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Primary Intrahepatic Biliary Tracts Tumors: Diagnosis and Treatment

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

The most frequent primary intrabiliary tracts tumors are intrabiliary cholangiocarcinoma and cystadenocarcinoma. Cholangiocarcinoma is a primary adenocarcinoma developed from the bile ducts cells and represents 15% of primary liver cancers. The cystadenocarcinoma often corresponds to the transformation of a biliary cystadenoma, which can develop on congenital anomalies of the bile ducts such as Caroli's disease, congenital hepatic fibrosis, hepatic polycystosis or bile duct cysts. The clinical symptoms are nonspecific and these primary intrabiliary tracts tumors are discovered at advanced stage. The upper right quadrant pain with abdominal mass are the typical signs. Their management depends on the stage and location of the tumor at the diagnosis time. The treatment is therefore surgical. The resectability rate of intrahepatic cholangiocarcinomas is between 50 and 70%. No systemic chemotherapy has yet proven its effectiveness in the treatment of cholangiocarcinoma. The prognosis for cholangiocarcinoma is poor. Early detection of intrahepatic cholangiocarcinoma is difficult, and the median survival at diagnosis is 12 months in the absence of surgical treatment. The prognosis of cystadecarcinoma is also poor but remain better than that of cholangiocarcinoma.

Keywords: Cholangiocarcinoma; clinical symptoms; malignant liver tumors; Caroli's disease.

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1. INTRODUCTION

Primary malignant liver tumors are the second leading causes of cancer related death in the world and therefore a major burden for public health. Their diagnosis and treatment remain a great challenge for physicians. They compound an heterogeneous group of malignant tumors with different histological origin. The most frequent are hepatocellular carcinoma (HCC) which arises from hepatocyte cells; cholangiocarcinoma (CC), gall bladder carcinoma and cystadenocarcinoma which arise from biliary tract cells and are known as biliary tracts cancers. There is also mixed tumors which compound hepatocellular and cholangiocarcinoma (HCCCCA). Fibrolamellar (FLC), and hepatoblastoma for pediatric neoplasm are the most rares malignant tumors of the liver [1]. Among the primary malignant tumors of the biliary tracts, the most frequent are cholangiocarcinoma, cystadenocarcinoma and the gallbladder carcinoma and are divided into extrahepatic and intrahepatic tumors [2,3]. “The biliary cystadenocarcinoma (BCAC) is often associated with biliary cystadenoma (BCA) and the two are rare intrahepatic cystic neoplasms and account for only 5%-10% of all intrahepatic cystic lesions of bile duct origin” [4]. “There are three subsets of cystadenocarcinoma based on pathology material submitted to institutional laboratories for primary diagnosis or consultation: 1) cystadenocarcinoma originating from a benign cystadenoma with ovarian-like stroma (occurs exclusively in women); 2) *de novo* cystadenocarcinoma occurring almost exclusively in men; and 3) cystadenocarcinoma in women without ovarian-like stroma” [5]. If the extrahepatic tumors are symptomatically diagnosed with jaundice, the second are asymptomatic for a long time with a diagnosis delay and a poor overall survival health for the patients because there are often discovered at advanced stage. The aim of this work is to make a review of the main features of intrahepatic biliary tracts tumors and the means of diagnosis and treatment.

2. SEARCH STRATEGY AND SELECTION CRITERIA

We searched in pubmed using terms : intrahepatic cholangiocarcinoma, primary liver tumors, intrahepatic cystadenocarcinoma as free text words. We also performed a manual search and review of reference lists. We have extensively selected publications over the past 20 years, including older, highly regarded publications to see the evolution of the management of the two major intrabiliary tracts tumors which are intrahepatic cholangiocarcinoma and cystadenocarcinoma.

