# Rare histotypes of epithelial biliary tract tumors: A literature review

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## ABSTRACT

Adenocarcinoma represents the most frequent biliary tract cancer. However, other rare histotypes can be found in the biliary tract, such as cholangiolocellular carcinoma, cholangiocarcinoma with ductal plate malformation pattern, adenosquamous carcinoma, mucinous carcinoma, signet ring cell carcinoma, clear cell carcinoma, mucoepidermoid carcinoma, lymphoepithelioma-like carcinoma, and sarcomatous cholangiocarcinoma. These cancer types account for less than 10 % of all the already rare biliary tract tumors. Yet, they represent a relevant issue in everyday clinical practice, given the lack of therapeutic recommendations and the overall scarcity of data, mainly deriving from isolated small center-specific cohorts of patients. The shifts of such histotypes from the most common ones reflect genetic and molecular differences, determine changes in clinical aggressiveness, and suggest a possible variability in sensitivity to the standard treatments of biliary adenocarcinomas. The consistency and degree of these variables are still to be solidly demonstrated and investigated. Therefore, this paper aims to review the current literature concerning very infrequent and rare epithelial biliary tract cancers, focusing our attention on the clinical, molecular, and immunohistochemical features of these tumors.

## 1. Introduction

Biliary tract cancers (BTCs) represent approximately 3 % of all gastrointestinal tumors and 15 % of primitive liver cancers, including gallbladder cancers (GBC), ampullary tumors, and cholangiocarcinomas (CCA), which are usually divided into intrahepatic CCA (iCCA) and extrahepatic CCA (eCCA) (Banales et al., 2020). The estimated incidence of BTCs is less than 0,6 cases per 100,000 inhabitants per year, and their prognosis is very poor, with a 5–15 % 5-year survival rate, when considering all stages together (Valle et al. 2021; Lamarca et al., 2022). Histologically, 90 % of epithelial BTCs are adenocarcinomas, whereas the remaining 10 % are constituted by rarer forms, such as adenosquamous carcinoma, signet ring cell carcinoma, clear cell carcinoma, lymphoepithelioma-like carcinoma, and sarcomatous cholangiocarcinoma, as classified by the latest 5th edition of the WHO Blue Book (WHO Classification of Tumours Editorial Board, 2019) (Table 1). Despite the common anatomic origin, these histotypes differ in incidence, prognosis, and survival. However, due to the low incidence of these subtypes, their main clinical features are reported only in the case of reports or in retrospective observational analyses. In this paper, we review the current literature, focusing on these infrequent and rare tumors' clinical, molecular and immunohistochemical features. We will

**Table 1**
Classification of rare biliary tract tumors.

| | |
|---|---|
| **iCCA subtypes** | adenosquamous carcinoma |
| | mucinous carcinoma |
| | signet ring cell carcinoma |
| | clear cell carcinoma |
| | mucoepidermoid carcinoma |
| | lymphoepithelioma-like carcinoma |
| | sarcomatous cholangiocarcinoma |
| | cholangiolocellular carcinoma |
| | iCCA with ductal plate malformation pattern |
| **eCCA subtypes** | adenosquamous carcinoma |
| | squamous cell cacinoma |
| | undifferentiated carcinoma |
| **GallBladder subtypes** | adenocarcinoma biliary type |
| | adenocarcinoma intestinal type |
| | clear cell carcinoma |
| | mucinous carcinoma |
| | signet ring cell carcinoma |
| | adenosquamous carcinoma |
| | intracholecystic papillary neoplasia associated with invasive carcinoma |
| | mucinous cystic neoplasm associated with invasive carcinoma |
| | squamous cell cacinoma |
| | undifferentiated carcinoma |

Abbreviations - eCCA: extracellular CholangioCArcinoma; iCCA: intracellular CholangioCArcinoma.

consider rare histotypes according to the WHO classification and all those histotypes of epithelial BTCs that have an incidence of less than 5 % of all BTCs or that fall within the definition of rare disease, with a prevalence lower than 5 per 10,000 inhabitants.

## 2. Adenosquamous carcinoma

### 2.1. Epidemiology

Adenosquamous carcinoma (ASC) is the most frequent among the rare subtypes of BTCs, and is characterized by variable proportions of two malignant components: adenocarcinoma (AC) and squamous cell carcinoma (SCC) (Fig. 1). So far, about one hundred cases of this histotype have been described in the literature (Gou et al., 2021), showing a variable incidence according to the site of onset, ranging from 2 % to 3
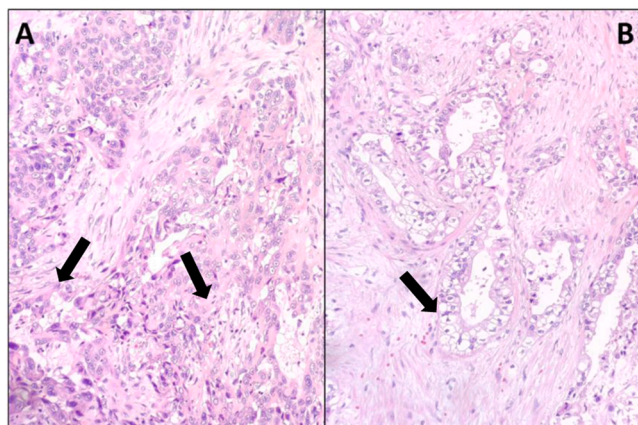


**Fig. 1.** Highly illustrative representation of two of the most important rare variants of cholangiocarcinoma (Hematoxylin-eosin, 10x magnification). A) Adenosquamous variant: the mixture of glandular and squamoid structures is evident (arrow on the left indicated the glandular aspect, while the arrow on the right indicates the squamous component); B) Clear cell variant: the most distinctive feature of this tumor subtype is the presence of neoplastic cells showing a large and pale cytoplasm (so-called "clear", indicated by black arrow).

% of all iCCAs (Kobayashi et al., 2005) to 2 % of all eCCAs and 4–8.9 % of all GCs (Hoshimoto et al., 2017).

### 2.2. Pathogenesis

There are two different theories about the pathogenesis of ASC, according to which ASC may result from the malignant transformation of squamous metaplasia, either evolving from a preexisting adenocarcinoma or appearing as a de novo phenomenon induced by chronic inflammation (Kim et al., 2009). In one case report, Galuppini and colleagues identified the positivity to the E542K point-mutation of the PI3KCA gene both in the squamous and in the adenomatous areas of one ASC-GB, thus suggesting the monoclonal origin of both the components (Galuppini et al., 2017).

### 2.3. Histological features

At least 25 % of squamous cells are necessary to diagnose ASC of the gallbladder (5thWHO classification), while a minimum cut-off value for the squamous component has not been established in intrahepatic and extrahepatic ASCs (Hong et al., 2008). Hoshimoto et al. analyzed 9 cases of biliary ASCs, reporting that the squamous component varied from 30 % to 90 %.

Interestingly, the squamous component presented the highest ki-67 positivity and showed more frequent perineural and lymphatic invasion, suggesting a more aggressive behavior for the squamous rather than the adenomatous component (Hoshimoto et al., 2017).

