Chapter 4

Multidisciplinary Approach of Malignant Tumors of the Biliary Tree

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Additional information is available at the end of the chapter

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Abstract

Biliary tract carcinomas are aggressive tumors that arise from epithelial cells of bile ducts. They present several difficulties in their clinical management. A late initial diagnosis (frequently in the form of locally advanced disease), jaundice, cholangitis, or poor performance status of patients are some of the medical issues that arise in this setting. Another clinical limitation is the lack of robust evidence for many of the standard procedures in this particular scenario. Biliary tumors are lethal tumors, and most of them present in the form of advanced disease or during late evolution. However, we are witnessing some exciting changes in clinical management of tumors of the biliary tract, such as the development of new radiological techniques and novel interventional radiology procedures, the emergence of new radiotherapy modalities, the establishment of standardized chemotherapy regimens, the advance in molecular knowledge, and the development of new treatments directed against therapeutic targets. On the other hand, the most important step for advancing the treatment of these complex diseases is the appearance of multidisciplinary management teams integrating qualified specialists to resolve appropriate treatment challenges. In this chapter, we summarize the most relevant advances in clinical management and new oncologic treatment in biliary tract carcinomas.

Keywords: biliary tract cancer, cholangiocarcinoma, multidisciplinary targeted therapy

1. Introduction

Biliary tract carcinomas are rare and highly lethal tumors that arise from epithelial cells of bile ducts. Bile duct carcinomas are divided into extrahepatic and intrahepatic carcinomas, and

most of them are locally advanced tumors at presentation. Intrahepatic tumors were classified typically as primary liver cancer, while extrahepatic tumors were traditionally divided into cancers of the gallbladder, the extrahepatic ducts, and the ampulla of Vater.

Usually, the term of cholangiocarcinoma has been used to describe bile duct cancers arising in the intrahepatic, perihilar or distal (extrahepatic) biliary tree, exclusive of the gallbladder, or ampulla of Vater. In general, perihilar disease represents 50%, distal disease 40%, and intrahepatic disease less than 10% of biliary tract cases [1].

Clinically, bile duct tumors can manifest different clinical presentations, mainly on the basis of the initial growth site. Thus, tumors of the intrahepatic biliary tract appear as locally advanced hepatic mass with or without satellite lesions, and mimic isolated metastases from the other primary sites, or they can pose a differential diagnosis with the other primary hepatic tumors, mainly with hepatocellular carcinoma (HCC). Gallbladder tumors can be difficult to differentiate from abscesses or be a part of an atypical choledocholithiasis evolution. Proximal biliary tumors may be morphologically similar to pancreatic head cancer and cholangiocarcinomas distal to duodenal tumors. The profile of serum tumor markers (especially CA 19.9), the morphology, and especially the pathological anatomy data are the key to its final diagnosis.

Incidence data worldwide are difficult to evaluate because intrahepatic and extrahepatic tumors are included in separate categories. Intrahepatic bile duct carcinomas are usually assigned as primary liver tumors, while extrahepatic duct carcinomas are independent entities rather than grouped gallbladder cancers. In the United States, gallbladder and other extrahepatic bile duct tumors represent 12,190 estimated new cases and 3790 estimated deaths for 2018 [2]. Some studies suggest that only 15% of biliary tree tumors are intrahepatic cholangiocarcinomas [3], a minimal proportion of 42,000 new cases and 32,000 deaths of primary liver tumors in this period.

Bile duct tumors in recent years have undergone several relevant modifications regarding their staging. Importantly, the newest version of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) Cancer Staging Manual differs in their definitions of T stage and the prognostic stage groupings [4]. Some of these changes in this newest version (2017) improved the prognostic stratification of the TNM staging system [5] and presented notable implications for interpretations and comparison of outcomes from trials and retrospective series that used older TNM staging criteria [6].

Tumors of the bile duct are entities that present many limitations in their clinical management. Globally, cholangiocarcinomas present with a marked poor prognosis and several difficulties in their initial diagnosis, frequently in the form of locally advanced disease, jaundice, cholangitis, or poor performance status of patients. On the other hand, the need for sophisticated diagnostic methods often includes the need for insertion of biliary stents that normalize bile flow, which increases cost and risk of severe complications. Similarly, surgery in cases of localized disease presents a relevant postsurgical morbidity and mortality. The management of locally advanced tumors is poorly defined, while disseminated tumors have a lack of effective treatments. For all of these reasons, bile duct tumors are a clinical challenge that requires specialized centers for proper management. The creation of multidisciplinary teams is mandatory to optimize the knowledge of each specialist in each field.

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Treatment of bile duct tumors is based on localization (intrahepatic, gallbladder, distal, perihilar, or proximal tumor), staging (potentially resectable, locally advanced—unresectable and advanced tumors), and the patient's general state at diagnosis (including liver function). Currently, we lack prognostic or predictive biomarkers of response whose optimizing decisions in clinical management of these tumors. Efforts should be directed toward improving and optimizing the clinical guidelines with which relevant clinical decisions are made.

