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ORIGINAL PAPER

Mucin-producing hepatic cystic neoplasms: an uncommon but challenging disease often misdiagnosed and mismanaged

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ABSTRACT

Background: Mucin-producing hepatic cystic neoplasms (MHCN) are uncommon and potentially malignant.

Methods: Nine MHCN were encountered in our centre for over 32 years. Patients' clinical, biological, radiological and pathological features were reviewed. Lesions were classified into Mucinous Cystic Neoplasms (MCN) and Intraductal Papillary Neoplasms of the Bile duct (IPNB) (WHO 2010 classification).

Results: Five MCN and 4 IPNB were reviewed. Serum and intracystic tumour markers were insufficient to diagnose malignancy. Complications were encountered in five out of nine patients (56%), mean symptom duration was 26 months (range: 1–132). Three patients were mismanaged pre-referral. Radiological features enabled preoperative diagnosis in eight out of nine patients (89%). Greater tumour size, unilocular lesion and mural nodularity indicated malignancy. Radical tumour excision was achieved in eight patients. One IPNB patient was misdiagnosed and underwent unroofing. For 103 months median follow-up, five out of six patients with benign tumours were alive and disease-free, whereas the misdiagnosed IPNB recurred with fatal malignant transformation seven years later. Among the three patients with malignancies (median follow-up: 77 months), two IPNB died, one from cancer recurrence and one from unrelated causes, whereas the malignant MCN was alive and disease-free.

Conclusions: Appropriate MHCN diagnosis is crucial, yet it is often misdiagnosed and mismanaged. The prognosis after complete excision is favourable

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Liver surgery; cystic tumour; mucinous cystic neoplasm; intraductal papillary neoplasm of the bile duct

Introduction

Mucin-producing hepatic cystic neoplasms (MHCN), initially described by Craig et al. and called hepatobiliary cystadenomas or cystadenocarcinomas (World Health Organization (WHO) 2000 [1,2]), were reclassified in 2010 (WHO) according to presence/absence of ovarian-like stroma into either mucinous cystic neoplasm (MCN) or intraductal papillary neoplasm of the bile duct (IPNB), the latter being correlated to worse prognosis [3]. These uncommon slow-growing cystic tumours account for less than 5% of all symptomatic cystic lesions of the liver [4,5]. Progress in imaging techniques and better clinical awareness enable them to be increasingly diagnosed [6,7]. However, the accurate distinction between MHCN and other hepatic cystic lesions such as parasitic or congenital liver cysts (CLC) may still be difficult [5,8]. Imaging cannot accurately distinguish between benign and malignant MHCN and since benign lesions carry a potential for malignant transformation, complete surgical resection is mandatory in any case [8–10].

The present study aimed to evaluate our centre's experience with such rare lesions, paying attention to adequate differential diagnosis from other hepatic cystic lesions, pathological classification and long-term results after surgical resection.

Patients and methods

Patients

Patients with MHCN were identified from the institutional pathology database. Over a 32-year period

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from July 1984 to June 2016, a total of nine patients were operated in our centre, some were previously reported [11–14].

Preoperative assessment

Preoperative tumour work-up routinely included biological tests, serum and intracystic tumour markers (CarcinoEmbryonic Antigen (CEA) and Carbohydrate Antigen 19-9 (CA 19-9)), imaging studies including Ultrasound (US), computed tomography (CT) and/or magnetic resonance imaging (MRI). Fluorodeoxyglucose (FDG) positron emission tomography (PET) scan was used only in four patients. Diagnostic criteria on imaging included the presence of a generally solitary, well-defined, multiloculated cystic lesion with vascularized internal septae containing mucinous fluid, hyperintense on T2 and hypo or hyperintense on T1 weighted images [7,15–17]. Mural nodules or intracystic projections were considered strongly suggestive of invasive neoplasms. Intrahepatic tumour extent was reported according to Couinaud's classification [18].