### 2.4. Biological behavior and clinical outcomes

These biological characteristics are consistent with the clinical features reported in a retrospective study by Hong and colleagues, based on 12 cases of ASC of the biliary tract, reporting that the median overall survival (mOS) was higher in patients affected by AC than in patients affected by ASC (Hong et al., 2008). Furthermore, in patients affected by ASC, mOS was related to the histological component preponderant on the margin of growth of the tumor. Patients with squamous cell carcinoma component at the advancing edge of growth had worse mOS when compared to those with AC component (6 months vs. 29 months, respectively) (Hong et al., 2008). Another retrospective analysis was conducted on cases registered in the Surveillance, Epidemiology and End Results (SEER) database: among the 106 collected cases, the survival rates were 30.1 %, 11.3 %, and 3.7 % at 1, 2, and 5 years from diagnosis, respectively (Qin et al., 2018). Therefore, OS rates were shorter than the OS rates of AC, but longer than the ones of SCC. The main impact on survival in ASC of the bile duct is provided by surgery, which is responsible for a 10-month increase in mOS, whereas radiotherapy alone or combined with chemotherapy does not affect survival (Qin et al., 2018). Tumor size, growth patterns, pancreatic or duodenal invasion, vascular invasion, lymph node metastases, and positive surgical margins are prognostic for worse OS (Hong et al. 2008). In the same analysis, no statistically significant correlations were found between gender, hepatic and perineural invasion, tumor site, and survival (Hong et al., 2008). Moreover, mOS of patients affected by intrahepatic ASC was 6 months, as compared to 20 months for patients with extrahepatic ASC (Hong et al., 2008; Gou et al., 2021).

Hong et al. have recently published a case report of a woman with biliary ASC with multiple lymph node metastases characterized by HER-2 amplification. This patient received chemotherapy with Gemcitabine, Cisplatin, and Trastuzumab, showing a progression-free survival (PFS) of 5 months. After progression, the patient was treated with a second-line therapy with Nab-paclitaxel, S-1 (TS-1; tegafur, gimeracil, oteracil potassium) and Trastuzumabobtaining stability of disease as the best response and presenting a PFS at the second line of treatment equal to 7 months at the time of publication of the case report (Hong et al., 2021).

## 2.5. Adenosquamous carcinoma of gallbladder

In a retrospective study, Murimwa et al. analyzed 13,158 cases of gallbladder cancers quantifying ASC of the gallbladder (ASC-GB) as 5 % of all gallbladder cancers. When compared to the more common adenocarcinoma of the gallbladder (AC-GB), patients with ASC-GB diagnosis showed a larger tumor size at the time of diagnosis, a poorer differentiation grade, and more frequent lymphovascular invasion. In patients affected by ASC-GB and AC-GB, mOS resulted in 10.3 and 20.5 months, respectively, with a statistically significant difference. The multivariate analysis showed that age, ethnicity, adenosquamous histology, differentiation grade, and lymphovascular invasion were independent prognostic factors for OS (Murimwa et al., 2021). ASCs of the ampulla of Vater have also been described in the literature, confirming its more aggressive behavior, with a worse prognosis than ampullary adenocarcinomas mainly due to the increased frequency of lymphovascular invasion and distant metastases (Maji et al., 2021).

## 3. Sarcomatous cholangiocarcinoma

### 3.1. Epidemiology

Sarcomatous variants of carcinomas have been described in many cancer types, including the liver, even more frequently in hepatocellular carcinoma than in biliary tract carcinoma (Chen et al., 2022). Sarcomatous cholangiocarcinoma (SICC) represents about 4.5 % of intrahepatic cholangiocarcinomas (Zhang et al., 2018b) and is more common in Asian Countries (Boonsinsukh et al., 2018). The median age at onset is 61.5 years (range from 37 to 87 years) (Wang et al., 2020).

### 3.2. Pathogenesis

Like iCCA, it usually occurs in the left lobe of the liver (Wang et al., 2020). No relationships were identified with viral hepatitis infection (HBV and HCV) or cirrhosis (Boonsinsukh et al., 2018), and the pathogenesis remains unclear, possibly due to either the biphasic differentiation from the same pluripotent cancer stem cells or the redifferentiation of an immature multipotent carcinoma cell clone.

### 3.3. Histological features

Morphologically, this histotype has both adenocarcinoma and sarcomatous components (Zhang et al., 2018b), presenting spindle-shaped and pleomorphic cells with adenoid structures (Wang et al., 2020). In particular, the sarcomatous area is constituted by spindle cells arranged in sheets or bundles, with an oval or elongated hyperchromatic nucleus and occasional mitotic figures. The proportion of carcinomatous and sarcomatous areas in the same tumor varies from case to case (Nakajima et al., 1993). The production of mucin is rare as a confirmation that this tumor behaves similarly to a poorly differentiated cholangiocarcinoma (Lim et al., 2004). The diagnosis is established by histopathological and immunohistochemical examinations (Zhang et al., 2018b). Watanabe et al. reported the following diagnostic criteria of SICC:

1) the coexistence of both adenocarcinoma and sarcomatous components and 2) the expression of molecular features of both mesenchyme (e.g., vimentin) and epithelium (e.g., cytokeratins) in the sarcomatous component (Watanabe et al., 2014). At differential diagnosis, SICC has the peculiarity of epithelial and mesenchymal features expressed in the sarcomatous component differently from carcinosarcoma, which has only mesenchymal features, and from cholangiocarcinoma with sarcomatoid transformation, which has only epithelial features expressed in the sarcomatous component (Sintra et al., 2018; Watanabe et al., 2014). One case report of SICC described a case with osteoclast-like giant cells in addition to spindle cells, but this has to be considered a rarer variant (Kim et al., 2015).

The sarcomatous cells show positivity for keratin and epithelial membrane antigen (EMA), and focal expression of Vimentin. Apart from sporadic cases, actin, desmin, S-100 protein, and Neuron-specific enolase (NSE) are negative in the sarcomatous component (Nakajima et al., 1993). These data are consistent with the sarcomatous transformation of epithelial cells that still retain some features of the original phenotype(Jung et al., 2012). Like normal bile duct epithelial cells, the adenocarcinoma component of SICC shows immunoreactivity for β-catenin and E-cadherin, which is absent in the round cells. In addition, the sarcomatoid cells can show a distinct membranous expression of CD44 standard isoform (CD44s), which is responsible for the interactions of cancer cells with other cells or the extracellular matrix. This immunoreactivity seems more intense than in the adenocarcinoma cells, suggesting that the overexpression of CD44s may be involved in vascular invasion (Sato et al., 2006). In a case report, the expression of p53 was evaluated, and a different expression was found between the adenocarcinoma and the round-cell components, but no mutation was detected in p53 gene in any of them (Sato et al., 2006). Two isolated case reports described 2 single cases of granulocyte colony-stimulating factor (G-CSF) producing SICC (Takenaka et al., 2013; Kuwano et al., 2021).

This histotype generally shows an insufficient neoangiogenic network; hence the usually poorly-differentiated, rapidly-growing sarcomatous cells lack adequate metabolic supply resulting in wide necrotic areas (Gu et al., 2017). For this reason, sarcomatous cholangiocarcinoma is radiologically a low-density lesion with a necrotic area in the inner part and a peripheral contrast enhancement at the arterial phase. This radiological behavior makes it difficult to distinguish SICC from an atypical liver abscess (Wang et al., 2020). Furthermore, clinicaland radiological features are not sufficient to distinguish SICC from ordinary iCCA.

### 3.4. Biological behavior and clinical outcomes

This type of BTC has a poor prognosis (Table 2), with a mOS of 3 months from diagnosis, as a consequence of its aggressive hepatic spreading and high tendency to metastasize. In addition, the survival rate of patients who underwent radical surgery with R0 resection is significantly higher than those without surgery (Wang et al., 2020). According to available data, survival rates of SICC treated with surgery alone are the same of untreated ordinary CCA (Watanabe et al., 2014). Yet, the best therapeutic option of this tumor is still radical resection (Boonsinsukh et al., 2018). The survival rates of patients with surgical resection were significantly higher than in patients without surgical resection. Kaibori et al. showed that the prognosis for patient with sarcomatous cholangiocarcinoma treated with hepatectomy was better than that without hepatectomy (Kaibori et al., 2003). Transarterial chemoembolization does not improve the survival rate in sarcomatous cholangiocarcinoma (Boonsinsukh et al., 2018). Median survival time of surgical patients affected by sarcomatous cholangiocarcinoma was 11 months, which was similar to that of patients with ordinary cholangiocarcinoma without surgery (Watanabe et al., 2014).