In this chapter, we summarize the most relevant advances in the clinical management and the treatment of bile duct carcinomas. In recent years, there has been a great variety of novelties in diagnosis management (especially new radiological techniques, vascular radiology, and nuclear medicine) and therapeutic (including the best knowledge of the molecular biology of cholangiocarcinoma and relevant advances in immunotherapy, liquid biopsy, or targeted therapies) that we will review in the following sections.

2. New radiological techniques

2.1. Abdominal ultrasound

Ultrasound is the initial modality of choice to evaluate the liver and biliary system frequently due to decreased associated cost, quick access, and no radiation. The assessment of biliary ductal dilatation is excellent with standard ultrasound given its satisfactory sensitivity of 85–95% [7]. However, just as clinically indicated, it is difficult to distinguish between cholestatic jaundice caused by benign entities and malignant etiologies, and standard ultrasound also suffers from some limitations. In the setting of a dilated biliary system and clinical suspicion for malignancy, the sonographer must perform a detailed scan of the liver parenchyma. Unfortunately, even with a detailed examination, standard ultrasound examination only results in correct diagnoses of benign lesions in 26–35% of cases and 28–39% in malignant lesions [8]. Contrast-enhanced ultrasound imaging thus represents a breakthrough in increased detection of hepatobiliary malignancy. With contrast-enhanced ultrasound, detection of malignant lesions is comparable and sometimes superior to those of contrast-enhanced computed tomography or magnetic resonance imaging, with sensitivity and specificity at 88 and 81%, respectively [9]. Notably, this requires advanced equipment fitted with a low-mechanical index option and pulse-inversion harmonic imaging in order to not degrade the microbubbles of the intravenous contrast agent. A contrast-enhanced examination typically utilizes three phases of contrast including arterial (early) phase at 15–35 s post injection, portal phase at 35–90 s, and delayed venous phase at 90–240 s [7]. A final limitation of ultrasound is the fact that it is very experience-dependent when compared with CT and MRI examinations, thus requiring a well-trained ultrasonographer for optimal results. Ultrasound is also not as accurate as CT and MRI with regard to the estimation of tumor spread and tumor resectability [10]. Thus, ultrasound is often used for initial evaluation to determine the next appropriate imaging modality of choice.

Endoscopic retrograde cholangiopancreatography (ERCP) was previously the standard established procedure for working-up patients with obstructive jaundice. Given its invasive characteristics and inherent complication rate of 3–9% and mortality of 0.2–0.5%, other modalities such as MRCP have become the initial test of choice [11]. ERCP is now almost exclusively used in a therapeutic role and not in initial diagnosis. However, when ERCP is used, endoscopic ultrasound (EUS) can be used as an adjunct procedure to detect and stage periampullary neoplasm and for ultrasound-guided fine needle aspiration.

2.2. Computed tomography

Although utilizing radiation, computed tomography (CT) is an excellent modality to assess the biliary tract given its quick acquisition and thus patient tolerance. Contrast-enhanced CT is highly accurate in the detection of biliary ductal dilatation and is easily used in this setting of a dilated biliary system. The normal common bile duct and common hepatic duct diameter are generally less than 7 mm with imperceptible or barely visible wall at the time of CT imaging [12]. The normal intrahepatic ducts should only be faintly seen at the time of contrast-enhanced CT imaging; if they are visualized, further search should be initiated as the differential includes proximal benign stricture, inflammation, biliary tract stones, or neoplasm. Distinguishing benign from malignant strictures can often be difficult, but, in general, malignant neoplasms demonstrate irregular, eccentric shouldering at the transition point from normal caliber to dilated ducts [12]. Benign strictures often demonstrate smooth, uniform narrowing as the ductal system transitions from normal caliber to dilated ducts [6]. Once biliary neoplasm is suspected, a multiphase contrast-enhanced CT approach is the key as cholangiocarcinoma is best discovered on delayed phase imaging (10–20 min, for example) with retention of contrast material in 40% of cholangiocarcinomas when compared with the normal surrounding liver parenchyma [12].

One of the major goals of imaging, particularly with CT, is to establish the presence or absence of satellite nodules or distant metastases, also identifying the relationship of the tumor to the biliary tree, hepatic vasculature, and the inferior vena cava [13]. CT is also useful to perform volumetric assessment, which allows evaluation for viable potential liver remnants if patients are considered for surgical resection. Extrahepatic disease evaluation is also importantly evaluated, often with a contrast-enhanced CT examination of the chest, abdomen, and pelvis. Limitations of CT include underestimation of longitudinal and proximal extent of the tumor and a sensitivity of only 54% for regional adenopathy. Other limitations include streak artifact and secondary inflammatory changes, which occur in the setting of patients with biliary stents [13].

2.3. Magnetic resonance imaging

Magnetic resonance imaging (MRI) is an excellent modality for the assessment of the biliary system due to its lack of ionizing radiation and excellent contrast resolution. MRCP is considered the radiologic modality of choice in the evaluation of patients with suspected cholangiocarcinoma given its accurate ability to map the biliary tree without requiring instrumentation [13]. MRCP takes advantage of the relatively high-signal intensity of static fluids in the biliary

tract with heavily T2-weighted sequences, resulting in excellent contrast given the associated low signal of the remaining background tissues [12]. It achieves better evaluation of peripheral ductal involvement in cholangiocarcinoma given that an obstructing tumor will often not allow the more peripheral ducts to be adequately be filled during ERCP [13].