2.1 Intrahepatic Cholangiocarcinoma

2.1.1 Epidemiology

Cholangiocarcinoma is a primary adenocarcinoma developed from the bile ducts cells. It represents 15% of primary liver cancers [6]. It is the second leading cause of death in primary malignancy of the liver (about 10% of primary tumors), and its incidence is increasing in Western countries [7]. “It can occur on any segment of the biliary tructs, from the interlobular ducts to the Vater ampulla. Cholangiocarcinomas are generally categorized as either intrahepatic or extrahepatic based on their anatomic location with respect to the second-order bile ducts. Approximately 5% to 10% of cholangiocarcinomas are intrahepatic and arise from peripheral bile ducts within the liver parenchyma proximal to the secondary biliary radicals” [8]. The term cholangiocarcinoma is rather reserved for intrahepatic tumors, and that of bile duct carcinoma for tumors of the extrahepatic biliary tructs. Its incidence is ten times higher in Japan and Asia compared to European countries and North America due to a prevalence of intrahepatic lithiasis and biliary parasitosis [9] and is increasing in the United States and in many countries [10,11]. The average age of diagnosis is between the sixth and seventh decades of life. However, patients with risk factors like primary sclerosing cholangitis usually develop the disease two decades earlier [12]. The sex ratio is equal to 1. The main risk factors are bile duct cysts [13], primary sclerosing cholangitis, chronic inflammatory bowel disease, biliary cirrhosis, biliary lithiasis, chronic non-alcoholic liver disease, diabetes, thyrotoxicosis, chronic pancreatitis, hepatitis C virus [14], tobacco, cryptogenic cirrhosis, thorostat, parasitic infection with Clonorchis sinensis after ingestion of fish [15,16]. The symptoms are therefore late and usually aspecific: abdominal pain, alteration of the overall health. They are linked to tumor mass syndrome. Jaundice is rare with an infiltrative form.

2.1.2 Clinical Presentations

The patients who present intrahepatic cholangiocarcinoma (ICC) are usually asymptomatic at early-stage disease and the symptoms are not specific even at advanced stage. Patients may present with weight loss, abdominal discomfort, hepatomegaly or a palpable mass of right hypochondrium in more advanced stages. Biliary tract obstruction with jaundice are relatively infrequent among patients with ICC [17].

2.1.3 Pathophysiology of Biliary Tracts Tumors

"There is two types of stem cells in the biliary tree: hepatic stem/progenitor cells (HSPCs) that can differentiate into hepatocytes and cholangiocytes and biliary tree stem/progenitor cells (BTSPCs) that can differentiate into hepatocytes, cholangiocytes, and pancreatic islets. These stem cells distribute to different locations according to type: The canals of Hering, the most peripheral portion of biliary drainage pathway connecting bile canaliculi to terminal bile ducts, are a HSPC niche, while peribiliary glands are a BTSPC niche. HSPC niches are involved in diseases affecting the small bile duct such as ICC, combined hepatocellular-cholangiocarcinoma, and cytokeratin 19–positive hepatocellular carcinoma. BTSPC niches are involved in diseases affecting the large intrahepatic and extrahepatic bile ducts such as mucin-producing CC and PSC. Thus, ICCs can arise either from the HSPC lineage or from the BTSPC lineage, which may correspond to tumors involving the small bile duct/canals of Hering or from the large intrahepatic bile duct, respectively" [18].

2.1.4 Imaging

Ultrasound shows a hypo- or hyperechoic mass. In the case of tumors of the hilum, the diagnosis is often indirect by the demonstration of a dilation of the bile ducts. For contrast ultrasound, these are lesions that are poorly vascularized in the arterial phase, can be iso, or slight hypointense. In portal and late stages, the hypoechoic character is particularly marked [19]. The CT shows an iso or hypodense lesion before injection, with an enhancement variable in the arterial phase, sometimes peripheral, late enhancement in more than 50% (5-10min) with a weak contrast [20]. On MRI, intrahepatic cholangiocarcinoma is a non-encapsulated lesion with frequently lobulated contours. It is in T1 hypointense and the signal is variable in T2, sometimes iso- or discreetly hyperintense compared to the liver, sometimes strongly hyperintense. The enhancement kinetics can simulate that of the hemangioma, however, the globular and discontinuous character is only observed in the latter [18].

2.1.5 Biological Assessment

Biology shows anicteric or icteric cholestasis. Carcinoembryonic antigen (CEA) may be increased (in about 30% of cases). CA 19-9 is increased, but its elevation is nonspecific when there is jaundice. It has more diagnostic value when cholestasis is moderate [21].

2.1.6 Anatomopathologie

Macroscopically, this tumor most often presents in sclerosing or nodular form, more rarely papillary. Microscopically, it is an adenocarcinoma in 95% [20] of cases, well differentiated in most cases but infiltrating, associated with significant fibrosis, the most commonly found form is a tubular adenocarcinoma, characterized by an abundant and fibrous stroma, we can find papillary aspects, more rarely mucous colloid aspects. According to WHO, there are also papillary, mucoid, or intestinal-type adenocarcinomas.