We know that in patients with biliary tract carcinoma undergoing resection with curative intent (R0 or R1) one of the most commonly used adjuvant chemotherapy regimens is capecitabine monotherapy (Primrose et al., 2019). There are not many data on the use of adjuvant chemotherapy in patient with SICC, Watanabe et al. report a case of a patient operated and treated with gemcitabine-based chemotherapy that showed disease progression 10 months after surgery (Watanabe et al., 2014). Jung et al. reported the case of a Korean patient treated with adjuvant chemotherapy based on 5-fluorouracil and cisplatin, who presented with disease progression with the appearance of seeded peritoneal metastases after three months and who received subsequent therapy with cisplatin and gemcitabine with mOS of 8 months (Jung et al., 2012). As known, combined therapy with gemcitabine and cisplatin is a potential treatment option in locally advanced or metastatic biliary tract cancer and sarcoma (Valle et al., 2010; Malhotra et al.,

**Table 2**
Case reports sarcomatoid cholangiocarcinoma.

| References | Sex | Age (Ys) | Size (cm) | Location | CEA (ng/ml) | Ca19.9 (U/L) | Treatment | OS (months) |
|---|---|---|---|---|---|---|---|---|
| (Sasaki et al., 1991) | M | 79 | 8 | Left | Normal | Normal | None | NA |
| (Haratake et al., 1992) | M | 59 | NA | Hilar portion | NA | NA | None | 1 |
| (Nakajima et al., 1993) | F | 84 | 3.5 | Hepatic hilium | NA | NA | None | 3 |
| (Nakajima et al., 1993) | F | 43 | 14 | Right | NA | NA | Surgery | 4.5 |
| (Nakajima et al., 1993) | F | 73 | 7 | Left | NA | NA | Chemotherapy | 5 |
| (Nakajima et al., 1993) | M | 37 | 10 | Left | NA | NA | None | 2.5 |
| (Nakajima et al., 1993) | M | 64 | 7.5 | Left | NA | NA | TAE | 1 |
| (Nakajima et al., 1993) | M | 52 | 7.5 | Right | NA | NA | TAE | 1 |
| (Nakajima et al., 1993) | M | 69 | 10 | Left | NA | NA | Surgery | 36+ |
| (Imazu et al., 1995) | M | 77 | 7 | Left | <0–5 | 17 | Surgery | 11+ |
| (Honda et al., 1996) | F | 61 | NA | Right | 9 | 13,394 | None | 3.8 |
| (Itamoto et al., 1999) | M | 70 | 8 | Right | Normal | 2634 | Surgery | 9+ |
| (Matsuo et al., 1999) | F | 77 | 7.7 | Left | Normal | Normal | Surgery | 5 |
| (Shimada et al., 2000) | M | 70 | 3.4 | NA | 2.4 | 44.7 | Surgery | 6 |
| (Shimada et al., 2000) | M | 55 | 6.7 | NA | 3.2 | 170 | Surgery | 7 |
| (Shimada et al., 2000) | F | 74 | 4 | NA | 2.9 | 21.6 | Surgery | 19 |
| (Shimada et al., 2000) | F | 64 | 8 | NA | 0.5 | 16 | Surgery | 29 |
| (Kaibori et al., 2003) | F | 69 | 22 | Left | Normal | 3665 | Surgery | 3 |
| (Lim et al., 2004) | F | 41 | 17 | Left | Normal | Normal | Surgery | 2+ |
| (Sato et al., 2006) | M | 87 | 4 | Left | 16.2 | 2894 | None | 3 |
| (Malhotra et al., 2010) | F | 60 | 20 | Right | NA | NA | Surgery | 29+ |
| (Bilgin et al., 2012) | M | 48 | 13 | Left | NA | 39 | Surgery | 12+ |
| (Inoue et al., 2012) | M | 61 | 25 | Left | 1.2 | 5 | Surgery | <1 |
| (Watanabe et al., 2014) | M | 62 | 5 | Right | 1.4 | 1109.9 | Surgery | 11 |
| (Kim et al., 2015) | F | 67 | 4.5 | Left | 109.6 | 1598 | Surgery | NA |
| (Gu et al., 2017) | M | 65 | NA | NA | NA | 11.25 | Chemotherapy/ radiotherapy | 2+ |
| (Gu et al., 2017) | M | 70 | NA | NA | NA | 22.44 | Surgery | 2+ |
| (Gu et al., 2017) | F | 48 | NA | NA | NA | 7.28 | Surgery | 18+ |
| (Gu et al., 2017) | M | 45 | NA | NA | NA | 103,844 | Chemotherapy/ radiotherapy | 4+ |
| (Gu et al., 2017) | F | 46 | NA | NA | NA | NAA | Chemotherapy/ radiotherapy | 1+ |
| (Gu et al., 2017) | M | 69 | NA | NA | NA | 25.81 | Surgery | 1+ |
| (Gu et al., 2017) | F | 54 | NA | NA | NA | 11.34 | Surgery | 6+ |
| (Gu et al., 2017) | M | 74 | NA | NA | NA | 6.07 | Surgery | 4+ |
| (Gu et al., 2017) | M | 57 | NA | NA | NA | 2 | Chemotherapy/ radiotherapy | 2+ |
| (Gu et al., 2017) | M | 51 | NA | NA | NA | 11.7 | Surgery | 1+ |
| (Gu et al., 2017) | M | 69 | NA | NA | NA | NA | Chemotherapy/ radiotherapy | 1+ |
| (Gu et al., 2017) | F | 61 | NA | NA | NA | 886.51 | Surgery | 4+ |
| (Gu et al., 2017) | M | 53 | NA | NA | NA | 10.5 | Surgery | 1+ |
| (Zhang et al., 2018b) | M | 63 | 8 | Left | 2.17 | 100.5 | Surgery | 1+ |
| (Kuwano et al., 2021) | M | 87 | 8 | Right | 2.7 | 122.2 | None | <1 |
| (Ono et al., 2019) | F | 75 | 6.5 | Right | 1.1 | 2 | Surgery | 5+ |

Abbreviations - F Female; M Male; NA Not available; TAE Transarterial embolization.

2010). After an early post-operative recurrence a patient received chemotherapy combined with gemcitabine and cisplatin that led to partial remission sustained and increased overall survival at 29 months (Malhotra et al., 2010). Early diagnosis and radical surgery represent the only chance for long-term survival. Nevertheless, molecular genetic studies may improve the treatment strategies.

### 3.5. Poorly cohesive cell carcinoma / Signet ring cell carcinoma

#### 3.5.1. Epidemiology and pathogenesis

Poorly cohesive cell carcinoma / signet ring cell carcinoma (PC/SRCC) constitutes 1.3 % of all cases of BTCs. It is most frequently diagnosticated in women than in men, with a peak between 50 and 60 years of age (Benesch and Mathieson, 2020). There are two possible pathogenetic hypotheses: the development of SRCC either from a preexisting ectopic gastric mucosa or from mucosal ulceration determining gastric epithelial metaplasia as a consequence of elevated intraluminal acidity (Lee et al., 2010).

