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REVIEW ARTICLE

Is preoperative histological diagnosis necessary before referral to major surgery for cholangiocarcinoma?

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Abstract
Major surgical resection is often the only curative treatment for cholangiocarcinoma. When imaging techniques fail to establish the accurate diagnosis, biopsy of the lesion is unavoidable. However, biopsy is not necessarily required for topography of the cholangiocarcinoma (intrahepatic or extrahepatic). 1) In extrahepatic cholangiocarcinoma (ECC), clinical features and radiological imaging relate to biliary obstruction. Provided that between 8% and 43% of bile duct strictures are not ECC, the lesions mimicking ECC that should be ruled out are gallbladder cancer, Mirizzi syndrome, primary sclerosing cholangitis (PSC), autoimmune pancreatitis and portal biliopathy. Systematic biopsy is usually difficult and has poor sensitivity, but a good knowledge of these mimicking ECC diseases, along with precise analysis of clinical and imaging semiology, may lead to a correct diagnosis without the need for biopsy. 2) Intrahepatic cholangiocarcinoma (ICC) developing in normal liver appears as a hypovascular tumour with fibrotic component and capsular retraction that can be confused with fibrous metastases such as breast and colorectal cancers. The lack of the primary site, a relatively large tumour size and ancillary findings such as bile duct dilatation may provide a clue to the diagnosis. If not, we advocate local resection with lymph node dissection, since ICC is the most likely diagnostis and surgery is the only curative treatment. In the event of adenocarcinoma from unknown primary, surgery is an effective treatment even if prognosis is poor.

Introduction

Radical resection is the only curative treatment of cholangiocarcinoma occurring at any level of the biliary tract, i.e. within the liver (intrahepatic cholangiocarcinoma; ICC) or from extrahepatic bile ducts (extrahepatic cholangiocarcinoma; ECC). Preoperative biopsy of the lesion seems unavoidable when major surgery is planned, which is necessary in most cases.

However, systematic biopsy is often difficult in patients with ECC, but we believe that a good knowledge of diseases mimicking cholangiocarcinoma combined with precise patient semiologic analysis may lead to a correct diagnosis without the need for biopsy. In our experience, and in accordance with a review of the literature, the aim of this article was to describe a preoperative strategy in patients suspected of cholangiocarcinoma.

Extrahepatic cholangiocarcinoma

ECC is generally an infiltrative and sclerosing adenocarcinoma leading to biliary obstruction. It affects men more often than it affects women, and in the age range 50 to 70 years. Clinical presentation of ECC is related to biliary obstruction, i.e. jaundice, dark urine, pale stool and pruritus [1,2]. Biochemical examination shows high levels of serum bilirubin, alcalin phosphatases and gamma glutamyl transpeptidase. Cancer Antigen 19-9 (CA19-9) is often elevated but without lack of specificity. Radiological examinations are essential for diagnosis and staging before treatment of ECC [3]. CT scan, which reveals intrahepatic bile duct dilatation up to the site of obstruction, assesses vessel encasement, often associated liver atrophy and detects lymphadenopathy. Magnetic resonance cholangiopancreatography (MRCP) refines these findings and allows cholangiography without the risk of cholangitis or pancreatitis. It shows localized strictures, often irregular, bile duct above and below the obstruction, vessel encasement, invasion of adjacent liver parenchyma by hilar cholangiocarcinomas, local lymphadenopathy and distant metastases. However, as indicated in Table I, between 8% and 43% of biliary strictures are not ECC, including malignant

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Table I. Studies dealing with biliary strictures mimicking ECC.

	n	ECC	Non-ECC (%)	Gallbladder cancer	Lithiasis	PSC	SSC	Others (malign)
Hadjis 1985 [8]	104	96	8 (17)				8	
Wetter 1991 [13]	98	68	30 (31)	12	2		6	10
Verbeek 1992 [12]	82	71	11 (13)				11	
Nakayama 1999 [10]	99	85	14 (14)				14	
Gerhards 2001 [7]	132	112	20 (15)		3		17	
Knoefel 2003 [14]	33	27	6 (18)				6	
Koea 2004 [9]	49	28	21 (43)	7	2		10	2
Corvera 2005 [6]	275	253	22 **(8)**		6	3	13	
Are 2006 [4]	171	141	30 (18)	16	1		8	5

ECC: extrahepatic cholangiocarcinoma; PSC: primary sclerosing cholangitis; SSC: secondary sclerosing cholangitis.

strictures other than ECC and benign strictures [4–14]. These non-ECC biliary strictures must be researched before patients are referred to long and risky surgical treatment of ECC.

