Introduction

Methodology

This is based on the guidelines (internal publications) of the Fédération Francophone de Cancérologie Digestive (FFCD) [1] and the Groupe d’Étude et de Recherche Clinique en Oncologie Radiothérapie (GERCOR) [2], and an update based on a bibliographic search of randomized trials, meta-analyses, consensus conferences, and clinical practice guidelines with the key words “biliary neoplasms,” “gallbladder carcinoma,” and “cholangiocarcinoma,” with no limits in terms of time period or language. The present guidelines were graded according to the level of evidence available in the literature, or when the level of evidence was insufficient, on expert opinion. The clinical trials accessible in France were searched by questioning the COTREC (Communication aux Oncologues en Temps Réel d’Essais Cliniques) database [3] and websites of national and international gastroenterology and oncology societies.

INCIDENCE

Biliary cancers are relatively rare, with an incidence of ~2000 new cases per year in France, accounting for ~3% of digestive tract cancers [4]. This incidence, which varies throughout the world (it is higher in Asians), has increased over the last 30 years in Western countries more than a simple improvement in diagnosis or coding of these cancers would account for [4, 5].

Pretherapeutic investigations

DIAGNOSING BILIARY CANCER

Clinical diagnosis

Biliary cancers are most often diagnosed at an advanced stage, in patients over 65 years of age in ~two-thirds of cases [5-8]. The circumstances of diagnosis differ according to tumor location [6-9]:

• Gallbladder cancer (~two-thirds of cases):
  — Incidence at least twice as high in women, paralleling the epidemiology of biliary gallstone, the main risk factor (relative risk $\geq 3$) (table I) [5, 10, 11]
  — Incidental diagnosis on a cholecystectomy surgical specimen
  — Gallbladder mass involving the liver (segments IV and V), often causing obstructive jaundice.

• Cholangiocarcinomas (~one-third of cases):
  — Perihilar cholangiocarcinomas (Klatskin tumors) (~60% of cases of cholangiocarcinoma) and extrahepatic cholangiocarcinomas (~25% of cases of cholangiocarcinoma):
    — Slightly more frequent in males [5, 10, 11]
    — Risk factors most often absent, in particular in patients over 50 years of age; primary sclerosing cholangitis (PSC) is the most frequent risk factor in Western countries (table I) [5-8, 11, 12]
    — Obstructive jaundice and its consequences: pain, cholestatic hepatomegaly, dark urine and discolored stools, pruritus, enlarged gallbladder in case of distal extrahepatic cholangiocarcinoma, malnutrition, cholangitis (uncommon before any biliary instrumental procedure)
  — Intrahepatic (peripheral) cholangiocarcinomas (~15% of cases of cholangiocarcinoma), which are located upstream of the right and left hepatic ducts, and perihilar cholangiocarcinomas obstructing only one hepatic duct:
    — Late, poorly specific symptoms (pain, asthenia, weight loss)
    — Liver mass, cholestasis.

• ~5%-10% of biliary cancers are diffuse or multifocal [6, 7].

Tumor markers

• There is no serum tumor marker specific for biliary cancers [13-15].
• Carbohydrate antigen (CA) 19.9 has a sensitivity and specificity of ~80%.
• Whether CA 19.9 dosage should be combined to the dosage of carcinoembryonic antigen (CEA) and/or CA 125, which alone are less sensitive (~30%-50%) and no more specific, remains controversial [13-20].
• Increased serum levels of these three tumor markers can
Table I. – Biliary cancers: risk factors (after [5-8, 10]).

- More common before age of 50, but absent in the majority of cases
- Share in common chronic biliary duct inflammation

**Gallbladder cancer: two main risk factors**

- Gallstone disease: 73-98% of patients with gallbladder cancer (vs. 20% of controls) in autopsy studies, but very low individual risk (0.25-0.5% at 20 years). Phytopathological cholecystectomy for gallstone disease is therefore not justified, except for calculated, sclerosing, chronic cholecystitis (lifetime risk of cancer, 10-30%; risk up to 40% in case of partially calcified gallbladder)
- Biliarypancreatic junction abnormalities (common biliopancreatic duct > 10 mm, which favors reflux of pancreatic juice in the gallbladder) (lifetime risk of cancer, 15%; lower risk in case of associated choledochal cyst, which may protect the gallbladder from pancreatic juice reflux)
- Other risk factors (less common): – Gallbladder adenoma – Chronic gallbladder Salmonella typhi infection (relative risk of cancer, 6-8) – PSC – Familial history of gallbladder cancer – Debated risk factors: – Tobacco, alcohol, occupational exposure to carcinogens – Gallbladder adenomyomatosis (often associated to biliopancreatic junction abnormality)