### 3.6. Histological features

Histologically, this histotype is represented by cells with abundant intracytoplasmic mucin dislocating the nucleus to the periphery. To perform the diagnosis, almost 50 % of signet ring cells should be present. Otherwise, it is named "adenocarcinomas with a signet ring cell component" (Benesch and Mathieson, 2020). Based on immunohistochemical characteristics, there are two types of SRCCs: a) intestinal type (CK7 negative and CK20/MUC2 positive) with better prognosis, and b) pancreatic-biliary type (CK7 positive and CK20/MUC2 negative) with worse prognosis (Kita et al., 2014; Roh et al., 2007).

#### 3.6.1. Biological behavior

Only a few cases are reported in the literature (Table 3). In any case, the patients affected by PC/SRCCs have a 5-year survival rate slightly worse than typical CCA (16.2 % vs. 22.1 %) (Benesch and Mathieson, 2020).

**Table 3**
Case reports of poorly cohesive cell / signet ring cell carcinoma of biliary tract.

| References | Sex | Age (Ys) | Ca19.9 (U/L) | Hystology | Stage | Surgery | Treatment | OS (months) |
|---|---|---|---|---|---|---|---|---|
| (Lee et al., 2010) | M | 55 | 45.9 | SRCC Pure | IIB | PPPD + lymphadenectomy | RT + CT (Gem + Cis) | 24+ |
| (Ogata et al., 2010) | F | 42 | Elevated | SRCC/AC | III | PPPD | NO | 6+ |
| (Kwon et al., 2014) | M | 63 | 3.9 | SRCC Pure | IIA | PPPD | NO | 15 |
| (Kita et al., 2014) | F | 73 | N/A | SRCC/AC | III | PPPD | (Gem + Cis) | 12+ |
| (Hua et al., 2015) | M | 52 | Normal | SRCC/AC | III | PPPD + lymphadenectomy | (Gem + Cis) | 6 |
| (Chedid et al., 2015) | F | 66 | N/A | SRCC | IVA | N/A | NO | 15 |
| (Welsh et al., 2018) | F | 55 | 1196 | SRCC | IV | None | Gem+Cis + palliative RT | 5 |
| (Zhang et al., 2018a) | F | 32 | 768.3 | SRCC/AC | NA | Yes | NA | 5 |

Abbreviations - AC adenocarcinoma; CT Chemotherapy; Cis Cisplatin; F Female; Gem Gemcitabine;; M Male; OS Overall Survival; PPPD pylorus-preserving pancreaticoduodenectomy; RT Radiotherapy; SRCC Signet-Ring Cell Carcinoma.

### 3.7. Cholangiolocellular carcinoma

#### 3.7.1. Epidemiology and pathogenesis

Cholangiolocellular carcinoma (CoCC) represents the 0.6–1 % of all primitive liver cancers (Komuta et al., 2008; Takakusagi et al., 2021). CoCC was firstly reported in 1959 by Steiner and Higginson who described the case of a neoplastic homolog of the smallest cholangioles and the canals of Hering (Steiner and Higginson, 1959), and more recent studies confirmed this hypothesis suggesting that this histotype originates from progenitors in the canals of Hering, endowed with stemness and therefore capable of differentiating to cholangiocytes or hepatocytes (Komuta et al., 2008).

#### 3.7.2. Histological features

Hence,CoCC originates from smaller ducts than those of iCCA and also behaves differently since, unlike iCCA, CoCCmainly occurs with "mass-forming" growth and rarely presents dilation of the biliary tract (Kondo and Fukusato, 2015). CoCC is made by small cuboidal cells with round hyperchromatic nuclei, scanty eosinophilic cytoplasm, and a high nuclear-cytoplasmic ratio, morphologically similar to HPCs. These cells formed tubular or cords glands with a growth pattern named "anter--like", and they are immersed in a fibrous stroma (Komutaet al, 2008). Some Authors used for diagnosis a cut-off of 90 % cholangiolocellular component (Komutaet al, 2008), while others used a cut-off of 50 % (Ariizumi et al., 2014). Immunohistochemistry is positive for CK19, KIT, CD56, and epithelial cell-adhesion molecule (EpCAM). Moreover, this histotype is characterized by a membranous EMA pattern, as opposed to the typical cytoplasmatic pattern of iCCA (Kondo and Fukusato, 2015). A more frequent characteristic the presence of peripheral areas with morphology like hepatocellular carcinoma (HCC). Typical mutations of iCCA, such as isocitrate dehydrogenase(IDH1/2) and fibroblast growth factor receptor 2 (FGFR2) were present in 90 % of cases of CoCC (Balitzer et al., 2019). Moreover, IDH1/2 mutations were found in CoCC with a frequency range from 23.5 % to 34.8 % (Kusano et al., 2020; Chen et al., 2017). These alterations could put the basis for a targeted therapy in this peculiar histotype.

### 3.8. Biological behavior and clinical outcomes

A recent article comparing the radiological characteristics of some primary liver tumors including iCCA and HCC compared to CoCC reported that CoCC could be distinguished from other primitive cancers by the presence of hepatic vein infiltration, intratumoral Glisson's pedicle, and tumor-staining pattern on angiography-assisted tomography. Moreover, when the PET was performed, CoCC was associated with a significantly lower SUV-max than that of iCCA (Takamura et al., 2020).

Ariizumi et al. retrospectively investigated 275 patients with iCCA who underwent curative partial hepatectomy between 1990 and 2011, 29 were CoCC. In the ICC group, the survival rate and mOS for 102 patients with ICC who underwent curative surgery were 33 % at 5 years and 19 months, respectively, with a 5-year survival rate significantly higher in the CoCC group than in the ICC group (75 % and 33 %, respectively;p = 0.0005). Also the 5-year recurrence-free survival rate was significantly higher in the CoC group than in the ICC group (41 % vs. 26 %, respectively, p = 0.0408) (Ariizumi et al., 2014). The independent risk factors affecting the survival were tumor size (cut-off of 40 mm), vascular invasion (e.g., portal vein and hepatic vein) and intrahepatic metastasis (Ariizumi et al., 2014; Hozaka et al., 2021). Regarding metastatic/advanced disease, few information is reported on systemic treatments. Gemcitabine and S-1, either combined (Tomioku et al., 2016) or alone (Yamaguchi et al., 2016) were the most reported drugs. Hozaka et al. reported a case of unresectable CoCC treated with 10 months neoadjuvant chemotherapy with gemcitabine plus cisplatin with a reduction of 42 % size of the primary tumor and subsequent extended left hepatectomy. After surgery, the patient received adjuvant chemotherapy with S-1, and radiological imaging showed no signs of tumor recurrence at 14 months from surgery (Hozaka et al., 2021).

### 3.9. Intrahepatic cholangiocarcinoma with ductal plate malformation pattern

#### 3.9.1. Epidemiology and pathogenesis

Intrahepatic cholangiocarcinoma with ductal plate malformation (DMP) pattern is a rare form of iCCA of the small ducts with 2.9 % of incidence among all iCCAs (Chung et al.,2021). The incidence is slightly higher in men than in women.The ductal plate is the embryological structure from which biliary ducts originate. The persistence of this structure in the adult age is observable in cases of Caroli disease, fibropolycystic disease, and congenital hepatic fibrosis (Nakanuma et al., 2012). Although the oncogenic mechanisms are unclear, the genetic and molecular alterations are similar between iCCA associated with DPM pattern and congenital diseases associated with DPM, such as the activation of the MEK5-ERK5 cascade and alterations involving hepatocyte nuclear factor-6 and cystin (Nakanuma et al., 2012).

#### 3.9.2. Histological features

This tumor appears like a greyish-white solid mass-forming nodule with irregular margins and nocapsule. It is formed by neoplastic glands characterized by irregular dilated lumen and microcystic dilatation. These glands are lined by a single layer of cuboidal or columnar malignant cells with small and hyperchromatic nuclei and scanty cytoplasm. Cellular bridges and bile plugs are often observed inside the lumen. Immunohistochemical staining are usually positive forEMA, EpCAM and Neural cell adhesion molecule (NCAM) on the luminal and basolateral surface, respectively. The nuclei of these cells have low expression of p53. Furthermore, this histotype has a moderate proliferative activity with a ki67 between 1.3 % and 9.8 % (Nakanuma et al., 2012).