There are several arguments in favour of preoperative biopsy, especially when imaging techniques fail to demonstrate a mass lesion [3]. Additionally, surgery can be performed in suitable candidates, and with greater confidence, when there is a positive tissue diagnosis. However, a percutaneous approach with ultrasonography (US) or computed tomography (CT) guidance may fail because of the absence of a visible mass. This approach has also been considered inadvisable because of the possible risk of intra-abdominal seeding of tumour cells [15]. It has therefore been proposed that direct methods tissue sampling – either via the biliary duct during endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous cholangiography (PTC), or by a trans-duodenal or trans-gastric route with endoscopic ultrasound (EUS) guidance – may yield better results, with a potentially lower risk of tumour cell spread. Ideally, any tissue sampling technique used should be highly sensitive in detecting cancer, and with absolute specificity. The technique should be simple, safe and relatively inexpensive for widespread used. Unfortunately, none of the currently used tissue sampling methods have all these characteristics. All current methods have relatively low to moderate sensitivity but almost 100% specificity [16].

The main tissue sampling methods during endoscopic procedures are ERCP brush cytology, forceps biopsy and fine-needle aspiration (FNA) and EUS-guided FNA [16]. Brushing is the most frequently used tissue sampling technique because it is technically easy, requires little time and is generally safe. Although it has specificity close to 100%, brush cytology is less sensitive in detecting cancer, ranging from 18% to 60% in most published series [17–26]. It has been suggested that this limited sensitivity is at least partially due to failure to obtain an adequate cellular yield. This may be attributed to submucosal tumour growth or to extrinsic location of the tumour with compression of the biliary tree [22,27]. Some authors have found that the cancer detection rate of bile cytology increases from 27% to 63% with stricture dilatation [28], and even more using a scraping brush [29]. Finally, two consecutives brushings increase the cancer detection rate from 33% (one brushing) to 44% [30]. The endobiliary forceps biopsy provides a sample of bile duct tissue deep to the epithelium, theoretically obviating the problem of inadequate sampling that may occur with brushing. This technique is more time-consuming than brushing and is less widely used [16]. Sensibility of the technique rises from 43% to 81%, with specificity of around 100% [20,24,25]. Several studies have shown that combining several techniques for obtaining tissue samples from biliary strictures at ERCP enhances the detection of cancer. When combining brushing, biopsy and endoscopic FNA, sensibility reaches 70% [20,31,32].

In a recent systematic survey of prospective studies including 16,855 patients, the rate of ERCP-attributable complications was 7%, including pancreatitis (3.5%), sepsis (1.4%), bleeding (1.3%) and perforations (0.6%) [33]. Complications directly related to brushing are very rare. One retroperitoneal perforation was reported in a series of 223 consecutive brushings [24], with the rate of post-procedure pancreatitis $<2\%$ [34]. Complications relating to the use of forceps are uncommon. Minor bleedings have been reported [24].

There are few published data with respect to EUS-FNA of biliary tumours. Recent studies have obtained excellent results, i.e. with 86% to 89% sensitivity [35,36]. In one prospective study comparing ERCP and EUS in the diagnosis of biliary strictures, it was concluded that ERCP-based tissue acquisition may be better for biliary tumours, whereas EUS-FNA is preferable for pancreatic mass lesions [37].

Finally, we did not find any cost effectiveness study in the literature about preoperative tissue sampling for cholangiocarcinoma. Thus, other aetiologies of biliary strictures which may mimic ECC must be considered before referring the patient for surgical resection. We advocate that good knowledge of the literature and precise semiologic analysis may lead to the true diagnosis without biopsy.

Malign aetiologies mimicking ECC

1) *Carcinoma of the gallbladder.* – Although the main location of stricture is usually below the biliary confluence, this diagnosis must be considered systematically. Indeed, it is the most common cause of malignant bile duct stricture in the mid-portion of the common duct. The mechanism can be either invasion or compression. On imaging, diagnosis can be suspected on: (a) presence of an enlarged gallbladder with gallstones, (b) localized gallbladder wall thickening, or (c) invasion of the liver. Occlusion of the cystic duct at endoscopic cholangiography suggests gallbladder carcinoma [38]. Anomaly of a pancreaticobiliary duct junction is associated with gallbladder carcinoma in about one-fifth, and must be investigated [39]. Finally, patients with carcinoma of gallbladder presenting with jaundice are at particularly high risk of portal vein invasion with poor prognosis because this is not amenable to surgery [40].