It compounds:

- an intrahepatic and extrahepatic extension assessment by an abdominopelvic CT looking for intrahepatic metastases, pedicular and celiac lymphadenopathy and indirect signs of peritoneal carcinoma and a chest scanner looking for secondary pulmonary lesions; a review of technical feasibility, in particular a study of the volume of the remaining liver;
- A vascular assessment by CT angiography or MRI angiography, looking for arterial and / or portal invasion, and a study of the relationship with the hepatic veins and the inferior vena cava.

2.1.7 Classifications of Intrabiliary Cholangiocarcinoma [22]

The 7th edition of the American Joint Committee on Cancer / InternationalUnion Against cancer (AJCC / IUACC) takes into account major prognostic factors such as the prognostic factors and the number of tumors (not tumor size, which is not related to prognosis) or vascular invasion. This classification allows to oriente the treatment. Four stages are identified:

Table 1. TNM classification of intrahepatic cholangiocarcinoma

TNM	Tumor features	Suvival
Stage 1(T1N0M0)	One nodular without vascular invasion	20 a 40% at 5 years
Stage 2 (T2N0M0)	Multiple nodulars localisation or vascular invasion	20% at 5 years if resectable and 15 months medium if unresectable
Stage 3 (T3N0M0)	Local structures invasion (periteneum, gall bladder, common bile duct...)	15 months of medium survival
Stage 4	Hilar invasion and/or N1 and/ orM1	12 months medium survival

Table 2. AJCC / IUACC Classification of intrahepatic cholangiocarcinoma [23]

T1a: solitary tumor ≤5 cm without vascular invasion
T1a: solitary tumor ≤5 cm without vascular invasion
T2: solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion
T3: tumor perforating the visceral peritoneum
T4: tumor involving local extrahepatic structures by direct invasion
N0: no regional lymph node metastasis
N1: regional lymph node metastasis present
IA: T1a N0 M0
IB: T1b N0 M0
II: T2 N0 M0
IIIA: T3 N0 M0
IIIB: T4 and/or N1, M0
IV: any T, any N, M1

2.1.8 Treatment [24]

"Treatment for cholangiocarcinoma is determined by the patient's performance status, the local extent of the tumor, the absence or presence of metastasis, and the availability and extent of surgical and endoscopic expertise" [8].

Intrahepatic cholangiocarcinoma is the most severe tumor of the liver. Its management depends on the stage and location of the tumor at the diagnosis time. The median spontaneous survival of cholangiocarcinomas is 3 to 6 months regardless of the series. Only surgical treatment can achieve prolonged survival. The median survival after surgical treatment is 2 years [25]. As intrahepatic cholangiocarcinoma is a rare tumor, only small retrospective series are available in the literature. Nevertheless, several studies have attempted to find prognostic factors for survival. In the series by Ueneshi et al. [26] 23 resected patients are reported. All patients with histologic lymph node involvement had died at 1 year. In patients without lymph node involvement, the overall 3-year survival was 71%. The poor prognostic factors found were the existence of liver metastases and invaded surgical resection limits. Weber et al. [27], in their series of 53 patients, show a resectability rate of 62%. None of these patients had lymph node involvement. Of the 33 resected patients, 3 poor prognostic factors were significantly demonstrated: the existence of vascular invasion of the invaded surgical resection limits and the existence of satellite nodules. The median survival was 12.5 months with a 3-year recurrence-free survival rate of 22%. In 2001, Isa et al. [28] studied the characteristics of 7 operated patients who were alive in the long term (including 4 without recurrence after more than 5 years). One factor is constant and definitely influences the prognosis, metastatic lymph node extension. In all the published series, no survival benefit was observed, regardless of the treatment, in the event of lymph node metastases. The second controllable factor is the macroscopic limit of surgical resection. Liver resection must therefore be carcinological. If necessary, an extemporaneous histological examination of the hepatic section may be requested. The further therapeutic management of the patient with intrahepatic cholangiocarcinoma after surgical resection will depend on the histology of tumor.

a- Tumor unresectable from the outset: This is unfortunately the most frequent case. The most common causes of irresectability are:

- distant lymph node, hepatic, peritoneal or pulmonary metastases
- the existence of vascular invasion, of the hepatic artery, of the portal vein, of the retrohepatic inferior vena cava.
- factors inherent to the patient, deterioration of the general condition, advanced age, anesthetic contraindication. The existence of metastatic lymph node involvement is a formal contraindication to surgical excision. No systemic chemotherapy has yet proven its effectiveness in the treatment of cholangiocarcinoma. The combination of Gemzar® and Eloxatin appears to be able to slow tumor progression. A few cases of tumor regression have been reported with a median survival of 11 months. Pre- or post-operative external radiotherapy [29], alone or in combination with chemotherapy, has not been shown to be effective but induces toxicity, sometimes severe or even fatal, such as cholangitis.