**Cholangiocarcinoma**

- PSC (commonest risk factor in Western countries) (lifetime risk of cancer, 10-15%; up to 40% in autopsy studies or liver transplant studies; risk may be increased in case of tobacco or alcohol excessive intake)
- Congenital bile duct abnormalities: – Choledochal cyst (lifetime risk of cancer, 5%; risk much lower if surgical resection before age of 20, but up 15-30% if late or no surgical resection) – Caroli’s disease (lifetime risk of cancer, 7-15%) (associated to a choledochal cyst in 20% of cases) and congenital liver fibrosis
- Liver flukes (Clonorchis sinensis (Japan, Korea, Vietnam)) relative risk of cancer, 15%; lower risk in case of associated choledochal cyst
- Chronic intrahepatic cholelithiasis (lifetime risk of cancer, 5%; risk much lower if surgical resection before age of 10, but up 15-30% if late or no surgical resection)
- Gallbladder adenoma (most commonly associated to adenomyomatosis, often associated to a biliopancreatic duct abnormality)
- Chronic intrahepatic cholangitis (relative risk of cancer, 10-15%; up to 40% in case of partially calcified gallbladder)
- Familial history of gallbladder cancer
- Debated risk factors: – Tobacco, alcohol, occupational exposure to carcinogens
- Biliopancreatic junction abnormality

**Imaging**

As the cytological or histological proof of biliary cancer is often difficult to obtain, imaging is essential to the diagnosis:

- Ultrasonography (US) confirms and localizes ~ 90% of bile duct obstructions, showing infrahepatic bile duct dilatation in case of perihilar cholangiocarcinoma, associated with extrahepatic bile duct dilatation in case of extrahepatic cholangiocarcinoma, with or without gallbladder enlargement depending on the tumor location and the level of cystic duct implantation. Moreover, US helps in the differential diagnosis with other causes of bile duct obstruction, notably gallstone (including the Mirizzi’s syndrome). However, US inconsistently shows and characterizes biliary tumors, notably in case of small, infiltrating, and/or perihilar or extrahepatic tumors.
- Magnetic resonance imaging (MRI) with MR cholangiography (MRC) is the first-choice examination for suspected bile duct obstruction, confirming and identifying the level of obstruction in ~ 95% of cases [21-23].
- When MRC is not possible or inconclusive – the accuracy for the differential diagnosis between benign and malignant obstructions is ~ 90%) [21] –, the diagnosis calls on helical computed tomography (CT), ideally with a multidetector device allowing multiplanar reconstructions, which are particularly useful in perihilar tumors [23-25].
- Percutaneous transhepatic cholangiography (PTC) or endoscopic retrograde cholangiography (ERC) should only be done with therapeutic intent (biliary drainage for cholangitis,…) or for tumor sampling, as morbidity is nonnegligible (cholangitis,…) [6].
- Fluorodesoxyglucose positron emission tomography scanning (FDG-PET) has a sensitivity and specificity of ~ 80%-90% for the diagnosis of gallbladder cancer or nodular forms of cholangiocarcinoma when US and/or CT are inconclusive; sensitivity is much lower (< 20% in some studies) in case of infiltrating cholangiocarcinoma, and false positives are possible in cases of PSC, bile duct stent, or granulomatous disease [26-28].
- Endoscopic ultrasonography (EUS) may help in the positive and differential diagnosis of extrahepatic bile duct and gallbladder tumors [29-31].
- Other imaging techniques (contrast-enhanced Doppler US, cholangioscopy, miniprobe endosonography,…) are not validated and not widely available, and should not be done except in clinical trials.

**Reference**

**Reference (level of evidence A)**

- MRC

**Alternative (level of evidence C)**

- Helical CT if MRC is not possible or inconclusive
- PTC or ERC if bile duct drainage and/or tumor samples are mandatory
- EUS when extrahepatic bile duct or gallbladder cancer is suspected and other imaging techniques are inconclusive