2) *Lymph node metastases.* – Lymph node metastases in the porta hepatis can also cause extrahepatic biliary tree compression. Main causes of lymph node metastasis include colorectal metastases, carcinoma of the breast, lung, stomach, kidney, malignant melanoma and lymphoid neoplasm [41–43]. Clinical features and imaging can usually make the difference from ECC. Treatment is endoscopic and/or aetiologic.

Benign aetiologies mimicking ECC

Between 8% and 28% of bile duct strictures are of benign origin [4–13]. According to the literature, the following aetiologies are the most frequent.

1) *Mirizzi syndrome.* – Mirizzi syndrome is defined as a common hepatic duct obstruction caused by an impacted stone in the gallbladder neck or cystic duct. Although its incidence is very low, at about 0.7–2.5% [38,44,45], this diagnosis requires US and magnetic resonance imaging (MRI) to reveal the presence of a large stone. Local inflammatory reaction at the site of stone intrusion can be diagnosed by CT. ERCP, PTC and especially MRCP can show the extrinsic narrowing that bows the main bile duct to the left, with a stricture usually long and smooth (Figure 1) [46–48].

2) *Primary sclerosing cholangitis (PSC)* (Figure 2). – This autoimmune disorder affects periductal tissues of the biliary tree, leading to multifocal strictures of intrahepatic and extrahepatic bile duct. It is associated with ulcerative rectocolitis in up to 75% of cases. This pre-cancerous lesion can degenerate in 8% of cases [49]. Management of a patient with PSC and suspected CC is difficult. In a patient with PSC, there are roughly two difficult situations. The first is the presence of localized bile duct stricture mimicking CC. In this setting, the patient should be extensively explored for indications in favour of PSC, including: (a) long-standing non-icteric cholestasis; (b) presence of ulcerative colitis; (c) radiologic features in intrahepatic bile ducts of distant strictures; and (d) liver biopsy showing aspects of PSC [50]. The second difficult situation is a high suspicion of CC in a patient with PSC, because cholangiocarcinoma in the setting of PSC is of poor prognosis, and usually contraindicates liver transplantation (LT). The presence of ECC should be highly suspected when the patient has had major changes in clinical symptoms, including during onset of the disease. However, results of LT in selected patients with PSC associated with early CC can be favourable providing the tumour is not associated with lymph node involvement and also providing the transplant procedure is initiated by radio-chemotherapy [51]. CA19-9 is useful in this case. A value >100 U/ml has great sensibility and specificity for the diagnosis of malignant transformation [52,53]. In this situation, histological or cytological examination of the stricture by means of biopsy or brush cytology is required [54].

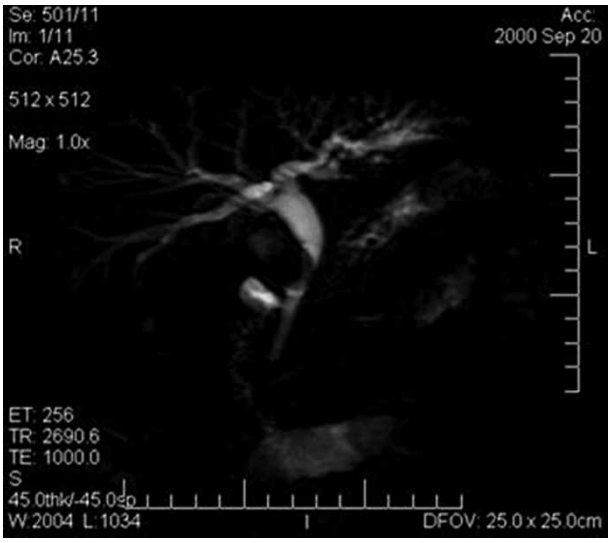

Figure 1. MRCP of mirizzi syndrome.