b- Resectable tumor: Depending on the surgical series, the resectability rate of intrahepatic cholangiocarcinomas is between 50 and 70%. The treatment is therefore surgical. The operation must always begin with an extensive pedicular and celiac lymph node dissection which is referred for extemporaneous pathological examination. Only if this is negative can the hepatectomy start. It is a wide anatomical hepatectomy with a safety margin of one centimeter. To be able to perform this hepatectomy, various techniques are used to protect the remaining hepatic parenchyma. In case of insufficient residual liver volume, preoperative PE [29] to obtain compensatory hypertrophy of the remaining liver is essential.

c- Unresectable tumor located in the liver: These are tumors localized to the liver, without lymph node metastasis. Liver transplantation is debated in young and generally preserved patients. The results are not very good and the literature is poor on the subject. The rate of recurrence, mainly lymph node, after liver transplantation is high, nearly 35% [30]. Shimoda et al. [31] reported a series of 16 transplant patients for intrahepatic cholangiocarcinoma. The actuarial 3-year recurrence-free survival was 32%, but many patients had small tumors that were therefore surgically resectable.

This clinical presentation may be due to a tumor with an endobiliary bud, obstructing a large bile duct or a tumor with infiltration of the biliary convergence. Its management is similar to that of Klatskin tumors. The added problem in relation to the management of central intrahepatic cholangiocarcinoma is that of the dilation of the bile ducts and the cholestasis that it causes. Percutaneous biliary drainage of the liver to be preserved is most often to be performed preoperatively. As with all hilar tumors, hepatectomy (right or left) is an enlarged hepatectomy to segments IV and I with resection of the biliary convergence and the main bile duct. For technical surgical management, the same strategies (preoperative portal embolization, hepatic cooling, vascular exclusion of the liver) can be used intraoperatively. The conditions for excision are the same, namely: negative complete pedicular lymph node dissection; wide hepatectomy; healthy surgical resection boundaries [32].

Chemotherapy: “There are not so much evidences for the evidence-based evaluation of the chemotherapeutic efficacy for ICC patients. An randomized controlled trial on chemotherapy and supportive treatment was conducted in patients with unresectable biliary tract cancer and pancreas cancer. In this study, fluorouracil (5-FU) + leucovorin or 5-FU + leucovorin + etoposide were used for chemotherapy. For all the patients, significantly prolonged survival was observed in the group with chemotherapy [median survival time (MST), 6.0 mo] compared with the group with supportive treatment alone (MST, 2.5 mo). In summary, recent advancement facilitates the chemotherapy to achieved a response rate of around-30% and a median survival of more than one year for ICC patients. Key drugs currently available for the therapy are gemcitabine, fluoropyrimidines, and platinums. Further investigations are required for the development of new agents, such as molecular-targeting drugs, and combined therapy with surgery” [33].

2.1.9 Prognosis and Evolution

The prognosis for cholangiocarcinoma is poor [34]. Early detection of intrahepatic cholangiocarcinoma is difficult, and the median survival at diagnosis is 12 months in the absence of surgical treatment. Death is most often related to complications from biliary obstruction, liver failure or end-stage cachexia related to the disease [21]. “Resection is rarely possible and 3-year survival is 5-10%. Intrahepatic cholangiocarcinoma represents the second most common primary liver cancer and is increasing in

incidence. Most patients are diagnosed at an advanced stage, with unresectable tumor and only about 1 in 5 cases are surgically resectable. Despite surgery, the 5-year survival is low at only 30%. No other therapy has shown any efficacy" [35]. The presence of multiple lesions, the degree of invasion of hepatic structures, the margin of non-carcinological section are associated with a high risk of recurrence and a poor prognosis. On histology, the presence of sarcomatous, squamous or mucinous cells, poor differentiation of the tumor and lymph node invasion represent the factors of poor prognosis [27,36].

"Factors associated with recurrence and worse survival after resection for intrahepatic cholangiocarcinoma" [37].