**STAGING**

- MRI with MRC shows tumor spreading: 1) to the bile ducts, notably in case of infiltrating tumor (accuracy, ~ 95%) [32], and helps in planning bile duct drainage by showing obstructed or isolated bile ducts that are not seen on PTC or ERC; 2) to the liver parenchyma (contiguous spreading or metastases); 3) to lymph nodes (~ 50% of patients at diagnosis) (of note, false positives (inflammatory lymph nodes) are frequent in case of PSC); 4) to the hepatic vessels (angio-MRI); 5) to the abdominal viscera and peritoneum [6, 7, 33, 34].
- Staging may also rely on color Doppler US, CT, PTC or ERC which should be reserved for therapeutic intent or tumor sampling, and EUS (in case of extrahepatic tumor, +/- tumor and/or lymph node fine-needle aspiration (FNA)) when necessary [6, 7, 29-31, 35, 36].
- FDG-PET detects ~ 50%-70% of metastases, ~ 30% of which are not recognized by other imaging procedures [26, 28, 37]. However, metastases are uncommon at diagnosis (10%-20%), except for peritoneal carcinomatosis [6, 7].
- Several studies, but not all, have underscored that laparoscopy is currently the single procedure able to detect not only peritoneal carcinomatosis, but also superficial (echo-laparoscopy) or occult liver metastases, as well as occult lymph node metastases [38-40].
- In case of gallbladder cancer, preoperative imaging (US and/or helical CT) is useful only when the tumor had already spread through the serosa.

Alternative

• Primarily resectable biliary cancers (no preoperative (neoadjuvant) treatment): preoperative histological or cytological confirmation should be discussed on a case by case basis and avoided in the majority of cases given the risk of tumor seeding along the needle track. Elsewhere, histological or cytological confirmation should be obtained (resectable biliary cancers when preoperative (neoadjuvant) treatment is decided; biliary cancers not amenable to curative treatment).

  • Tests:
    — Bile duct cytology or biopsies if PTC or ERC is performed
    — Percutaneous US- or CT-guided needle biopsy (after bile duct drainage or through liver segments without bile duct dilatation to prevent post-biopsy peritoneal bile leakage).

CONFIRMING BILIARY CANCER

• Bile duct cancers are adenocarcinomas in ~ 95% of cases [6, 7]. They are often characterized by submucosal infiltration of the biliary tree, both radially and longitudinally, rendering the cytological or histological confirmation often difficult to obtain [6, 7].

• Papillary tumors are peculiar in that they present often as large, mucin-secreting tumors resembling intraductal papillary mucinous tumors (IPMT) of the pancreas and causing often huge bile duct dilatation; they are important to recognize as they are often resectable and with a better prognosis than more common forms of bile duct carcinomas [41, 42].

• The diagnostic yield of bile duct cytology (if PTC or ERC is performed) is ~ 30%, reaching only 40%-70% when combining different techniques (cytospin, fine-layer preparations, brush cytology before and after dilatation of bile duct stenoses, digitalized image analysis, FISH,...). A negative cytology therefore does not rule out bile duct cancer [6, 43-46].

• Excepted for the rare cases in which adenocarcinoma and carcinoma in situ coexist in vicinity, intrahepatic biliary carcinoma may be undistinguishable from a liver metastasis from a non bilary adenocarcinoma. In such case, the differential diagnosis relies on thorough clinical examination and complementary investigations, which should be discussed on a case by case basis, searching most particularly for pancreas, stomach, colorectal, breast, or lung adenocarcinoma: abdominal and lung imaging, lower and upper digestive tract endoscopies, and mammography if there is a breast mass at clinical examination. Serum tumor marker dosages, FDG-PET, and tumor immunohistochemistry (cytokeratins 7, 18, 19, 20,...) can be useful [6, 47-50] (recommendation grade A, B).

• Intrahepatic cholangiocarcinomas should be distinguished from cholangiocellular carcinomas (~ 5%-10% of primary liver cancers), which generally develop on an underlying liver disease (notably hemochromatosis or cirrhosis (relative risk, 9, and even 19 in case of mixed, cholangiocellular-hepatocellular carcinoma) [51, 52].

• In ~ 10% of cases, the suspicion of biliary cancer is not confirmed, most often on pathological examination of a surgical specimen only: postoperative or inflammatory (chronic pancreatitis, PSC) bile duct stenosis, benign tumor,... [53, 54].

Resectability and operability criteria

Operability workup

Reference

• Liver status (aminotransferases, gamma-glutamyltranspeptidase, alkaline phosphatases, bilirubin, albumin, prothrombin, factor V)
• Nutritional status (% weight loss, protidemia, albuminemia)
• Comorbidities (particularly among elderly patients, and/or in case of major liver resection)