3) *Secondary sclerosing cholangitis (SSC).* – SSC is a disease that is morphologically similar to PSC but differs in pathological process. Among several infections that can lead to SSC and mimic ECC are:

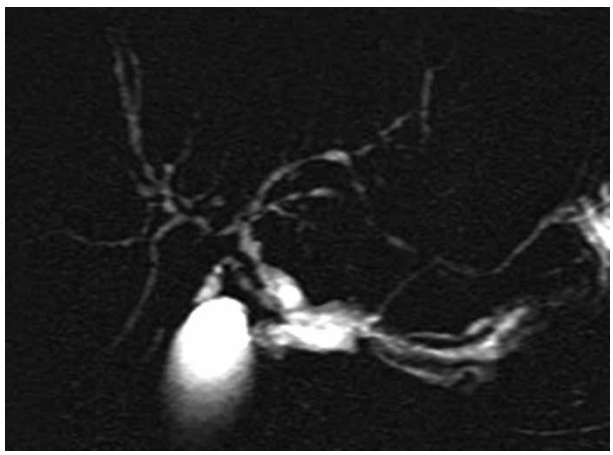

Figure 2. MRCP of primary sclerosing cholangitis.

3-1) *Inflammatory pseudotumour (IPT)*. IPT is an entity that re-groups non-malignant lesions of the extrahepatic bile duct with inflammatory components. Histopathology findings are non-specific inflammation, fibrosis, cholangitis and granulomatosis [4–13]. Aetiology remains unknown and the exact incidence of this disease is difficult to evaluate. However, between 5% and 20% of bile duct strictures are IPT, which represents almost all the benign aetiologies [4–13]. Associations with phlebitis, Crohn disease and sclerosing cholangitis have been described [55–59]. In the case of mimicking tumours of common bile duct, IPT occurs at 50 years, i.e. 10 years younger than CC occurs [9]. It develops near extrahepatic bile duct and gallbladder. CA19-9 can be normal or slightly elevated [38]. Radiological findings cannot accurately distinguish benign from malignant strictures. Indeed, 30% to 75% of IPTs show tumoral syndrome on abdominal CT or MRCP even though vascular invasion and/or encasement has never been described in IPT [6–9,12,14]. Moreover, at least one half of tumours seem to be maligns at laparotomy [6,7,14]. That's why Hadjis first called them "malignant masquerade" [8].

3-2) *Autoimmune pancreatocholangitis (lymphoplasmacytic pancreatitis with cholangitis)* (Figure 3). – Autoimmune pancreatocholangitis (AIP) is characterized by lymphoplasmacytic cellular infiltrates that may cause sclerosing inflammation of the biliary tree or pancreatic duct [60–62]. Patients present with obstructive jaundice. Imaging shows an inflammatory mass of the lower part of the bile duct and the pancreas, with enlargement of the gland [38,63]. The strictures may be long and multiple and often mimic PSC [62]. Serum IgG4 value >100 mg/ml is helpful in distinguishing AIP from malignancy [61]. In suspected cases, initial treatment with corticosteroid can be proposed [64].

3-3) *AIDS cholangiopathy* (Figure 4). – First described by Margulis in 1986, this event has become rare since the introduction of antiviral therapy [65]. Patients are generally in advanced stages of their

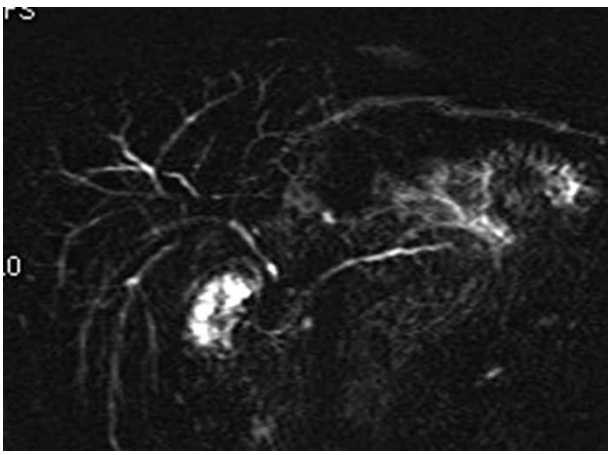

Figure 3. MRCP of autoimmune pancreatocholangitis.

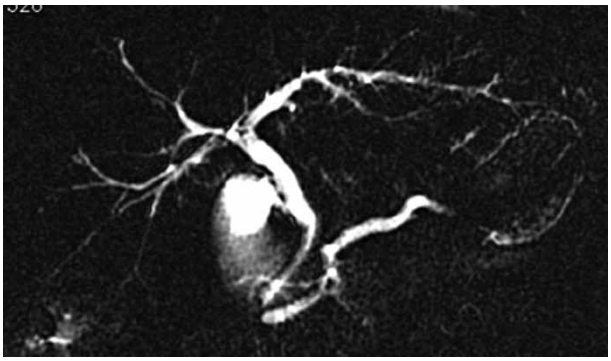

Figure 4. MRCP of AIDS cholangiopathy.

disease [66]. At MRCP or cholangiography, the entire biliary tree can be affected, but papillary stenosis with or without dilatation of the main pancreatic duct is unique in AIDS cholangiopathy and establishes the diagnosis [66].