### 3.9.3. Biological behavior and clinical outcomes

Whit hepatocyte-specific magnetic resonance imaging, the iCCA with DPM pattern has radiological features suggesting malignancy in general (e.g. restricted diffusion, T2 hyperintensity,transitional phase hypo-intensity and hepatobiliary phase hypointensity) (Chung et al., 2021).

The clinical behavior of iCCA with DMP pattern is unclear. In a recent retrospective study, the authors analyzed genetic, clinicopathological, and radiological features of 5 cases of iCCA with DPM pattern. Each case had an average of 15 somatic mutations, with a total of 64 mutated genes (Chung et al., 2021). The most frequent genetic alterations were FGFR2, PTPRT, ARID1A and CDKN2A. In particular, missense mutations in FGFR2 were identified in three cases. p.F276C was the most frequently identified FGFR2 variant. Furthermore, fusions of FGFR2 with TNC were detected in one patient (Chung et al., 2021). In addition, they evaluated the tumor-specific inflammatory response and identified tumor-infiltrating T-cells and macrophages. At the same time, programmed death-ligand 1 (PD-L1) was not expressed on the tumor and immune cells to indicate that tumor-infiltrating T-cells were immunologically active. According to the 5th edition of the WHO classification, there are two molecular subtypes of iCCA: the proliferation subclass associated with mutation in KRAS, BRAF and other oncogenic signaling pathways, and the inflammation subclass with overexpression of cytokines and better prognosis (5th WHO classification). All five cases analyzed by Chung et al. presented c-reactive protein positivity in tumor cells. This condition and the genetic characteristic of this tumor would allow classifying iCCA with DMP pattern as an inflammatory subtype of iCCA. This consideration may explain the good prognosis of these five patients, who were free from recurrence and from progression during the follow-up period (22–122 months) (Chung et al., 2021).

## 4. Clear cell carcinoma

### 4.1. Epidemiology and pathogenesis

The Clear cell carcinoma (CCC) is an extremely rare variant of BTCs. Tyson named this histotypes "Hypernephroma" in 1926 due to similarity with renal clear cell carcinoma. Since 1992 it is considered a subtype of BTCs (Gu et al., 2010). To our knowledge, the CCC represents 1 % of all gallbladder tumors (Yamamoto et al., 2020).

### 4.1.1. Histological features

Glandular and trabecular growth patterns with abundant highly vascularized desmoplastic stroma are the microscopic characteristics (Fig. 1, B). For the diagnosis, more than 80 % of clear cells should be present. Most of cancer cells present express membranousNCAM or CD56, which are rarely expressed on CCA cells (Haas et al., 2007). Furthermore, pathologists usually use the absence of CD10 to distinguish CCC from a metastatic lesion of clear cell renal carcinoma. The absence of thyroid transcription factor 1 expression disclaims metastatic clear cell carcinomas of the thyroid or lung (Haas et al., 2007).

### 4.1.2. Biological behavior and clinical outcomes

This histotype has a less aggressive behavior and therefore, it is characterized by a better prognosis than the more common histotypes of CCA (Haas et al., 2007; Fernandes et al., 2017; Yamamoto et al., 2020). Nevertheless, some authors attribute this difference exclusively to the different expression of p53 and the lower mitotic index (Gu et al., 2010). So far, given its favorable biological behavior, surgery represents the best therapeutic approach to improve survival or to palliative symptomatic purposes. There are only a few case reports in the literature on adjuvant therapy: with Gemcitabine, which showing a relapse-free survival of two years (Fernandes et al., 2017) or with S-1, with a relapse-free survival of 7 months in a Japanese patient (Toriyama et al., 2010).

### 4.2. Mucinous cholangiocarcinoma

### 4.2.1. Epidemiology and pathogenesis

Mucinous cholangiocarcinoma (mCCA) is a rare variant of CCA. It represents 0.5 % of intrahepatic cholangiocarcinoma (Laohawetwanit and Klaikaew, 2020). This rare BTC is more common in males, with a median age of 59.3 years at diagnosis (range 40 years-82 years). The pathogenesis is unknown, but some papers report a possible association with a history of the chronic bilio-hepatic disease, like choledocholithiasis and primary sclerosing cholangitis (Laohawetwanit and Klaikaew, 2020; Sasaki et al., 1995). So far, only one case was described of a patient with a genetically determined syndrome, as the case of a patient with mucinous cholangiocarcinoma associated with Muir-Torre syndrome (Vernez et al., 2007).

### 4.2.2. Histological features

MCCA is characterized by a plentiful extracellular mucin pool representing at least 50 % of total tumor volume (Laohawetwanit and Klaikaew, 2020) with a gelatinous cut surface. Similar to large duct-iCCA, it arises from intraductal papillary neoplasms of the bile duct or mucinous cystic neoplasms, yet it mainly does not arise on precancerous lesions (Laohawetwanit and Klaikaew, 2020). Mucinous cholangiocarcinoma is usually infiltrating (Motoo et al., 1993), as favored by the frequent absence of peritumoral fibrous capsule and the intrinsic aggressiveness of tumor cells themselves, showing direct invasion of the adjacent hepatic parenchyma (Sumiyoshi et al., 2017). Differential diagnosis with other hepatic mucin-producing tumors with a good prognosis (i.e. biliary papillomatosis and biliary cystadenocarcinoma) is mandatory (Sasaki et al., 1995).

Like conventional cholangiocarcinoma, especially iCCA, the mucinous neoplastic cells exhibit immunoreactivity for CK7 but not CK20 and CDX2. In addition, other stainings can be positive for MUC1, MUC2, MUC5AC and MUC6 (Laohawetwanit and Klaikaew, 2020). Unlike other gastrointestinal mucinous carcinomas, mucinous cholangiocarcinoma is usually microsatellite stable (Laohawetwanit and Klaikaew, 2020).

### 4.2.3. Biological behavior and clinical outcomes

The proportion of the mucinous component in the tumor mass influences the overall radiological appearance of mCCA: CTscans show low-density masses with peripheral enhancement ranging from small mostly solid nodules with high cellularity and little intercellular component to large cystic lesions with wide hypodense areas (Sumiyoshi et al., 2017).

The prognosis is poor because of the difficulty of early detection of this tumor type (Sumiyoshi et al., 2017). In fact, 1 year mortality rate is approximately 50 % (Laohawetwanit and Klaikaew, 2020).

In the literature, we found 21 cases of mucinous cholangiocarcinoma; the OS was variable from less than 1 month to 134 months(Table 4).

### 4.3. Lymphoepithelioma-like carcinoma

### 4.3.1. Epidemiology and pathogenesis

Lymphoepithelioma-like carcinoma (LECL) is a rare BTC formed by epithelial tumor cells immersed in adense lymphoid infiltrate. It was firstly described in the biliary tract in 1996 (Hsu et al., 1996), and is more frequent in the Asian population and in women. It was recently demonstrated a strong association with viral infections, mainly Epstein-Barr virus (EBV) infection (Khandakar et al., 2022), even if some reports associate LECL with hepatitis B virus or hepatitis C virus infections.