Resectability criteria

• In every case (unless the patient is deemed not suitable for resection), resectability should be rapidly assessed by an experienced medical-surgical team.
• Tumor resectability should be assessed before any instrumental bile duct procedure, as subsequent bile duct inflammation, infection or stenting may hamper the resectability workup.
• Resectability, and whether liver or pancreas resection are needed, depend on the existence of liver atrophy and of vascular spreading (a major independent prognostic factor for non-resectability and 5-year survival), and of the level of bile duct spreading [55-58].
• Liver volemury (CT) is mandatory before major hepatectomy.
• Individual variations in liver, bile duct, or vascular anatomy should be recognized and taken into account (MRI with MRC and angio-MRI).
• Physicians should be aware that the tumor usually infiltrates the bile duct submucosa 1-2 cm beyond the extension delineated by imaging procedures.
• TNM classifications, which are mostly based on pathological examination of a surgical specimen [55, 56, 59, 60] (table II), and the Bismuth-Corlette classification for peripheral cholangiocarcinomas [61] (table III) often cannot predict resectability accurately. In these cases, resectability
**Table II. – TNM staging system (UICC 2002) (after [59, 60]).**

**Extramural cholangiocarcinomas**
- Tis: carcinoma in situ
- T1: tumor limited to bile duct
- T2: tumor extending beyond bile duct wall
- T3: tumor invading the liver, gallbladder, pancreas, and/or portal vein or hepatic artery unilaterally
- T4: tumor invading the portal vein or hepatic artery bilaterally, or an adjacent organ (colon, stomach, duodenum, abdominal wall, ...)

**Stage**
- N0: no regional lymph node metastasis
- N1: lymph node metastases (cystic, pericholedochal and/or hilar lymph nodes)

At least 3 lymph nodes should be analyzed. If less than 3 lymph nodes are assessed, the tumor is staged N0 (and not Nx) if they are not involved.

**M0: no distant metastasis**

**M1: distant metastases**

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**Intrahepatic cholangiocarcinomas**
- T1: single tumor, with vascular involvement, or multiple tumors ≤ 5 cm
- T2: single tumor with vascular involvement, or multiple tumors > 5 cm
- T3: multiple tumors > 5 cm on bilateral portal vein or hepatic artery involvement
- T4: multiple or single tumors involving an adjacent organ (other than gallbladder) or visceral peritoneum

**Stage**
- N0: no regional lymph node metastasis
- N1: regional lymph node metastases

**M0: no distant metastasis**

**M1: distant metastases**

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**Galbladder cancer**
- Carcinoma in situ
- T1a: tumor invading the lamina propria
- T1b: tumor invading the muscular propria
- T2: tumor invading the perimuscular connective tissue, but without extension beyond the serosa or to the liver
- T3: tumor extending beyond the serosa (visceral peritoneum) and/or invading the liver and/or other adjacent tissues/organisms (colon, stomach, duodenum, pancreas, amputated bile ducts, etc.)
- T4: tumor invading the portal vein trunk or hepatic artery or at least two extrahepatic tissues/organisms

**Stage**
- N0: no regional lymph node metastasis
- N1: regional lymph node metastases (cystic, pericholedochal, hilar, peripancreatic (behind the pancreatic head), periudodenal, celiac or superior mesenteric arterial lymph nodes)

**M0: no distant metastasis**

**M1: distant metastases (including lymph node metastases located behind the body and tail of the pancreas)**

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**Other investigations if chemotherapy planned**
- 5-fluorouracil (5FU), cisplatin (hyperhydration): electrocardiogram, referral to a cardiologist
- Cisplatin, oxaliplatin: search for peripheral or auditory neuropathy
- Cisplatin: creatinin, creatinin clearance

**Treatment**

The treatment of biliary cancers is complex and poorly codified. Only curative (R0) surgical resection may result in prolonged survival. It should always be discussed by a multidisciplinary oncology staff.

**Operable patient and resectable tumor**

**Preoperative biliary duct drainage**
- Preoperative biliary duct drainage has several theoretical advantages, including: 1) allowing cytological or histological tumor sampling; 2) aiding the surgeon in case of difficult hilar dissection; and 3) reducing the high morbidity (~ 50%) and mortality (~ 10%-15%) of hepatotomies (notably major ones) performed on a cholestatic liver [55, 62, 63]. Resection is generally postponed until bilirubin has fallen below 50 μM.
- The morbidity of preoperative biliary duct drainage is related to PTC or ERC (acute pancreatitis, ...), tumor seeding, and most of all bile duct infection [64].
- Several randomized trials suggest a detrimental effect of bile duct drainage before hepatotomies or pancreaticoduodenectomy [65-68]. When performed alone, preoperative biliary duct drainage advantage is debatable; rather, drainage should be integrated into a preoperative strategy

**Table V. – Blumgart staging system.**

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**Table IV. – Non-resectability criteria.**

| Tumor involving secondary bile ducts bilaterally, or unilaterally but with controlateral portal vein involvement or controlateral liver atrophy | Liver atrophy and controlateral portal vein involvement | Bile duct drainage or portal vein embolization. The laparoscopy yield increases with tumor stage: ~ 10%-15% for T1 tumors (Blumgart classification) (Table IV), ~ 30%-40% for T2 or T3 tumors [38-40]. Non-resectability criteria are summarized in table V.
| Distant metastases (including distant lymph node metastases)
in which it should drain the future liver remnant and preceede the portal vein embolization of the liver part which is planned to be resected [68-71].