3-4) *Other cholangitis*. – Ischaemic cholangitis, recurrent pyogenic cholangitis and mast cell cholangiopathy can result in biochemical and radiological findings such as PSC [66]. However, these aetiologies are rare, and clinical presentation often suggests non-malignant disease.

4) *Portal biliopathy* (Figure 5). – Patients presenting with bile duct stricture and portal cavernoma are usually suspected of having malignant disease. However, cavernoma can cause biliary obstruction. The mechanism is either compression by venous dilatation or ischaemia by cavernoma thrombosis [67–69]. Extrahepatic portal vein thrombosis is the most common cause of portal biliopathy, but cirrhosis, portal vein fibrosis without cirrhosis and congenital hepatic fibrosis have been reported, too [70]. Most patients have no symptoms [71–73]. Direct cholangiographic findings, including segmental upstream dilatation, calibre irregularity, stricture and extrinsic impression on the bile duct due to collaterals, have been called "pseudocholangiocarcinoma signs" [71]. However, transabdominal sonography or endoscopic sonography can reveal venous collaterals within or surrounding the extrahepatic bile duct [74]. Portal MR and MRCP show paracholedochal and/or epicholedochal dilatations, and identify portosystemic shunts and morphology of the bile duct [69,71]. Treatment by portosystemic shunt surgery allows regression of biliopathy only when the mechanism is compression [69].

5) *Adenoma and papilloma of the bile duct* (Figure 6). – This is a rare benign epithelial tumour, with only 100 cases reported in the literature [75]. The mean age of diagnosis of adenoma of the bile duct is 58 years, with a slight female predominance [76]. The radiographic features are often difficult to distinguish from cholangiocarcinoma, particularly in the intraductal growing type [77]. Most of these lesions predominate in common bile duct, especially in distal common duct and ampulla of Vater [78–80]. US

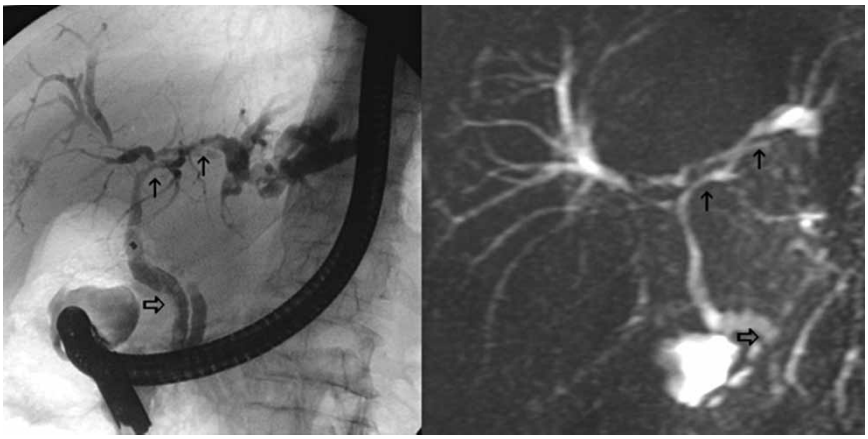

Figure 5. CPRE and MRCP of portal biliopathy.

indicates non-shadowing intraluminal mass, sometimes with a pedicle [81]. Endoscopic sonography of the bile ducts and cholangiography show complete or incomplete obstruction of the bile ducts by an endoluminal mass [80]. Treatment of this lesion is surgery. Diagnostic may be suspected intraoperatively if the tumour appears polypoid and moveable within the bile duct. Then simple local resection is sufficient.

Finally, ECC is difficult to differentiate from other aetiologies (benign or malignant). These findings suggest aggressive surgical therapy in front of suspected malignant stricture of the bile duct. Biopsy is not mandatory because of lack of sensibility and cost-effectiveness. However, we believe that a good knowledge of the literature and accurate semiological analysis can lead to diagnosis in most cases. In our experience, this approach has resulted in a dramatic decrease of mimicking tumours less than 10% (personal data). We believe that the dogma "accurate differentiation of benign and malignant hilar lesions is currently not possible outside the operating room, so resection remains the most reliable way to rule out biliary malignancy" has to be considered with great care and circumspection [9].