### 4.3.2. Histological features

In this histotype, cancer cells are poorly differentiated, with cords formed by glands and dense a lymphoid infiltrate. In comparison with

**Table 4**
Case reports of mucinous cholangiocarcinoma.

| References | Sex | Age (Ys) | Size (cm) | Location | Treatment | OS (months) |
|---|---|---|---|---|---|---|
| (Motoo et al., 1993) | M | 65 | 4 | Right | Surgery | 4 |
| (Sasaki et al., 1995) | F | 49 | 3.5 | Right | Chemotherapy (Cisplatin) | 5 |
| (Sonobe et al., 1995) | M | 78 | NA | Right | None | 3 |
| (Chow et al., 1997) | M | 41 | NA | Right | None | NA |
| (Nishiyama et al., 1997) | F | 73 | 12.4 | Left | Surgery | 15+ |
| (Gotoh et al., 1999) | F | 33 | 7.5 | Left | Surgery | 12+ |
| (Mizukami et al.,1999) | M | 74 | NA | Both | None | <1 |
| (Bu-Ghanim et al., 2004) | F | 50 | NA | Right | Liver trasplantation | NA |
| (Matsuda et al., 2005) | M | 69 | 7 | Left | Surgery | 7 |
| (Zen et al., 2006) | M | 66 | NA | Left | Surgery | 134+ |
| (Zen et al., 2006) | F | 52 | NA | Left | Surgery | 28+ |
| (Vernez et al., 2007) | F | 41 | NA | Right | Surgery | 10+ |
| (Oshiro and Esaki, 2011) | F | 63 | 12 | Right | Surgery | 6+ |
| (Kang et al., 2012) | F | 63 | 12 | Right | Surgery | 6+ |
| (Kai et al., 2013) | M | 51 | NA | Right | Surgery | 26 |
| (Sumiyoshi et al., 2017) | M | 49 | 6 | Left | Surgery | 3+ |
| (Hagiwara et al., 2018) | M | 68 | 13.6 | Left | Surgery | 6+ |
| (Laohawetwanit and Klaikaew, 2020) | M | 58 | 3 | Right | Surgery | 15+ |
| (Laohawetwanit and Klaikaew, 2020) | F | 57 | 15 | Right | Surgery | 39+ |
| (Laohawetwanit and Klaikaew, 2020) | M | 65 | 3 | Right | Surgery | 52+ |
| (Laohawetwanit and Klaikaew 2020) | M | 66 | 6 | Right | Surgery | 11 |

Abbreviations - F female; M Male; NA Not available.

typical iCCA, LECL tumor cells are bigger and have more abundant cytoplasm and well-represented nucleoli (Labgaa et al., 2017). In classical iCCA the inflammatory infiltrate is uncommon and made by neutrophils when present (Mostyka et al., 2020). Immunohistochemically, LECL cells are positive for pan keratin (eg, AE1/AE2), EMA, biliary type keratins K19 and K7 and biliary lineage markers like EpCAMand CA19–9 and negative for CK20 and HepPar1. In addition, more than half of tumors show positive expression of p53. In tumors associated with EBV infection, EBV latent membrane protein 1 (LMP1) is negative and EBV encoded RNA (EBERs) is positive, frequently(Labgaa et al., 2017). The molecular and genetic aspects of this histotype are understudied. Therefore, there are poor scientific evidence. To date, no substantial genetic differences have been found between LECL and iCCA other than a hypermethylation of CRBP1 and CRBPIV genes (Labgaa et al., 2017). A recent study has evaluated 27 cases of LECLs with next-generation sequencing (NGS) and Fluorescent in situ hybridization (FISH) techniques. Genetic alterations typically of iCCA were not found, like IDH1, IDH2, ARID1A, ARID2 and BAP1 mutations or fusion of FGFR2. Another interesting and potentially useful finding is the expression of PD-L1 in more than 50 % of lymphoepithelioma-like carcinomas(Tsai et al., 2021).

## 5. Biological behavior and clinical outcomes

The prognosis appears to be better than that classical CCA. After surgery, almost all patients have a mOS of more than one year. Nogami et al. reported an interesting case of LECL treating with radiofrequency ablation. A young Chinese female received diagnosis of HCC, based on radiological features of 10 mm lesion on right lobe liver. Ultrasound-guided percutaneous biopsy and radiofrequency ablation were performed at the same time. HCC was excluded on histological examination and LECL was diagnosed. One year after radiofrequency therapy, the patient is still free from recurrence (Nogami et al., 2021).

### 5.1. Mucoepidermoid carcinoma

#### 5.1.1. Epidemiology and pathogenesis

Mucoepidermoid carcinoma (MEC) is a tumor formed by mucin-secreting cells, epithelioid cells and intermittent cells. Though usually described as one of the most common salivary gland carcinomas, MEC has also been identified as a primitive biliary tract cancer, as first

reported by Pianzola and Drut in 1971(Pianzola and Drut, 1971). The authors initially considered MEC as the product of squamous metaplasia involving the terminal ramifications of bile canaliculi (Pianzola and Drut, 1971). In contrast, more recently several other authors have inferred that MEC might evolve from congenital cysts. This hypothesis is supported by the frequent evidence of multiple seromucous cysts close to the tumor with no connection to the biliary system presenting histological similarity with MEC cells (Choi et al., 2004). Some authors hypothesize that the origin of the biliary MEC should be attributed to subepithelial secretory glands called peribiliary glands (Kato et al., 2022). However, this hypothesis does not explain the origin of the gallbladder MEC, of which only one case has been described in the literature (Nallacheruvu et al., 2019). Other authors suggest that MEC is related to Clonorchis sinensis infestation (Koo et al., 1982). Other etiological hypotheses arethorotrast contrast administration (Lambrianides et al., 1986) and intrahepatic stones. Data on real incidence are lacking in literature. To our knowledge, only 21 cases of MEC of the biliary tract have been described so far (Table 3). The low number of cases is due not only to the rarity of this histotype but also to the diagnostic difficulty and possible misdiagnoses. In particular, when epidermoid and intermediate cells prevail, differential diagnosis with ASC of biliary tract is difficult, especially with small tumoral specimens available.

#### 5.1.2. Histological features

In the ASC the different components are well distinct, while in the MEC, epidermoid cells and mucin-secreting cells are intimately mixed (Guo et al., 2014). The ratio of incidence in women and men is 8:9, it is different from this tumor occurring in salivary gland with a 3:2 female predilection. Hepatic MEC seems to occur frequently in elderly patients, with a median age at onset of 60 years (Guo et al., 2014). It is possible to make a diagnosis of MEC using mucicarmine and Alcian blue or Periodic Acid Shiff stains to demonstrate the presence of mucin inside the tumor cells (Moul et al., 2013). Immunohistochemical analysis shows mucus-producing cells positive for CK7 and MUC1 and negative for CK5/6 and p63. Diversely, epidermoid cells are positive for p63 and CK5/6 and negative for CK7 (Kato et al., 2022; Moul et al., 2013, Choi et al., 2004; Guo et al., 2014; Hou et al.,2021) In a korean case report, nuclear positivity for p16 was found in epidermoid cells (Song et al., 2011). Only one case reported tumor cells positive both CK7 and C20 (Arakawa et al., 2008). In salivary MEC, a growing number of studies has

shown the presence of the recurring chromosomal translocation t(11;19) which results in a fusion transcript from the exon 1 of the CRTC1 gene at 19p13 with exons 2–5 of the MAML2 gene, resulting in a CRTC1/MAML2 translocation (Pérez-de-Oliveira et al., 2020). This fusion transcript seems associated with favorable clinicopathologic features and an indolent clinical course. Only one case of biliary MEC with CRTC1/MAML2 fusion is reported in the literature: a patient with 10 years survival. The authors hypothesized that hepatic MEC with MAML2 fusion is also associated with a favorable prognosis, the same as salivary MECs. However, the prognostic role of this gene alteration has never been considered before in biliary MECs (Watanabe et al., 2014).