The previously long-imaging times for MRCP have been diminished by the use of short-breath hold T2-weighted acquisitions, parallel imaging, and sophisticated respiratory triggering mechanisms [12]. Utilizing a 1.5 Tesla strength magnet scanner or greater and modern multichannel surface coil technology also shortens the imaging times. T1-weighted images with and without gadolinium contrast are performed as well, particularly in the staging of biliary malignancies. 3D isotropic MRCP is often utilized to improve visualization of the intrahepatic bile ducts, allowing thinner sections without intersection gaps and the ability to manipulate the images into any projection for surgical planning [12].

MRI hepatobiliary-specific contrast agents are a particular advantage for imaging the biliary system. These initially distribute in the extracellular fluid compartment, thus providing initial excellent vascular evaluation during the arterial and portal venous phases. They are also actively taken up by the hepatocytes and excreted into the bile, providing excellent imaging of the biliary system on more delayed imaging. These agents are separated into two main categories: manganese-based (mangafodipir trisodium, Teslascan®) and gadolinium-based (gadobenate dimeglumine, MultiHance® and gadoxetic acid, Primovist® in Europe and Eovist® in the United States) agents [13].

2.4. Interventional radiology

In cases of malignant biliary obstruction, interventional management may be indicated. Percutaneous biliary drainage can be performed to decrease serum bilirubin levels, which may facilitate medical therapy, chemotherapy, or possible surgical interventions. However, not all patients may be good candidates for this procedure and preprocedural total serum bilirubin levels, international normalized ratio (INR) and the degree of biliary drainage should be utilized as prognostic factors for subsequent patient selection [14].

Before considering biliary intervention, appropriate cross-sectional imaging should be performed such as thin-slice computer tomography (CT) and magnetic resonance (MR) imaging with MR cholangiopancreatography (MRCP) protocol. Low bile duct obstructions can frequently be managed by using a single catheter or stent across the obstruction through endoscopic retrograde cholangiopancreatography (ERCP). Conversely, high bile duct obstruction involving the confluence or more proximal ducts may not be amenable to such a procedure. Depending on the unique circumstances of each case, interventional procedures such as percutaneous cholangiography, percutaneous transhepatic biliary drainage (PTBD), stent placement, and bile duct biopsy may need to be performed [14].

2.5. Nuclear medicine in biliary tree tumors

Positron emission tomography (PET) appearance in the clinical practice scenario has been revealed as a usefulness advancement in the staging and clinical management of a wide

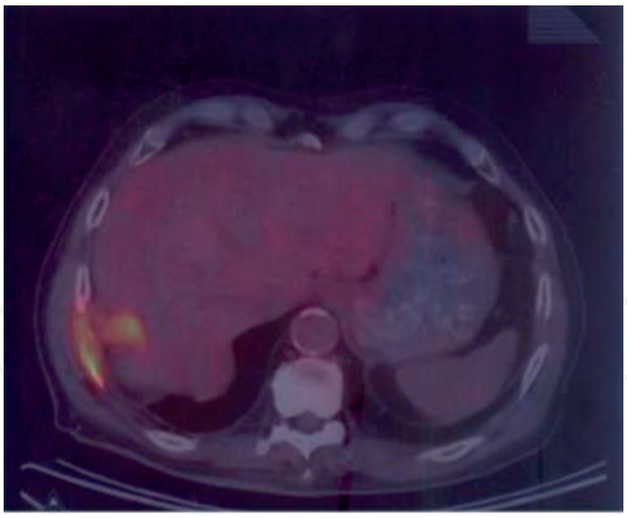

Figure 1. Positron emission tomography. Biliary tract relapse on a drainage sinus scar.

variety of tumors, such as colon cancer, lung cancer, melanoma, and many others. However, the role of PET in bile duct tumors is not well defined. Clinical studies focused on the value of the extension study in potentially resectable tumors, both intrahepatic cholangiocarcinoma and cholangiocarcinoma, gallbladder cancer or common bile duct cancer [15, 16]. Preliminary studies point to some utility in the neoadjuvant setting. It seems to be a technique especially useful in the detection of affected lymph nodes. The value of the high SUV-max glucose uptake is also associated with an unfavorable prognostic value [15]. Local or distant tumor relapse detection by PET during clinical surveillance after radical resection has been described [17], but the value for this setting needs to be developed (**Figure 1**).