PREOPERATIVE PORTAL VEIN EMBOLIZATION

- Preoperative portal vein embolization aims to induce hypertrophy of the future liver remnant (most often the left lobe; more rarely the posterior segment of the liver) when its volume is less than ~30% on CT volumetry [71-75].
- Combined with (preceded by) preoperative bile duct drainage of the future liver remnant, preoperative portal vein embolization may help in reducing morbidity and mortality after major liver resection for biliary cancer in jaundiced patients [71-76].

RESECTION

- Biliary cancer resections harbor a postoperative morbidity and mortality (5%-10%) higher than for resections performed for other indications or bile duct resections alone (2%-4%). This is mostly due to the fact that major liver or pancreatic resections are often required, in often elderly or frail patients [62, 72, 73, 77]. Therefore, surgical resection for biliary cancer should be discussed or undertaken only by experienced teams.
- Overall, curative (R0) surgical resection, the only chance for cure, is only possible in ~20% of cases of biliary cancer.
- Five-year survival after R0 resection is ~10%-20% (median survival, 12-24 months). It is has been suggested to be higher for papillary cancer, distal extrahepatic cancer (>40%), and superficial cancer of the gallbladder (>85%), although differences seem more subtle after adjustment on tumor stage [6, 62, 78-83]. R1 resection (positive surgical margins) roughly halves the median overall survival (9-24 months vs. 19-44 months) and drastically reduces 5-year survival (0%-12% vs. 19%-57%) [56, 62, 63, 71, 77]. Lymph node invasion (5-year survival <5%) and perineural or portal invasion also predict a poor prognosis [71, 84]. Surgical exploration with extemporaneous sampling of biliary sections and lymph nodes is therefore essential.
- Surgical resection include:
  - A monobloc resection of the involved biliary ducts (and/or gallbladder). This coincides with resection of the invaded liver segments in case of peripheral infrahepatic cholangiocarcinoma. After resection of the common bile duct, alone extrahepatic cholangiocarcinoma, advanced gallbladder cancer invading the cystic duct [85, 86] or associated with resection of the common hepatic duct convergence (perihepatic tumors), a terminalateral, transmesocolic, Roux-en-Y hepatojejunal anastomosis is performed, long enough (60-70 cm) to prevent reflux;
  - Regional lymphadenectomy (hepatic pedicle, hepatic artery, or even celiac artery lymph nodes). The benefit of extended lymphadenectomy (to the lymph nodes posterior to the duodenopancreas or even further [87]) has not been demonstrated, except in some studies for advanced gallbladder cancer;
  - If necessary, liver resection, or pancreaticoduodenectomy (in case of tumor involvement of the lower third of the common bile duct), exceptionally both [71, 82, 88-90]. The type of liver resection depends on the existence of liver atrophy or vascular involvement, and on the extent of bile duct tumor involvement, which may require major liver resection even if it appears limited [71, 91]. For example, tumor involvement of the common hepatic duct convergence (Bismuth type II) requires resection of the segment I of the liver, in which bile ducts are invaded in ~90% of cases at this stage [55, 56, 62, 63, 92, 93]. Finally, right hepatectomy is often preferred, since the left hepatic duct is anatomically longer;
  - If necessary, vascular resection (portal vein, exceptionally hepatic artery) [57, 94-96];
  - If necessary, resection of organs invaded by vicinity (colon, stomach).
- In conclusion:
  - Intrahepatic (peripheral) cholangiocarcinomas: liver resection
  - Perihilar cholangiocarcinomas: bile duct and liver resection
  - Extrahepatic cholangiocarcinomas:
    - Upper third of the common bile duct: same as for perihilar tumors
    - Middle third of the common bile duct: common bile duct resection, usually without liver or pancreas resection
    - Lower third of the common bile duct: pancreaticoduodenectomy
  - Gallbladder cancers:
    - Superficial (limited to mucosa; no lymphatic, venous or perineural invasion; negative cystic duct lymph nodes): cholecystectomy alone [97, 98]
    - Involvement of the muscularis propriae (notably on the juxtahepatic wall);
    - At least resection of the gallbladder bed (segment V and anterior and lower part of segment IV),
    - Or even bi- or trisegmentectomy [IV, V, +/- VI],
    - Or right hepatectomy extended to segment IV [99, 100].
    - With wide resection of the trocart orifices if resection performed after laparoscopic cholecystectomy [101, 102].
- The pathological report should be standardized: carcinoma in situ, underlying PSC or liver disease, tumor type, grade, and stage, surgical margin status (R0, R1, R2), lymphatic, venous, or perineural invasion, lymph node metastases, visceral involvement by vicinity, or distant visceral metastases.