### 5.1.3. Biological behavior and clinical outcomes

The prognosis of MEC of the hepatobiliary system is poor, with a post-surgery survival varying from a few days to a few months, as shown in Tables 5 and 6.

## 5.2. Combined hepatocellular cholangiocarcinoma

### 5.2.1. Epidemiology

Combined Hepatocellular Cholangiocarcinoma (cHCC-CCA) is a biphenotypic tumor with unequivocal morphological characteristics of both hepatocytic and cholangiocytic differentiation. The incidence of cHCC-CCA among primary liver tumors ranges from 0.4 % to 14.2 % (Stavraka et al., 2018). This wide variability could be due to the evolution over time of the diagnostic definition. The latest analysis of the SEER database shows an incidence of 0.77 % per year, with a possible underestimation caused by radiological diagnoses that avoid surgical resections of cancers leading to misdiagnoses of either HCC or iCCA (Beaufrère et al., 2021). cHCC-CCA is more frequent in males, with an incidence ratio of male: female of 2.26, and a median age at diagnosis is 65 years old (Ramai et al. 2019; Azizi et al., 2020).

### 5.2.2. Histological features

cHCC-CCA was firstly described in 1903 by Wells H.G. (Wells, 1903). The percentual threshold of each phenotype to make the diagnosis has yet to be defined (Brunt et al., 2018). Given the phenotypic characteristics of these components, routine hematoxylin and eosin staining is sufficient for diagnosis, as stated by a recent consensus paper, that considers immunohistochemistry as accessory to the mandatory morphological evaluation. Over time, different authors proposed further classifications of this tumor, including Allen and Lisa (ALLEN and LISA, 1949), who divided cHCC-CCAs according to histological features, focusing on "transition zone" between two malignant components.

In particular, Xue et al. reported that type B cHCC-CCA was genetically more similar to CCA, with frequent KRSA and IDH1 mutations and type C was similar to poorly differentiated HCC, with more frequent TP53 mutations (Xue et al., 2019). Genomic studies reported that cHCC-CCA shows amplifications and gains on function in MYC, and genetic alterations in RYR2 and FBN2. Conversely, molecular alterations seen in CCA, such as PBRM1, IDH1/2 and FGFR2, were not present in cHCC-CCA (Azizi et al., 2020). In addition, by evaluating the mutation rate of the tumor suppressor p53 it was observed that it is more frequently mutated in cHCC-CCA than in HCC and CCA with a frequency of 49.2 %,31 % and 22 %, respectively (Xue et al., 2019).

### 5.2.3. Biological behavior and clinical outcomes

Similarly to the double morphological nature of cHCC-CCA, radiological imaging of cHCC-CCA is widely variable, ranging from HCC-like behaviors presenting arterial contrast enhancement and subsequent washout, to iCCA-like behaviours with gradual peripheral enhancement (Kim et al., 2021). Recent studies have shown the prognostic value of imaging patterns (Park et al., 2017; Mao et al., 2017, Zhou et al., 2022).

The prognosis of patients with cHCC-CCA is worse than that of patients with HCC, and similar to that of patients with iCCA. This is probably correlated to vascular invasion and to the frequent presence of lymph node metastases (Beaufrère et al., 2021). According to locoregional spread, surgery would be the only curative therapy, but recurrence rates at 1-, 3- and 5-years are 60.8 %, 71.8 %, and 80 %, respectively (Azizi et al., 2020). Wang et al. conducted a population analysis and the median OS reported was 9 months from diagnosis. The 1, 3 and 5-years survival rates were 43.4 %, 21.5 %, and 17.1 %, respectively (Wang et al., 2019).

Comparative data on systemic cHCC-CCA therapy are scarce, but cytotoxic regimens with gemcitabine and cisplatin appear to have a higher response rate and OS. In a retrospective multicentric analysis, Kobayashi et al. reported that platinum-containing chemotherapy had more favorable outcomes than the sorafenib treatment (Kobayashi et al., 2018). Similar results were found in other retrospective studies (Salimon et al. 2018; Trikalinos et al. 2018). On the other hand, Futsukaichi et al.

**Table 5**
Case reports mucoepidermoid carcinoma of biliary tract.

| References | Sex | Age (Ys) | Size (cm) | Location | Metastasis | Treatment | OS (months) |
|---|---|---|---|---|---|---|---|
| (Pianzola and Drut, 1971) | M | 44 | 15 | Right lobe | None | Surgery | 1 |
| (Ho, 1980) | M | 65 | 8 | NA | Lymph nodes | Conservation | <1 |
| (Ho, 1980) | F | 63 | 6 | NA | Pancreas, portal vein, lymph nodes | Conservation | <1 |
| (Koo et al., 1982) | F | 44 | 12 | Left lobe | None | Surgery and CT | 6 |
| (Koo et al., 1982) | M | 66 | 4 | Common hepatic duct | Gallbladder, lymph nodes | Surgery | <1 |
| (Koo et al., 1982) | M | 62 | 1.5 | Common hepatic duct | None | Surgery | 10+ |
| (Katsuda et al., 1984) | M | 78 | 11 | Left lobe | Lymph nodes, lung, kidney | CT | 3 |
| (Lambrianides et al., 1986) | F | 59 | 18 | Right lobe | Kidney | Conservation | <1 |
| (Hayashi et al., 1987) | F | 46 | 3 | Left lobe | None | Surgery | 11 |
| (Di Palma et al., 1992) | F | 66 | 9.5 | NA | Diaphragm, pericardium, portal vein | Surgery | 6 |
| (Shuangshoti and Shuangshoti, 2000) | M | 64 | 5 | Left lobe | Lymph nodes | BSC | <1 |
| (Kang et al., 2003) | M | 52 | 9 | Left lobe | Diaphragm | TAE + surgery | 6 |
| (Choi et al., 2004) | F | 69 | 16 | Right lobe | Diaphragm | Surgery | 4 |
| (Arakawa et al., 2008) | F | 81 | 10 | Right lobe | Lymph nodes, portal vein | RT + CT (Gem+ 5FU+Cis) | 4 |
| (Song et al., 2011) | M | 68 | NA | Common bile duct | NA | Surgery + CT | 3+ |
| (Moul et al., 2013) | F | 83 | 2 | Common bile duct | Liver | Surgery + CT | 13 |
| (Guo et al., 2014) | F | 60 | 8.5 | Left lobe | Lymph nodes | Surgery + CT | 6 |
| (Nallacheruvu et al., 2019) | M | 50 | 8 | Gallbladder | Liver | Surgery | 6 |
| (Watanabe et al., 2019) | F | 79 | 5.3 | Left lobe | None | Surgery + CT | 120+ |
| (Hou et al., 2021) | M | 64 | 10 | Left lobe | None | Surgery | 3 |
| (Kato et al., 2022) | M | 74 | 4.5 | Left lobe | Lymph nodes | Surgery + CT | 15+ |

Abbreviations – BSC Best Supportive Care; CT Chemotherapy; Cis Cisplatin; F Female; Gem Gemcitabine; M Male; NA Not available; RT Radiotherapy; TAE Trans-arterial embolization; 5-FU 5-fluorouracil.