3. Surgical approaches

3.1. Management of resectable bile duct carcinomas

Surgical resection of bile duct tumors is the only curative treatment in these tumors. Distal cholangiocarcinomas have the highest rates of resection, while proximal tumors have the lowest rates (particularly, perihilar neoplasms) [16–18]. Resection rates of distal, intrahepatic, and perihilar lesions are 91, 60, and 56%, respectively [19], in some studies. Even in patients who undergo potentially curative resection, margins free of tumor involvement can be obtained in only 20–40% of distal tumors and 50% of distal tumors [20]. A tumor-free proximal margin of at least 5 mm is necessary, so the series presented with these criteria are markedly low; this is an important issue because resection with margins is the only curative procedure [21]. Therefore, although surgical resection remains the gold standard for this disease, it is not so frequent to obtain long-term survival due to frequent postoperative recurrences [22, 23].

The main clinical requirements for resectability are absence of distant hepatic metastases or disseminated disease, absence of retropancreatic node metastases involvement, absence of

portal vein invasion or major hepatic artery (although in many oncological centers, where our institution, en-bloc resection with vascular recovery can be considered), and the absence of invasion of adjacent extrahepatic organs [24].

Patients with positive margins after resection or regional lymph nodes should have been prepared for adjuvant chemotherapy based on 5FU as well as radiation. Unfortunately, no randomized trials that support a standard regimen are defined. People with negative margins after surgery and negative involvement of the lymph nodes can be observed or treated with adjuvant strategies [25]. Radiotherapy and postoperative chemotherapy as clinical options in this setting are discussed in the following sections.

3.2. Computer-assisted surgery

Robotic surgery or robotically assisted surgery refers to technological developments in base to robotic systems aiding the surgical interventions, overcoming the surgical limitations, and enhancing the capabilities of surgeons performing traditional surgery. There are several theoretical advantages of robotic surgery: possibility of surgeries under remote control, improvement in precision procedures, minimum invasion, and lower postoperative morbidity.

The use of robotic surgery in tumors of the bile duct is currently considered to be nonstandard of care procedure. We can mention some theoretical limitations: surgical procedures need optimal software services and marked efforts for coordination among other specialist (i.e., pathological evaluation). Other limitations could be the high cost and the complexity of surgeon's training.

3.3. Orthotopic liver transplantation

Orthotopic liver transplantation is an option that should be considered, exceptionally, generally in highly selected proximal cholangiocarcinomas in combination with neoadjuvant treatment. Only a minority of patients will result in their eligibility, due to the restrictive criteria for their inclusion and the availability of liver transplant programs [26].

Selection criteria include the presence of a tumor without the possibility of a wide margin of resection, a good liver function, and the absence of metastasis (intra- or extrahepatic). These patients frequently begin their treatment with EBRT with concurrent chemotherapy 1–3 months; during a period, it is possible to demonstrate the absence of rapid systemic dissemination. Some clinical series offers remarkable survival rates [27]. However, its complex management and the restrictive conditions for participation make difficult to interpret the real benefit of this technique in overall management of bile duct patients.

3.4. Follow-up after resection and diagnosis of loco-regional relapse

No clear guidelines exist for follow-up after surgery in this particular tumor type. A reasonable approach seems to be physical exam with routine laboratory tests every 3–4 months for the first 3 years post-surgery and subsequently at longer intervals of 6 months until Year 5. The role of CA 19-9 level in surveillance is not clear, but persistently, rising levels often

precede radiological evidence of recurrence by a number of months. Therefore, this marker has been routinely incorporated in follow-up schemas. Which imaging tests to be performed is a topic that has not been specifically addressed in prospective trials, although CT scans of the abdomen every 6 months for 2–3 years after surgery are probably the most common approach in routine practice. However, depending on the case presented, CT and abdominal ultrasound are often not sufficient to detect loco-regional relapses, which could be easily determined on MRI and PET.

While recurrence is mostly loco-regional in the majority of proximal tumors, distal cholangiocarcinomas recur frequently at distant sites including the liver, peritoneum, and lung [28, 29]. Like pancreatic, gallbladder, and hepatocellular cancers, adenocarcinomas of the bile duct have a predisposition to seed and can recur in needle biopsy tracts, abdominal wall incision wounds, and the peritoneal cavity, and therefore, it is recommended to be especially careful in the physical exams of each follow-up visit [17].

3.5. Clinical management of loco-regional relapse

The ideal management of loco-regional relapse still remains undefined. No prospective data exist to set definitive recommendations about the optimum treatment after a curative resection of adenocarcinoma of the extrahepatic bile ducts. Currently, decisions are made based on different clinical parameters that have been established as prognostic factors in retrospective series, such as tumor grade, surgical margins, or lymph node involvement.

Surgery is generally not indicated for recurrent bile duct adenocarcinoma due largely to the location of recurrence, technical difficulty, frequent distant metastases, and aggressiveness. However, in patients with prolonged relapse-free interval and favorable location, surgery should be an option to consider [17]. Radiotherapy and systemic chemotherapy will be commented in the following sections.

4. Radiotherapy

4.1. Radiation techniques

Historically, radiotherapy was used in patients with locally unresectable advanced bile duct tumors as a palliative treatment in search of local control. However, a measurable benefit of radiotherapy treatment in terms of survival in this setting has not been well established [30, 31] because of a small size and retrospective design of the studies.