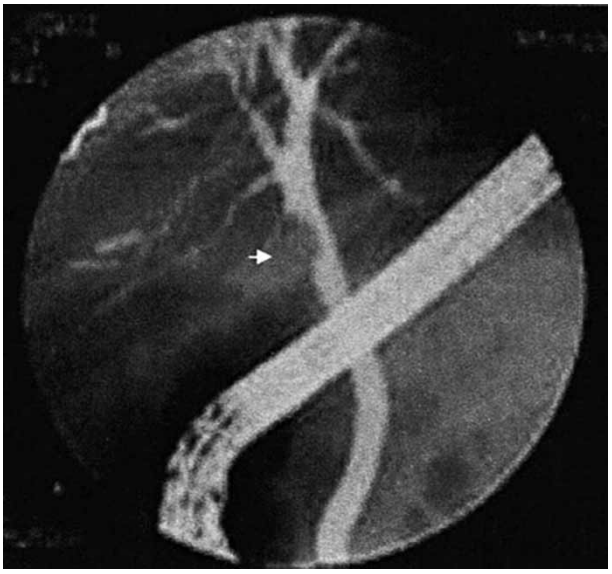

Figure 6. ERCP of bile duct adenoma.

Intrahepatic cholangiocarcinoma (ICC)

ICC is a biliary tumour developed within the liver. The incidence is tending to rise throughout the world and, in all age groups, both genders, median size as well as tumour stage remain unchanged, suggesting a real increase rather than improvement in detection rate [3]. Risk factors of ICC are PSC, hepatolithiasis, parasitic infections, chemical carcinogen exposure and viral hepatitis [3]. Symptoms as well as biochemical investigation are often non-specific [1]. Curative treatment consists in partial liver resection with lymph node dissection. Factors of poor prognosis are infiltrative type of ICC with satellite nodules and positive lymph nodes.

ICC develops in normal liver. Classically, in the mass-forming type it appears as a hypovascular tumour with fibrotic component that can induce portal compression [82]. Capsular retraction and localized dilatation of peritumoral bile ducts are frequent. ICC is often associated with lymph node metastases.

ICC can be confused with fibrous metastases of carcinomas such as breast cancer and colorectal cancer [82]. These tumours develop within normal liver like ICC, with similar age of incidence. Absence of the possible primary site, a relatively large tumour size and ancillary findings such as bile duct dilatation can be clues in differentiating mass-forming cholangiocarcinomas from metastases. If not, we advocate two approaches: 1) Biopsy of the lesion has not yet been performed: clinical examination, colonoscopy and mammography are useful, first to eliminate a primary related to liver metastases, and second because patients of 50 years of age or more are usually candidates for screening for these two diseases [83]. If these examinations are negative, we retain the diagnosis of ICC and perform liver resection with lymph node dissection. 2) Biopsy has been realized

but is non-conclusive: the lesion is a metastasis of adenocarcinoma from unknown primary (ACUP). Thirty per cent of metastases from ACUP are within the liver [84]. Prognosis is very poor, with a median survival between 6 and 12 months [85–87]. Even chemotherapy cannot improve survival significantly [85,87,88]. Surgery has never been evaluated in ACUP because of often advanced disease with metastases at other sites. However, when resections have been made, no further study has found a poorer prognosis than chemotherapy [87,89,90]. Therefore, in the case of a unique lesion with no extrahepatic disease, we advocate local resection with lymph node dissection because: (a) survival is not different from chemotherapy [89], (b) postoperative morbidity is low in liver resections, (c) histological and molecular analysis of the entire lesion can lead to the final diagnosis and permits accurate adjuvant therapy [91], and (d) in case atypical ICC treatment is complete.

In our opinion, ACUP has become a rare event. The incidence of ICC has been increasing for several decades, whereas the incidence of ACUP has been decreasing simultaneously. Some authors have postulated that a rise in incidence rate of ICC is a true increase because there are no significant changes in the staging and size of tumour at diagnosis [2]. However, the reason for this increase remains unknown [92]. We therefore believe that many ACUPs in past decades were ICC misdiagnosed. The rise in incidence of ICC is in fact due to improvement of diagnostic tools that help towards the correct diagnosis in most cases.

For this reason, all intrahepatic fibrous tumours with no evidence of primary tumour site must be considered as ICC. Biopsy is not mandatory, and surgical therapy with segmental liver resection and lymph node dissection must be performed.

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