Large tumor size >5 cm

- Tumor multifocality
- Higher TMN stage
- Lymph node metastases
- Lymphovascular invasion
- Margin status (R1 resection in node negative disease)
- Intraductal growth IHCCA type
- Elevated neutrophil-to-lymphocyte ratio
- Low prognostic nutritional index
- Perineural invasion
- Elevated CA 19-9

2.2 Cystadenocarcinoma

2.2.1 Epidemiology

This tumor is discovered in adults between the ages of 40 and 60 [38]. It affects women more frequently (80%). It most often corresponds to the transformation of a biliary cystadenoma, but which can develop on congenital anomalies of the bile ducts such as Caroli's disease, congenital hepatic fibrosis, hepatic polycystosis or bile duct cysts. The clinical symptomatology is pain and sometimes a palpable mass in the right hypochondrium. Jaundice is rare; it can be either compressive by the tumor or obstructive by mucin if it communicates with the bile ducts. Its evolution is slow and is discovered with an average size of 12.4 cm [39].

2.2.2 Clinical presentations

"The clinical presentation of cystadenocarcinoma is variable and nonspecific. Patients are asymptomatic. The most typical symptoms were upper abdomen pain, abdominal mass, dyspepsia, anorexia, nausea and fever, jaundice caused by compression, protrusion, invasion of bile ducts, or secretion of dense mucinous material" [5].

2.2.3 Imaging

Ultrasound shows the cystic nature of the lesion, which is often large with a thickened wall. The lesion can be single or multilocular with irregular partitions, papillary projections and wall nodules, parietal or septal calcifications can be seen but are rare and would be a diagnostic element in favor of cystadenocarcinoma. The non-enhanced CT scan confirms the cystic nature of the lesion. It makes it possible to better specify the topography of the lesion and its relationship with the adjacent parenchyma. The enhanced CT scan shows an enhancement of the nodules wall making them more visible [40]. The MRI shows a partitioned multilocular mass with variation of the signal level in the different cubicles on the T1 and T2 weighted sequences, the septa would be in T2 hypo signal [41].

2.2.4 Biological assessment

Liver biology is often normal or may show a moderate increase in gammaglutamyl transpeptidase and alkaline phosphatase activity. The serology of hydatidosis should be checked for negativity, which sometimes constitutes a differential diagnosis. Serum tumor markers have little diagnostic value. It is possible to see a high level of CA19-9, but the level of ACE and AFP is often normal [39].

2.2.5 Anatomopathology

Macroscopically, these large tumors appear single, more often multilocular, limited by a thick and fibrous wall, and wall nodules can be observed. Microscopic examination shows that the wall of the cyst is more or less covered with papillary formations, with a connective axis, coated with cuboid epithelial cells in unicellular seating or in mucosecreting columns [42].

2.2.6 Differential diagnosis

"The differential diagnosis of this tumor are other cystic lesions of the liver. It mainly occurs with complicated biliary cyst, ciliated cyst, hydatid cyst, remodeled hematoma, liver abscess, cystic hemangioma, lymphangioma, hepatic foregut

cyst, mesenchymal hamartoma, and teratoma and necrotic metastases" [43].

2.2.7 Treatment, prognosis and outcomes of cystadenocarcinoma

Surgical resection still the standard current treatment of cystadenocarcinoma. Patients who have undergone radical excision have a chance of long-term survival [44] adjuvant chemo and / or radiotherapy have no place if the cystadenocarcinoma is non-invasive unless there is a contraindication at resection [45]. Slow progression than cholangiocarcinoma [22] by contiguity in the rest of the liver but liver metastases distant from the primary are possible. Due to the low incidence of this tumor, the prognosis is poorly understood, but it remains better than that of cholangiocarcinoma [46]. "Tumor subtype and their stroma are prognostic factors associated with survival following resection of BCAC. The BCAC is classified into two subtypes: invasive and non-invasive based on the carcinoma extension into the liver with a significant difference in survival. Specifically, there were no recurrences or deaths noted among patients with non-invasive BCAC compared with a median survival of only 7 months among those patients who had the invasive subtype. The patients with a BCAC characterized by ovarian-like stroma on pathology had a significantly better longterm prognosis compared with patients whose tumors lacked ovarian-like mesenchymal stroma. There is also a worse prognosis among men with BCAC, probably due to the higher likelihood of BCAC without mesenchymal stroma in males" [47].

3. CONCLUSION

The primary intrahepatic biliary tracts tumors are rare but severe tumors with a poor survival rate. The clinical symptoms are not specific and the diagnosis is made at advanced stage when curative treatment is impossible. Liver resection is the only curative treatment for resectable tumors. The early diagnosis can help to improve the survival even to perform a curative treatment. The diagnosis mighty be kept in mind by physicians when there symptoms and it is better first to rule out those tumors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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