New advances in technology and improvements in safety and effectiveness may have resulted in some benefit using radiotherapy in locally or locally advanced disease. In addition, the improvement in imaging techniques has allowed a more precise planning in the treatment of upper gastrointestinal tumors. Specifically, in the last decade, treatments have been optimized based on the new EBRTs, such as 3D conformational radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT). IMRT uses computer-generated images to evaluate the

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size and shape of the tumor mass, generating different intensities of radiation in base to a multiple-angle emission, reducing damage of normal tissues near the tumor.

Studies with accelerated or hypofractionated regimens (i.e., stereotaxic body radiation therapy—SBRT) have been tested in cholangiocarcinoma. SBRT is defined as an external beam radiotherapy method used to deliver a high dose of radiation therapy to an extracranial target using single or small number of fractions. Those treatments have also been tested in patients in the adjuvant setting. However, the difficulty in grouping cases in large and comparative clinical trials is a limitation to obtain definitive conclusions from standardized procedures.

4.2. Adjuvant and neoadjuvant therapy

At present, the role of neoadjuvant treatment prior to surgical resection is considered experimental. No comparative study has shown a survival benefit or an improvement in resectability in this setting. Safety data are not well defined. Neoadjuvant therapy in cholangiocarcinoma is a field open to research. The theoretical basis of neoadjuvant treatment offers several attractive advantages in the clinical management of bile duct tumors. Bile duct carcinomas present a high local recurrence rate (even in the context of disease-free surgical margins) and frequently preset systemic metastases. Neoadjuvant treatment would allow a theoretical biological control of the initial micrometastases, a "screening" of the responding patients with a selection of patients who would rapidly progress to treatment. Finally, the pathological evaluation of the tumor piece after the response to the preoperative treatment could be an excellent prognostic marker of the disease, as it happens in the majority of tumors where neoadjuvant treatments are used in a habitual way, as in rectal cancer.

On the other hand, the role of postoperative radiotherapy or chemoradiotherapy treatment versus chemotherapy alone in patients with resection of bile duct tumors has not been clearly defined. In general, preliminary studies offer hopeful results, generally with complementary radiotherapy compilation with single-agent therapies. The same considerations should be made with intraoperative radiotherapy.

4.3. Therapy for locally advanced disease

Locally advanced bile duct cancer is especially difficult to treat. In many cases, conclusions are based on studies that grouped patients with locally advanced adenocarcinoma of the pancreas. Globally, locally advanced bile duct tumors are treated in a similar way. Locally advanced unresectable tumors, especially symptomatic masses, can benefit from palliative EBRT. Usually, the treatment is combined simultaneously with single-agent chemotherapy (5-fluouracil, capecitabine). Treatment is usually continued either after the end of treatment or after the progression of disease with palliative chemotherapy (see next section).

Currently, the optimal sequence of treatment in locally advanced disease is unknown: chemotherapy as a first step (also called "induction chemotherapy") and then radiotherapy with

or without concomitant chemotherapy, or radical radiotherapy, or initial radical chemoradiotherapy. Neither is known the real therapeutic value of surgery after radical radiotherapy treatment, and what is the contribution of maintenance chemotherapy in this setting. All these questions must be answered with studies during the following years.

5. Chemotherapy

5.1. Adjuvant chemotherapy

Chemotherapy administration after resection of bile duct tumors is controversial. The evidence of benefit in intrahepatic tumors is very limited. The most important studies include tumors of the extrahepatic bile duct along with pancreatic cancer and use of single-agent chemotherapy schemes (5'fluouracil plus leucovorin, capecitabine, gemcitabine) with a marginal or no significant benefit.

At the present time, after complete curative surgical resection, clinical options are observed without treatment, chemotherapy (usually with single-agent chemotherapy as fluoropyrimidines or gemcitabine for 4–6 months) or chemoradiotherapy (discussed in detail in the next section). The results of meta-analysis are conflicting, although patients with node-positive and margin-positive tumors seem to benefit from treatment with chemotherapy alone or chemoradiotherapy.

5.2. Hepatic artery-based therapies

The rationale of hepatic artery-based therapies is based on the knowledge of the blood flow in the liver parenchyma, which is made from the hepatic artery rather than the portal vein. Thus, selective catheterization may be performed with the infusion of particles with embolization capacity or with cytotoxic chemotherapy infusions into the branch of the hepatic artery that feeds the tumor mass (TACE—transarterial embolization). This technique has had a broad development in hepatocellular carcinoma (HCC) and is an option to be considered in intrahepatic cholangiocarcinomas, although with less evidence. The administration of radioisotopes is also well defined in HCC. At present, there are no comparative studies among all the different procedures and techniques.

5.3. Chemotherapy in advanced disease

Systemic chemotherapy provides a modest benefit in the treatment of advanced biliary tract carcinomas. At present, cancer of the bile duct is considered an incurable and progressive disease with few cases whose median survival is greater than 1 year. There is a wide variety of chemotherapy treatments for advanced disease. The different combinations try to adapt to a great variety of factors such as different locations, presence or absence of previous treatments, performance status condition of the patient, and the remaining liver function.