NEOADJUVANT TREATMENT

- Neoadjuvant treatment is frequently impossible because of jaundice or poor performance status.
- No randomized trial of neoadjuvant chemotherapy, radiotherapy, or chemoradiotherapy in patients with resectable biliary cancer has been conducted so far.
- Small, non randomized trials have suggested that selected patients may benefit from neoadjuvant chemoradiotherapy in terms of pathological response – in some instances, complete pathological responses have been observed – and R0 resection rate [103].
- A phase II study showed in seven patients that neoadjuvant photodynamic therapy (PTD) (injection of a photosensitizing agent followed by direct endoscopic illumination of the tumor) may lead to local tumor response and R0 surgical resection; however, the recurrence rate was 17% at 1 year [104].
ADJUVANT TREATMENT

Adjuvant chemotherapy
- One randomized trial suggested a benefit from adjuvant chemotherapy with continuous 5FU and mitomycin C, then oral 5FU in terms of 5-year survival in the subgroup of patients operated on for gallbladder cancer (26% vs. 14%, \( p = 0.04 \)). However, no survival benefit was observed in the whole group of patients with biliary cancer, whatever the surgical margin status (R0 vs. R1). Moreover, this trial raised several methodological concerns (inclusion of patients with ampullary or pancreatic cancer, violations to eligibility criteria, exclusion of a significant proportion of patients from the survival analysis) [105].

Adjuvant radiotherapy
- No randomized trial of adjuvant radiotherapy in patients with resectable biliary cancer has been conducted so far.
- Non randomized trials have suggested a survival benefit with radiotherapy administered at a dose of 45–60 Gy (the latter dose having been usually administered in case of positive surgical margins), alone or associated with intraoperative radiotherapy (in particular in case of positive surgical margins or lymph node invasion) [106-108]. Other studies did not show any benefit, notably in terms of local control [109].
- The combination of endobiliary brachytherapy and external radiotherapy did not seem to provide any survival benefit and may even be harmful, with significantly higher rates of cholangitis and bile duct leakage [110, 111].

Adjuvant chemoradiotherapy
- No randomized trial of adjuvant chemoradiotherapy in patients with resectable biliary cancer has been conducted so far.
- Non randomized trials have suggested a survival benefit with chemoradiotherapy (e.g., 40 Gy plus 5FU bolus) [112, 113], notably in case of positive surgical margins (R1, but not R2), the benefit in case of negative surgical margins being more uncertain [114, 115].
- One retrospective study did not show any benefit with adjuvant chemoradiotherapy compared to adjuvant radiotherapy alone [116].

Reference
- Bile duct drainage should be postponed after the end of the resectability workup. It should be avoided in the vast majority of operable patients with resectable biliary cancer, except when portal vein embolization is planned, or in case of severe cholangitis, severe malnutrition, or severe jaundice (bilirubin >200 µM), or when time to surgery exceeds several weeks (level of evidence A).
- Portal vein embolization should be discussed before major liver resection (level of evidence C).
- Surgical resection should be performed only in a curative intent (negative surgical margin (R0) status) (level of evidence B).
- There is no validated indication for neoadjuvant or adjuvant chemotherapy, radiotherapy, or chemoradiotherapy (level of evidence C).

Therapeutic trials
- None

Liver transplantation
- Five-year survival after liver transplantation for resectable or non resectable biliary cancer is ~ 25%–30%; however, the majority of patients experience recurrence within 2 years after liver transplantation [117-123].
- 5-year survival rates reaching 80% have been obtained in highly selected patients (single tumor < 3 cm) [124], notably in combination with neoadjuvant chemoradiotherapy and brachytherapy in pilot studies in patients with stage I-II perihilar cholangiocarcinoma [125].
- Cluster transplantations of the liver and pancreas are currently nearly abandoned, due to very high mortality rates [118].

Inoperable patient and/or non resectable tumor

Patients with non resectable biliary cancer have a median overall survival of ~ 9–15 months [6-8]. The main causes of death are liver failure and cholangitis. Given this short life expectancy, the main goal of palliative treatment should be to relieve main symptoms (e.g., jaundice, pruritus, pain) in order to maintain or improve patient’s quality of life. Awaiting for the pathological confirmation of biliary cancer should not delay palliative treatment.