Surgical procedure

Surgery aimed for intended complete tumour excision, whether by standard hepatectomy or tumour enucleation for presumed noninvasive lesions, bilobar liver involvement or coexistent liver cirrhosis. Frozen section analysis was realized in six patients. The intracystic liquid aspiration for tumour markers and cytology and cholangiography plus methylene blue test at the end of the procedure were performed in all but one patient, to confirm biliary tree integrity and exclude biliary leakage. The final diagnosis was based on the complete surgical specimen's pathological analysis.

Pathological analysis

Liver specimens were fixed in 5% buffered formalin then paraffin embedded. Consecutive 4–5-mm-thick sections were stained with haematoxylin and eosin. Ovarian-like stroma (OLS) was confirmed by immunohistochemical staining using oestrogen receptors. Previously labelled hepatic cystadenomas and cystadenocarcinomas (2000 WHO), these lesions were reclassified according to WHO's 2010 WHO classification [1,3]. Pathology-based MCN-diagnosis depended on finding a cyst-forming epithelial neoplasm composed of mucin-producing epithelium with OLS. Diagnosis of IPNB was founded on observing papillary proliferations of neoplastic biliary epithelial cells with delicate fibrovascular stalks within bile ducts, microscopic or macroscopic presence of mucin, and variable dilatation or multilocular cystic changes in affected bile ducts. A cyst-forming epithelial neoplasm composed of mucin-producing epithelium without OLS was also diagnosed as cyst-forming IPNB (Table 1).

Postoperative follow-up

Postoperative complications were assessed according to DINDO-CLAVIEN classification [19]. Long-term follow-up included 6-monthly clinical assessment, blood samples, hepatic MRI or abdominal CT during the first year, then annually.

Table 1. Pathological features of mucin-producing hepatic cystic neoplasms (MHCN) according to 2010 WHO classification.

	MHCN: mucin-producing hepatic cystic neoplasm	
Definition	Cyst-forming epithelial neoplasm	
ICD-O codes	8470	
Macroscopy	Multilocular Watery, haemorrhagic or mucinous content No direct communications with larger bile ducts Invasive: papillary mass, solid thickened wall	
Spreading	Slow growing Secondary malignant transformation within the primary lesion Rarely secondary liver lesions or positive lymph nodes	
Histopathology	MCN: mucinous cystic neoplasm	IPNB: intraductal papillary neoplasm of the bile duct
	Extensive sampling mandatory	Extensive sampling mandatory
	Columnar, cuboidal or flattened mucus-secreting epithelial cells on a basement membrane	Papillary proliferation of neoplastic biliary epithelial cells
	Ovarian-like mesenchymal stroma	Mucin
	Polypoid or papillary projection may be presents	No ovarian-like stroma Communication with bile ducts
FNA	Poor sensitivity Clusters of cuboidal to columnar cells	

Statistics

Differences between two groups were analyzed using Mann–Whitney's *U*-test. For categorical variables, we used Nurminen and Mutanen's exact Bayesian analysis of two proportions, convenient for very small samples [20]. The Kaplan–Meier method was used to estimate overall survival. For all tests, a two-sided p value $\leq .05$ was considered significant.

Ethical approval

The ethics committee approved the study.

Results

Patients

Patients' data are outlined in Table 2. The nine patients' tumours, previously classified as six cystadenomas and three cystadenocarcinomas, were, respectively, reclassified into four MCN plus two IPNB, and one MCN plus two IPNB according to WHO's 2010 classification. Although IPNB and malignant tumour patients were older than patients with MCN or benign tumours (median age IPNB vs. MCN: 71.5 vs. 34.0 years, malignant vs. benign tumours 71.0 vs. 34.0 years, respectively), the difference was not statistically significant for either subgroup. All MCN patients were female (5/5) compared with IPNB (1/4, $p < .031$).