Most of the drugs used in this setting are commonly used in other tumors of the upper gastrointestinal tract and have some activity on these tumors: gemcitabine, fluoropyrimidines (i.e., combinations of 5'fluouracil and leucovorin, capecitabine), platinums (usually oxaliplatin),

irinotecan, and anthracyclines. In general, single-agent therapy is usually used for people with poor prognosis or poor performance status, while those of good performance status are usually treated with chemotherapy combinations.

The most commonly used treatment is the combination of gemcitabine plus cisplatin. The treatment has shown a superior overall survival [32] in comparison to treatment with single-agent gemcitabine (11.7 versus 8.1 months) with an acceptable toxicity profile. However, the treatment is not compared with other combinations, also active. Randomized trials will be necessary to determine if this is the standard regime.

Second-line treatment lacks robust evidence. In routine clinical practice, progression to gemcitabine-based treatment is usually treated with fluoropyrimidine-based chemotherapy (oxaliplatin plus leucovorin/5-fluouracil, the FOLFOX regimen).

Initially, any patient with locally advanced incurable bile duct tumors or disseminated tumors should be considered for entry into a clinical trial. Within the standard choice, this has to be a priority, due to the poor prognosis and the lack of curative treatments in this setting. The possibility of genomic sequencing is a fact, and many of the major oncological treatment centers in the world are initially offering the possibility of such studies within the usual clinical practice. Unfortunately, at the present time, there are no specific treatments available for any molecular target in the bile duct in routine clinical practice; in addition, some targets have been tested in other biologically similar tumors but not in biliary tumors. However, not all the entire theoretical therapeutic targets have associated a new molecule or drug in development. Despite all these, the need for researchers, physicians, and patients to initiate innovative studies to improve the prognosis of these tumors is mandatory.

6. Targeted therapy

6.1. Molecular basis

Bile duct carcinoma is one of the most interesting gastrointestinal tumors in terms of genomic alterations, as it has been shown in different publications since 2013. However, results of targeted therapy for these alterations have been quite disappointing. Compared to other gastrointestinal malignancies such as gastric or colorectal carcinoma, no targeted drug has yet been approved in cholangiocarcinoma. Despite these poor results, some promising drugs are now being evaluated targeting different aberrations observed when whole exome sequencing is performed. It is remarkable that bile duct carcinoma should not be considered as a unique disease. Intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder carcinoma have a different molecular landscape, and this could explain the low rate of success of targeted therapy in these carcinomas.

One of the most relevant analyses in this field [33] based on a whole exome sequencing of 260 tumors from the biliary tract surprisingly revealed that almost 40% of cases harbored targetable genetic alterations comprising a total of 32 genes. Moreover, these genetic alterations differ among the different locations, as summarized in **Table 1**. A total of 137 intrahepatic

Tumor subtype	Alteration	Targetable
Intrahepatic cholangiocarcinoma	FGFR2 fusion	Yes
	IDH1/2 mutation	Yes
	EPHA2	No
	BAP1 mutation	No
Gallbladder carcinoma	EFGR mutation	Yes
	ERBB2 mutation	Yes
	PTEN mutation	Yes
	ARID 1 mutation	No
	MLL2/MLL3 mutation	No
	TERT promoter mutation	No
Extrahepatic cholangiocarcinoma	PRKACA/B fusion	Yes
	ELF3 mutation	No
	ARID1B mutation	No
Biliary duct common carcinoma	TP53 mutation	No
	BRCA mutation	Yes
	PI3KCA mutation	Yes

Table 1. Targeted therapies in biliary tract tumors.

cholangiocarcinomas, 74 extrahepatic cholangiocarcinomas, and 28 gallbladder tumors were analyzed. Main alterations can be classified under five different modules: MAPK pathway (RAS, BRAF, EGFR, ERBB2, FGFR, and PTEN), TFG-β pathway (TGF-B, SMAD4, and ARID), TP53 pathway (TP53, ATM, and MDM2), cell cycle regulation (CDKN2A/B, RB1), and epigenetics (IDH1, IDH2, and BAP1, among others) (**Table 1**).

A worldwide consortium analyzing the genome of different tumors (the Cancer Genome Atlas) has recently revealed a comprehensive study of intrahepatic cholangiocarcinoma based on somatic mutations, RNA expression, copy number, and DNA methylation [34]. Similarly, inactivating mutations have been found in tumor-suppressor genes, such as ARID1A, ARID1B, BAP1, TP53, and PTEN, and gain-of-function mutations have been found in the oncogenes, such as IDH1, IDH2, BRAF, and KRAS. Moreover, alterations in the regulation of the cell cycle have been reported: recurrent focal losses of CDKN2A, encoding p16INK4A, which inhibit the cyclin-dependent kinases CDK4 and CDK6, have been observed in 47% of the tumors.