Palliative Surgery
- Surgical resections performed in a palliative intent (macroscopically positive (R2) surgical margins) should be avoided, as postoperative survival is not superior to that after palliative biliary stenting.
- Surgical biliary drainage procedures (including tumor stenting) have not been proven to be superior to non surgical biliary stenting in terms of quality of life or survival, and harbor a non negligible mortality (> 25% in several studies) and morbidity; however, surgical biliary drainage generally allows palliation of jaundice standing for the whole patient’s survival [126-129].
- Cholecystectomy may be associated to surgical biliary drainage in order to avoid infectious complications (cholecystitis), and a gastrojejunostomy is recommended in case of distal extrahepatic cholangiocarcinoma [130].
- Celiac neurolysis has not been proven effective for pain control in patients with advanced biliary cancer.

Biliary drainage
- Effective biliary drainage has a positive impact on patient’s quality of life and even overall survival. It should be the main goal of palliative treatment in patients with advanced biliary cancer and jaundice, and has to be rapidly obtained in case of cholangitis, uncontrolled pruritus, and when normal bilirubin is required before chemotherapy [6, 8].
- Efforts should be attempted to drain not only all functional liver segments, but also all opacified ones in order to avoid postprocedural cholangitis (along with periprocedural antibioprophylaxis). As such, patients should be managed in a center with particular expertise in ERC and PTC, which frequently need to be used successively or simultaneously, notably for perihilar tumors. In such cases, MRC
is the first-choice examination to plan stenting, in order to limit the postprocedural risk of cholangitis [131].

- Whether PTC or ERC should be attempted first depends on the location and extent of the tumor: ERC is often preferred for extrahepatic cholangiocarcinomas (then PTC in case of failure), and either ERC or PTC (depending on local skills) for type II-IV perihilar cholangiocarcinomas.

- Currently, no recommendation can be made for stent choice [132-134]. Randomized trials have shown that metallic stents remain permeable for a longer period of time, and hence are more cost-effective than plastic stents when patient's survival is likely to be longer than 6 months (e.g., tumor < 3 cm and no liver metastases); alternatively, plastic stents may be chosen and systematically changed every 3 months [135-141]. Covered stents have not been demonstrated to have a longer permeability, and may be associated with a higher incidence of cholecystitis and acute pancreatitis [142-144].

- A review of more than 100 trials (mostly small-sized, non randomized phase II studies) available in the literature did not unequivocally demonstrate any survival benefit with palliative chemotherapy compared to biliary stenting alone [6, 8]. Objective response rates (often difficult to assess in patients with biliary cancers) varied between 0% and 60%:

  - Single-agent chemotherapy regimens using either older cytotoxic drugs (e.g., 5FU, mitomycin C, cisplatin, etoposide, methotrexate, Adriamycin, nitrosoureas) or modern cytotoxic drugs (e.g., irinotecan, docetaxel, paclitaxel, ...): ~ 10% (range, 0%-21%), with median overall survival generally < 10 months [166-170]

  - Fluoropyrimidine-based combination regimens (5FU or oral agents): ~ 20% (range, 0%-40%), and up to 20%-30% when combined with platinum salts (cisplatin or oxaliplatin); however, toxicity is higher and median overall survival generally < 10 months [166, 171-177]

  - Single-agent gemcitabine: ~ 20%-30% (range, 0%-60%), with generally mild toxicity, but median overall survival generally < 10 months (range, 5-16 months) [178, 179]

  - Gemcitabine-based combination regimens: ~ 30%-40% (range 9%-53%), notably with platinum salts (cisplatin, carboplatin or oxaliplatin); but toxicity is higher, and median overall survival rarely exceeds 12 months (range, 4.5-15.4 months) [179-185]

- The best objective response and survival rates were observed with 5FU-cisplatin ± epirubicin combination regimens [172] (response rate, 19%-40%; median overall survival, 8-11 months) and fixed-dose rate gemcitabine plus oxaliplatin (GEMOX regimen: 36% response rate, median overall survival of 15.4 months [185]). The latter regimen does not require hyperhydration (an advantage compared to cisplatin-based regimens), and seems acceptably tolerable even in patients with liver dysfunction or suboptimal performance status.

- Regional palliative chemotherapy

Hepatic arterial chemotherapy or chemobolization is a logical approach, since biliary tree blood supply derives for the most part from the hepatic artery. Although encouraging tumor response rates have been observed in pilot studies, tumor responses are generally short-lived. Moreover, these techniques are technically demanding, harbor significant morbidity (liver toxicity, catheter obstruction, ...), and expose the patients to a high risk of extrapancreatic tumor progression [6, 8, 186].

