assessment of the lesion by determining its locoregional extension assessment with average sensitivity and good specificity. In the literature, the sensitivity for detection of hepatic invasion is excellent (100%) if the hepatic lesions are more than 2 cm in diameter, whereas it is 65% if the diameter is less than 2 cm. With respect to extension to the main biliary tract, duodenum and pancreas, CT is particularly sensitive compared to other imaging tests, but less sensitive than echoendoscopy. This examination leads to a positive diagnosis in 60 to 74% of cases, which is in line with our results where CT scan was performed in 35 patients and led to a diagnosis in 58% of the cases. Magnetic resonance imaging allows the lesion in advanced infiltrating forms to be better visualized compared with CT scan. On parenchymal sections, the tumour process appears as a budding or infiltrating sessile lesion in hyposignal in T1 and hypersignal in T2.

Transhepatic cholangiography must be carried out in case of biliary tract involvement if surgery is envisaged. It makes it possible to determine the level and nature of the obstacle, also shows its proximal extension, specifies the state of the upper biliary convergence and evaluates the length of the healthy main bile duct with a view to an anastomosis. Most often, the stenosis is tight and circumferential, with significant dilatation of the upper bile ducts. An eccentric stenosis, with smoother contours, should evoke extrinsic compression by adenopathies. Transhepatic

cholangiography also allows palliative biliary decompression to be performed when necessary [41]. Endoscopic retrograde cholangiography like cholangiography allows the obstacle to be highlighted if it exists. It visualizes the lower limit of the obstacle, but its disadvantage is that it does not always allow the obstacle to be crossed and therefore does not study the obstacle over its entire height. However, if the obstacle is crossed, the contribution of ERCP is the same as that of direct cholangiography [42].

The discovery of gallbladder cancer offers two perspectives: firstly, to ensure complete surgical resection for curative purposes, and secondly, to recommend palliative procedure in the case of no resectable tumours. Curative surgery combines tumour removal with lymph node removal. The aim is to perform an R0 type resection, i.e. without macroscopic (type R2) or microscopic (type R1) tumour residue [43]. According to Glenn, curative surgery removes the gallbladder, the entire cystic duct and the hepatic parenchyma of the vesicular bed. This resection is done at the expense of segments IV and V, over a thickness of about 3 cm. An N1 type curettage is associated with it. The thickness of the resected hepatic parenchyma depends on the distance separating the vesicle from the glissal elements, the shortest distances were at the neck: 1.6 +/- 0.7 mm from the neck to the right hepatic duct, 5.9 +/- 1.3 mm from the neck to the convergence of the right sectorial ducts [44]. Cholecystectomy is a controlled perivesicular hepatic exeresis, removing the entire segment V and the anterior part of segment IV (segment IVb). Trisegmentectomy IV-V-VIII is proposed because of the risk of spreading to the entire segment IV and the difficulties of identification between segments V and VIII [45]. Trisegmentectomy IVb-V-VI, proposed by Couinaud, seen that possible venous drainage of the gallbladder in segment VI. Cholecystectomy with right hepatectomy extended to segment IV, recommended as early as 1955 by Pack [46], is very satisfactory from a carcinological point of view and can only be performed if the left lobe represents more than 15 to 20% of the total volume of the liver.

The role of palliative surgical techniques has been significantly reduced in favour of endoscopic and interventional radiology methods. These techniques aim to allow bile to flow into the digestive tract [47]. Two techniques can be used: Prosthetic drainage or biliodigestive shunts. They are identical to the derivation



techniques proposed for cancers of the upper portion of the bile ducts. They are used if locoregional invasion contraindicates removal of the lesion during laparotomy.

Neo-adjuvant treatments are frequently impossible due to jaundice and altered general condition. There are no randomized trials of neo-adjuvant chemotherapy, radiotherapy or radiochemotherapy [48]. External radiotherapy, as an adjuvant treatment, has shown a survival benefit [49]. These results are encouraging and the role of radiotherapy as adjuvant therapy to surgery needs further study before being recommended as standard treatment for gallbladder cancer. The studies on chemotherapy alone were performed on small numbers, mixing biliary tumours with liver and pancreatic cancers, although they differ considerably in terms of etiological, epidemiological and molecular genetic characteristics [50]. The operative mortality is defined by its occurrence during the month following the surgical procedure [51]. It varies according to the type of operation (exploratory laparotomy, palliative procedure or excisional procedure), the resections carried out and according to the staging of the tumour.

Surgical treatment of gallbladder cancer is associated with significant post-operative morbidity. It varies between 15 and 33% according to different authors. The post-operative survival of patients with gallbladder cancer is known to be poor. However, recent work shows encouraging results for radical surgical attitudes (mention the reference). However, survival is still heavily influenced by the stage of the tumour at diagnosis and the type of surgery performed.

## 5. CONCLUSION

Gallbladder cancer is still a dreaded cancer which retains a reserved prognosis on the whole; despite the use of recent imaging assays for its diagnosis, the more precise study of its locoregional extension, despite the progress in therapeutic attitude its remain limited by the rapid spread of the tumour. Earlier detection, a better understanding of the mechanisms of carcinogenesis, and the contribution of new anti-cancer molecules targeting this type of tumor should make it possible to significantly improve the prognosis in future years.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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