6.2. Developing targeted therapies

Drugs targeting MAPK, FGFR, and IDH pathways have been developed widely in biliary duct carcinoma. One of the most prevalent alterations in cholangiocarcinoma is mutations in the proteins involved in RAF-MEK-ERK pathway. Targeting epithelial growth factor receptor

(EGFR) as the first member of the MAPK pathway has not been successful. A phase III trial comparing platinum-based chemotherapy and gemcitabine with and without erlotinib did not show an improvement in progression-free survival [35]. Similar results were obtained with sorafenib (a multikinase inhibitor of RAF and VEGFR family) [36]. MET, a regulator of this pathway, can be inhibited by different drugs, such as tivantinib or cabozantinib. Despite preliminary efficacy of tivantinib combined with gemcitabine, cabozantinib (targeting MET and VEGFR2) showed limited activity [37–39].

KRAS mutation is observed in up to 25% of cholangiocarcinomas, and it has been associated to a worse prognosis in terms of progression-free survival and overall survival [40]. Targeting KRAS has been a challenge in oncology, and currently, there is not any available drug against it. However, it is possible to target downstream proteins, such as MEK. Selumetinib, an allosteric MEK inhibitor, was tested in advanced biliary cancer with good results as single therapy in refractory setting (progression-free survival around 3 months and overall survival of 9.7 months). This drug was also combined with standard first-line chemotherapy (cisplatin-gemcitabine), but results were quite modest. Nevertheless, there was no selection according to KRAS mutation [41]. BRAF mutations are less prevalent, but results with therapies targeting this protein have shown better results.

For instance, in the vemurafenib basket trial (BRAF inhibitor in BRAF V600E mutant tumors), there was a partial response of eight patients treated with this drug [42]. However, there was up to 62% rate of disease control. Combinations of BRAF inhibitor and MEK inhibitor such as dabrafenib and trametinib are now being evaluated in clinical trials (NTC02034110).

Fibroblast growth factor receptor (FGFR) has been suggested as a potential target in cholangiocarcinoma, especially in intrahepatic cholangiocarcinoma with 20% of them showing any alteration. Most frequent alterations are fusions and mutations in FGFR2 and FGFR3. Some selective and nonselective small-molecule inhibitors of this receptor have been investigated in early phase clinical trials. Preliminary activity of oral pan-FGFR inhibitor BGJ398 has shown a disease-control rate of 82% in advanced cholangiocarcinoma in a phase II study, which is still recruiting (NCT02150967) [43]. Similarly, erdafitinib showed a 91% disease-control rate in this setting [44], and a phase II is ongoing to confirm these results. Derazantinib is another multikinase potent inhibitor, with a potent pan-FGFR inhibition. In the phase I trial [45], a 20% response rate was observed in FGFR-2 fusion-positive cholangiocarcinoma. Stable disease was observed in another 48% of the patients [45, 46]. TAS-120, Debio1347, and ponatinib are also drugs targeting FGFR in early phase I trials.

Other alterations in cholangiocarcinoma are ROS1 fusions with some interesting results with ALK/ROS inhibitors, such as ceritinib. Similarly, entrectinib (targeting not only ALK/ROS but also NTKR) has shown encouraging responses.

As previously described, alterations in IDH1, IDH2, BAP1, and ARID1A are frequently observed in cholangiocarcinoma. These genes are considered epigenetic regulators, as they are responsible for remodulating chromatin and histone regulation. Therefore, drugs targeting epigenetic alterations could be a strategy in biliary tract carcinoma. The most frequent mutated gene is IDH1, a gene that encodes isocitrate dehydrogenase, responsible among

others, for the Krebs cycle or mitigating the oxidative stress. One of the most promising therapies is AG-120, a selective inhibitor of mutant IDH1. A 60% rate of disease control has been observed in a phase I trial. A phase III trial is now recruiting to confirm these results (NCT 02989857). Enasidenib is another IDH inhibitor, specific for IDH2 mutant tumors, which is currently being evaluated in another trial (NCT02273739). Other drugs that have been tested but without definitive results are histone deacetylase and DNA methyltransferase inhibitors.

7. Immunotherapy and cholangiocarcinomas

Treatment based on altering the immune response of the patient generating an intrinsic antitumor effect is supposed to have a new change of paradigm in the field of medical oncology. Several tumors have seen their therapeutic arsenal expanded and have benefited from incredible responses with a favorable toxic profile. It is a field in full scientific development, and poor prognosis tumors such as melanoma or nonsmall cell lung have been benefited.

Biliary tract tumors are infrequent tumors with low prevalence in Western Countries, which delay and complicate their recruitment in clinical studies. However, there are several clinical and biological characteristics of these tumors that make them attractive to the use of immunotherapy. These are tumors especially linked to chronic infection and inflammation processes, similar to other tumors with good immune responses (i.e., HCC or head and neck carcinoma). These are tumors with a high rate of presentation of neoantigens associated with viral infection.

At least one subgroup of patients with cholangiocarcinoma has a high mutational load with abundant neoantigens and a high expression of immune-related genes, including inhibitory-encoded genes. These are tumors with a poorer prognosis but with a good theoretical response profile to immunotherapy. New studies underway will delimit the role of these therapies in biliary tumors in the next few years. On the other hand, new therapies based on immune response are not exempt from possible high-risk secondary effects for these patients; cholangiocarcinomas often present a high risk of inflammatory life-threating complications (biliary stent, biliary superinfection).