**Table 6**
Summary table of the main characteristics of rare epithelial histotypes of biliary tract tumors.

| Histotypes | Incidence | Histological features | Molecular profiling | Clinical outcomes |
|---|---|---|---|---|
| **Adenosquamous carcinoma** | 2–3 % of CCA (Kobayashi et al., 2005) 4–8.9 % of Gallbladder (Hoshimoto et al., 2017) | Variable proportions of two malignant components: adenocarcinoma (AC) and squamous cell carcinoma (SCC) (Gou et al., 2021) | Point-mutation of the *PI3KCA* gene (Galuppini et al., 2017) | mOS 6–20 months (Hong et al., 2008; Gou et al., 2021) |
| **Sarcomatous CCA** | 4.5 % of iCCA (Zhang et al., 2018b) | Variable proportions of two malignant components: adenocarcinoma and sarcomatous components (Watanabe et al., 2014) | Unknown | mOS 3 months (Nakajima et al., 1993) |
| **Poorly cohesive carcinoma with or without ignet ring cells** | 1.3 % of all BTCs (Benesch and Mathieson, 2020) | Almost 50 % of cells with abundant intracytoplasmic mucin dislocating the nucleus to the periphery (Benesch and Mathieson, 2020). | Unknown | 5-years survival rate 16.2 % (Benesch and Mathieson, 2020). |
| **Cholangiolocellular carcinoma** | 0,6–1 % of primitive liver cancers (Takakusagi et al., 2021) | Small cells, with oval and hyperchromatic nuclei with a high N: C ratio. Antler-like growth pattern in a fibrous stroma. They do not produce mucin and have a low cellular atypia (Komuta et al., 2008) | *IDH1/2* mutations and fusion of *FGFR2* are present in 90 % of cases of CoCC (Balitzer et al., 2019) | 5-years survival rate 33 % (Ariizumi et al., 2014) |
| **Intrahepatic cholangiocarcinoma with ductal plate malformation pattern** | 2.9 % of incidence among all iCCAs (Chung et al., 2021) | Greyish-white solid mass-forming nodule with irregular margins and nocapsule. (Nakanuma et al., 2012) | The most frequent genetic alterations *FGFR2, PTPRT, ARID1A* and *CDKN2A* (Chung et al., 2021) | mOS 22–122 months (Chung et al., 2021) |
| **Clear Cell Carcinoma** | Unknown for CCA, represent 1 % of gallbladder tumors (Yamamoto et al., 2020). | More than 80 % of cubic shape cells, intermediate size, clear cytoplasm, vacuolar. Arranged with a glandular and trabecular growth pattern in abundant desmoplastic stroma (Haas et al., 2007) | Unknown | Unknown |
| **Muscinous cholangiocarcinoma** | 0.5 % of iCCA (Laohawetwanit and Klaikaew, 2020). | Plentiful extracellular mucin pool representing at least 50 % of total tumor volume with a gelatinous cut surface (Laohawetwanit and Klaikaew, 2020). | Unknown | 1 year mortality rate is approximately 50 % (Laohawetwanit and Klaikaew, 2020) |
| **Lymphoepithelioma-like carcinoma** | Unknown | Poorly differentiated cells arranged in cords and surrounded by lymphocyte infiltrate. Cells larger than the typical CCA with abundant cytoplasm and well represented nucleoli (Labgaa et al., 2017) | Hypermethylation of *CRBP1* and *CRBPIV CCND1* amplifications (Labgaa et al, 2017) | mOS > 12 months after surgery (Nogami et al., 2021) |
| **Mucoepidermoid carcinoma** | Unknown | Epidermoid cells and mucin-secreting cells are intimately mixed (Guo et al., 2014). | Only one case of biliary MEC with *CRTC1/MAML2* fusion is reported in the literature (Watanabe et al., 2014). | Post-surgery survival varying from a few days to a few months (Pianzola and Drut, 1971) |
| **Combined hepatocellular cholangiocarcinoma** | 0.4–14.2 % of primary liver tumors (Stavraka et al., 2018) | Unequivocal morphological characteristics of both hepatocytic and cholangiocytic differentiation (Stavraka et al., 2018) | Amplifications and gains on function in *MYC*, and genetic alterations in *RYR2* and *FBN2* (Azizi et al., 2020) | mOS 9 months from diagnosis (Wang et al., 2019) |

described a case of a patient with multiple metastases of cHCC-CCA treated after surgery with sorafenib who achieved a complete remission (Futsukaichi et al., 2019). A recent retrospective study about the efficacy of systemic therapy in patients with unresectable or metastatic cHCC-CCA reported no significant difference between sorafenib and cytotoxic chemotherapy in terms of overall response rate (ORR), median progression free survival (mPFS) and mOS. It was detected a not statistically significant difference between platinum-containing and non-platinum-containing chemotherapy (e.g.mOS 12.4 vs 9.8 months). Therefore, sorafenib or cytotoxic chemotherapy could be used in patients with cHCC-CCA, regardless of the predominant histotype (Kim et al., 2021).

According to the increasing evidence for immune checkpoint inhibitors in the management of both iCCA and HCC, there would be rationale in the use of this therapy even in the combined forms. Nguyen at al, recently identified two main immune subtypes of cHCC-CCA and they suggest that a specific subset of patients may benefit from immunotherapy (Nguyen et al., 2022). A case report describing a complete radiological remission of pulmonary metastases to third-line treatment with Pembrolizumab in a patient with cHCC-CCA radically resected (Rizell et al., 2020). Although these patients are excluded in the prospective trials, observational or retrospective studies in the real-life setting could generate results to guide the management of patients with cHCC-CCA in the future.

## 6. Conclusions

Our review has shown how the knowledge of these less frequent histotypes of choloangiocarcinomas is quite limited by the scarcity of numerous cohorts to be studied in depth. The low frequency of these tumors also poses two problems: the difficulty of making a precise diagnosis of these subtypes and the difficult clinical management of these patients of whom little or nothing is known about the pathogenesis and therefore few are the possibilities of using targeted therapies. Regarding the first point, the centralization of the diagnosis of these rare histotpes in the specialized health sector could be useful, this could allow a more precise histological definition by experts who would be better able to make a differential diagnosis. Furthermore, this approach would allow to have and store a significant number of cases for the different subtypes, allowing significative molecular investigations and clinical trial studies. However, a reasonable timing of diagnosis should be respected as much as possible for a timely therapeutic approach considering the biological aggressiveness of these tumors.

Currently, in consideration of the poor prognosis, the European Society for Medical Oncology (ESMO) guidelines recommend next-generation sequencing (NGS) with the use of medium-large panels for all patients with CCA (Mosele et al., 2020) to highlight the importance of genomic profiling in the choice of a possible targeted therapy for patients affected by BTCs.This suggestion is also extensible to the rare histotypes of biliary tract tumors for which we know that in the

literature the studies aimed at identifying the possible molecular driver alterations are few and sometimes not significant. Although, the use of NGS for therapeutic purposes in rare histotypes of cholangiocarcinoma is raccomanded, on the contrary, the use of NGS analysis in these rare subtypes for diagnostic purpose is still not very useful, since there are scarce literature data, often contradictory and mostly based on statistically insignificant case studies, about specific and pathognomonic molecular alterations in these histotypes.

Regarding the immunotherapy, recently the therapeutic armamentarium for BTCs has extended to immunocheckpoint inhibitors (ICIs), with the approval of first-line Durvalumab in combination with chemotherapy without the need for a specific marker such as PD-L1 expression (Oh et al.,2022). We do not know the possible efficacy of ICIs in rare histology, considering the absence of specific studies in this patient setting. However, it is possible to hypothesize that this type of therapy may lead to a therapeutic benefit in some patients, especially in forms such as LELC which presents a high expression of PD-L1 (Tsai et al., 2021).

To our knowledge, there is no other review about rare subtypes of an epithelial tumor of the biliary tract. At the moment, tumor resection would appear to be still the only potentially curative option for these patients, although only a small percentage of the patient are eligible because diagnosis is often late and in advanced stage. Due to the very low incidence of these malignancies, the lack of current treatment options, and the limited effectiveness of standard chemotherapy, "molecular diagnosis" provides an essential opportunity for improved personalized treatment plans.

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## Conflict of interests

The authors declare the absence of conflicts of interest.

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