Clinical presentation

All patients were symptomatic except one (incidental cystadenoma discovered during a laparoscopic appendectomy, patient 1, Table 2). Five patients presented with complications (5/9, 62.5%). Complications were biliary (2 biliary thrombi, one with jaundice from bile duct compression), paraneoplastic (1: fever and chills) and inferior vena cava (IVC) compression syndrome due to large tumour size, with bilateral lower limb oedema (2 patients). Among the latter, one also had a biliary thrombus, whereas the other suffered concurrent left common iliac vein thrombosis and pulmonary embolism, then intra-cystic haemorrhage secondary to intravenous heparin. Median disease duration before diagnosis was 6 months (mean 26, range 1–132 months), with no significant difference between benign and malignant MHCN. Interestingly, one invasive lesion had been present for 11 years (case 9) [14].

Table 2. Preoperative patient and tumour characteristics.

N	Age	Sex	Size (cm)	Liver segments[a] involved	Previous treatment	Duration of disease (months)	Symptoms	Complications	Biliary communication	Final diagnosis
1	25	M	7	II–III–IV	None	5	None	–	no	IPNB-B
2	30	F	5	IV	Unroofing	22	Pain	Biliary thrombus LHD	Thrombus	MCN-B
3	72	F	9	V	Aspiration + alcohol injection	40	Pain	Jaundice (compression)	Bile into the cyst	IPNB-B
4	34	F	15	V–VI–VII	None	2	Pain	–	no	MCN-B
5	72	F	9	VIII	None	1	Pain	–	Bile into the cyst	MCN-B
6	30	F	18	II–III–IV	Aspiration + alcohol injection + unroofing	20	Pain	–	no	MCN-B
7	59	F	26	III–IV–V	None	5	Pain	LLO (IVCS), DVT and pulmonary embolism	no	MCN-M
8	71	M	15	II–III–IV	None	6	Pain	Fever, chills	Extravasation at IOC	IPNB-M
9	74	M	30	II–III–IV–V–VI–VII–VIII	None	132	Pain	LLO (IVCS), biliary thrombus LHD	Thrombus	IPNB-M

[a]According to the Couinaud classification.
IPNB: intraductal papillary neoplasm of the bile duct; MCN: mucinous cystic neoplasm of the liver; B: benign; M: malignant; LLO: lower limb oedema; IVCS: inferior vena cava syndrome; DVT: deep venous thrombosis; LHD: left hepatic duct; IOC: intraoperative cholangiography before resection.

Previous interventions

Three MHCN patients (50% benign lesions, Table 2: patients 2, 3 and 6) were mismanaged prior to referral to our centre (7, 14 and 22 months earlier, respectively). Despite typical MHCN imaging for two out of three patients, they were misdiagnosed as CLC and had undergone cyst aspiration, alcohol injection or unroofing surgical procedures followed by cyst recurrence.

Preoperative assessment

Serum and intracystic tumour markers, radiological features and accuracy of preoperative diagnosis are reported in Table 3. None of the biological tests enabled either MHCN prediction or differentiation between benign and malignant lesions. Liver function tests were normal in six out of nine patients, only three out of nine had mildly elevated serum gamma-glutamyl-transferase (1 benign (patient 4), 2 malignant (patients 8–9)). Serum and intracystic CEA and CA19-9 were not discriminant for either benign or malignant MHCN.

There was no preferred location for either MCN or IPNB, half of which were equally located in left or right hemiliver. The average maximal MCN/IPNB diameter was not significantly different but was significantly increased in malignant lesions compared to benign ones (median 26 vs. 9 cm, respectively, $p < .048$). The presence of vascularized septae, calcifications and intracystic projections were diagnostic though not significantly different in benign and malignant lesions. Unilocular lesions and mural nodules were significantly more frequent in invasive MHCN (invasive vs. noninvasive lesions: $p < .031$ and $p = .049$, respectively). PET-CT diagnosis was falsely negative for one malignant MCN with only limited focal invasion, which turned out to be high-grade dysplasia. Based on preoperative imaging studies, the diagnosis was thus accurate in five out of six benign lesions (83%) and two out of three malignant lesions (66%). In addition to the malignant case described above, one low-grade unilocular IPNB, atypical on imaging (case 3), was misdiagnosed as CLC.