8. Liquid biopsy: new steps toward better monitoring

Liquid biopsy (LqB) presents the possibility of detecting circulating tumor cells (CTCs) or small fragments of tumor DNA (cell-free DNA or cfDNA) in the circulatory system of patients, analyzing both primary tumors and metastases. This new technology has obvious advantages: it allows a global analysis of genetic changes in the global tumor mass, independently of the location of foci with independent genomic progression or novel mutations in isolated regions of the tumor tissue. LqB allows to study the tumor heterogeneity and to evaluate a dynamic tumor analysis over time, including the assessment of cancer-resistant subclone appearance,

and its results potentially predict the molecular dynamics associated with tumor response and drug resistance. Liquid biopsy monitoring of patients with cancer is a technically available procedure. However, our current knowledge should be expanded before it can be routinely implemented in daily clinical use.

Improvements have been made in technology, and there have been decreases in the response time and the costs of the procedure. In the near future, cancer research centers and even direct patient care centers will routinely request LqB for cancer patients using kits and genetic panels available. At this time, however, it is necessary to expand the available information about the LqB utility, especially the clinical interpretation of its results and limitations of the technique. Unfortunately, at this time, there are no studies that validate its usefulness in bile duct tumors.

9. Conclusions: multimodality approach

At present, we are witnessing some exciting changes in the clinical management of tumors of the biliary tract. Primarily, the development of new radiological techniques allows an earlier and more accurate diagnosis of these diseases; they also provide many anatomic and functional relevant information with a prognostic value. A critical advancement in nearly all of extrahepatic bile duct tumor management is the improvement in interventional radiology techniques, especially biliary stents in locally advanced disease. Their staging has improved a better global approach and more accurate prognostic allocation. The emergence of more accurate radiotherapy treatments can expand the indications of the most novel techniques, such as IMRT, in the near future. Standard chemotherapy regimens, although still with discrete results in advanced disease in terms of survival, allow the comparison with other

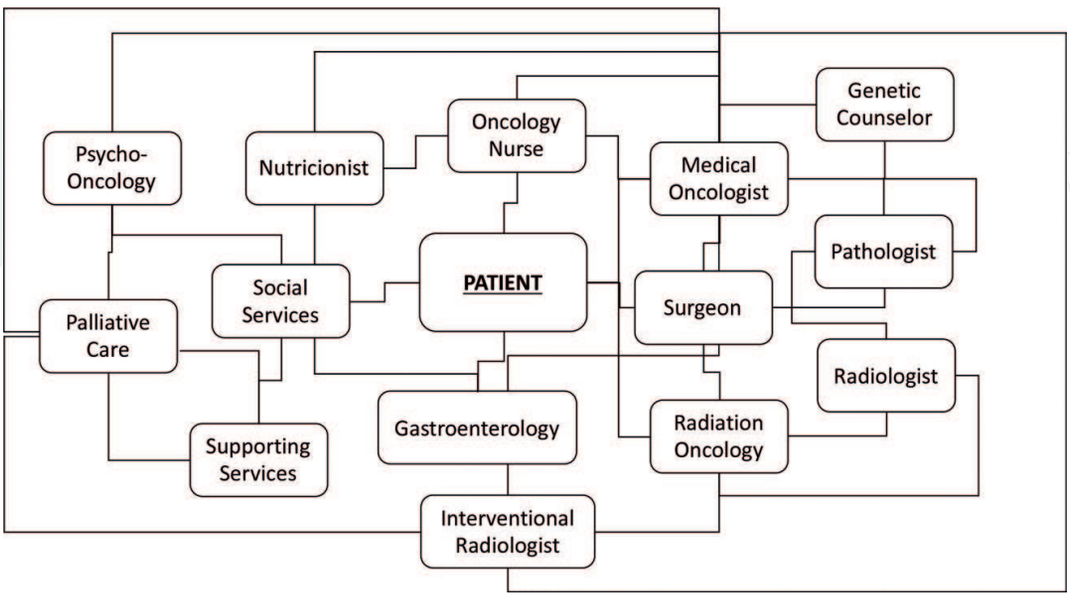

Figure 2. Multimodality approach in patients with biliary tract tumors.

novel treatments. Finally, the advancement in molecular knowledge is critical to understand the pathogenesis and for the development of new treatments directed against therapeutic targets.

However, the most important step yet for advancing the treatment of these complex diseases is the appearance of multidisciplinary management teams focusing on patient treatment in a comprehensive approach. It is critical for the development of new strategies to assess each case from the point of view of multiple specialists in reference centers that can integrate the careful work of qualified specialists. Similarly, the most appropriate treatment should respond to the variable disease evolution of each patient, both in the curative approach and in the advanced disease of worse prognosis.

Finally, it is very important to remember, as shown in **Figure 2**, that the treatment of a tumor as aggressive as cholangiocarcinoma in a patient needs the participation and use of psychological, spiritual, social, family, voluntary, economic, that should be considered in each center of each specific region, resources that exceed the realization of this article. Unfortunately, the current advances have not translated into a change in the natural history of these diseases.

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