**Palliative chemotherapy**

**Systemic palliative chemotherapy**

- A controlled randomized trial (the only one to date) showed that chemotherapy with 5FU, folinic acid +/- etoposide (FELV) increased quality of life and survival compared to best supportive care in patients with advanced pancreatic or biliary cancer (6.0 vs. 2.5 months, p < 0.01); however, the survival benefit did not reach statistical significance in the subgroup of patients with biliary cancer, and toxicity was considerable (grade 3-4 toxicity, 41%) [165].

- Whether PTC or ERC should be attempted first depends on the location and extent of the tumor: ERC is often preferred for extrahepatic cholangiocarcinomas (then PTC in case of failure), and either ERC or PTC (depending on local skills) for type II-IV perihilar cholangiocarcinomas.
After curative treatment

- **Follow-up**

  - Clinical examination and abdominal US or CT every 3 months for one year, then every 6 months
  - Yearly chest x-ray
  - Bone scintigraphy and brain CT if warning signs

<table>
<thead>
<tr>
<th>Table V. – Main palliative chemotherapy regimens</th>
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<tbody>
<tr>
<td><strong>SFU-cisplatin:</strong> every 28 days [171]</td>
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<tr>
<td>• Continuous infusion of SFU 800 mg/m²/day, day 1 to 5 (1000 mg/m²/day on cycle 2 and thereafter if toxicity &lt; grade 3)</td>
</tr>
<tr>
<td>• Cisplatin 100 mg/m² in 1-hr perfusion on day 2 (with hydration)</td>
</tr>
<tr>
<td><strong>LVSFU2-cisplatin:</strong> every 14 days [172]</td>
</tr>
<tr>
<td>• Cisplatin 50 mg/m² in 1-hr perfusion on day 1, then</td>
</tr>
<tr>
<td>• Folinic acid 200 mg/m² in 2-hr perfusion on day 1, then</td>
</tr>
<tr>
<td>• Bolus SFU 400 mg/m², then</td>
</tr>
<tr>
<td>• 22-hr infusion of SFU 1200 mg/m²</td>
</tr>
<tr>
<td>• Repeat folinic acid, bolus SFU, then continuous SFU on day 2</td>
</tr>
<tr>
<td><strong>Gemcitabine-cisplatin (GEMCIS): every 28 days [184]</strong></td>
</tr>
<tr>
<td>• Gemcitabine 1000 mg/m² in 30-min perfusion on day 1, 8, 15, then</td>
</tr>
<tr>
<td>• Bolus cisplatin 30 mg/m² on day 1, 8, 15</td>
</tr>
<tr>
<td><strong>Gemcitabine-oxaliplatin (GEMOX): every 14 days [185]</strong></td>
</tr>
<tr>
<td>• Fixed-dose rate gemcitabine 1000 mg/m² [10mg/m²/min] on day 1</td>
</tr>
<tr>
<td>• Oxaliplatin 100 mg/m² in 2-hr perfusion on day 2</td>
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</table>

**Therapeutic trials**

- **FFCD 9902** (randomized phase II-III trial in patients with locally advanced (non resectable, non metastatic) biliary cancer): biliary drainage plus chemoradiotherapy (50 Gy, SFU 300 mg/m²/day, 5 days/week, D1–33 + cisplatin 20 mg/m² D1–5 and D29–33) vs. biliary drainage plus chemotherapy (GEMOX regimen)
- **EXELIXIS** (randomized, controlled phase III trial in patients with locally advanced or metastatic biliary cancer): bolus SFU and folic acid (D1–5 every 28 days) vs. XL119 (rebeccamycin analog)

**After palliative treatment**

- **After biliary stenting:**
  - Clinical examination and bilirubin on D8 and D30; then every 6–8 weeks with US in case of cholestasis, or complete blood count, liver tests and US if jaundice and/or signs of cholangitis
  - Stent replacement if cholangitis or jaundice (except if caused by intrahepatic tumor progression)
  - Chest x-ray, bone scintigraphy, or brain CT if warning signs
- **After chemoradiotherapy:** abdominal US or CT every 2 months
- **Repeated serum tumor marker dosages have not been proven useful for follow-up during or after treatment.**

**8.6. Treatment for recurrences**

Tumor recurrences are often local-regional. In case of localized tumor recurrence after curative surgical resection, biliary drainage requires a surgical or PTC approach (hepaticojugal anastomosis precluding ERC).

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