Surgical treatment

Biliary communications (bile within the cyst), intracystic extravasation at cholangiography, or presence of biliary thrombus, were identified

Table 3. Serum and intracystic tumour markers, radiological features and preoperative diagnosis.

			Tumour markers (ng/ml)				Imaging features						
N	Preop- diagnosis	Final diagnosis	Serum CEA	Serum CA 19.9	Intra-cystic CEA	Intra-cystic CA 19-9	Multi-loculated	Septae	Vascula-rized septae	Calcification	Intracystic projections	Mural nodules	PET-CT
1	HCN	IPNB low-grade	3.2	6.9	ND	ND	Yes	Yes	Yes	Yes	No	No	(–)
2	HCN	MCN low-grade	2.5	12.9	ND	ND	Yes	Yes	Yes	No	No	No	(–)
3	CLC	IPNB low- grade	2.2	10.1	26.4	>240	No	No	No	No	No	No	ND
4	HCN	MCN low-grade	1.3	17.7	25.6	5,554,000	Yes	Yes	Yes	No	Yes	No	ND
5	HCN	MCN low-grade	1.4	2700	78.0	24,000	Yes	Yes	No	Yes	No	No	ND
6	HCN	MCN low-grade	0.7	1314	ND	ND	Yes	Yes	No	No	No	No	ND
7	HCN	MCN high-grade + focally invasive	1.3	295.3	55.2	2,049,000	No	Yes	Yes	Yes	No	No	(–)
8	Malignant HCN	IPNB invasive	11.0	4.9	ND	ND	No	Yes	Yes	No	Yes	Yes	(+)
9	Malignant HCN	IPNB invasive	3.9	13.0	3.9	34.5	No	No	ND	No	Yes	Yes	ND

HCN: hepatic cystic neoplasm; CLC: congenital liver cyst; IPNB: intraductal papillary neoplasm of the bile duct; MCN: mucinous cystic neoplasm of the liver; ND: not done.

peroperatively in three out of four IPNB patients (75%) and two out of five MCN patients (40%), the difference was not significant.

Surgical procedures were as follows (Table 4): anatomical resection of two benign and two invasive MHCN (cases 1, 2, 8, 9), enucleation of three benign MHCN (cases 4, 5, 6; case 5 had coexistent cryptogenic liver cirrhosis) and of one large bilobar malignant MHCN (case 7). The latter was presumed benign MHCN but high-grade dysplasia (HGD) with focal invasion was detected on final pathology, resulting in retrospective radical R0 resection. Finally, case 3, a unilocular atypical cystic lesion, underwent the unroofing procedure. Bile – within a macroscopically normal-looking cyst – was thought to stem from previous percutaneous cyst aspirations and alcohol sclerotherapy performed elsewhere. The laparoscopic procedure was converted to open surgery for closure of the biliary fistula.

Pathological analysis

Peroperative cytology identified two patients with invasive IPNB, whereas the patient suffering from MCN with HGD and focal invasion had false negative cytology. Frozen section analysis concluded to correct definitive diagnosis in five out of six (3 benign, 2 invasive). One low-grade MCN was falsely diagnosed as CLC (patient 5). It was completely resected as peroperative ultrasound was highly suggestive of MHCN (presence of septations). No frozen section analysis was done for patient 3. Final pathological analysis reclassified the nine patients into five MCN with OLS (4 low-grade, 1 high-grade with focal invasion) and four IPNB without OLS (2 low-grade, 2 invasive). Importantly, all IPNB showed cystic formation macroscopically. Radical resection was achieved in all patients. Final pathological examination of the unroofed cystic wall of misdiagnosed/mismanaged patient 3 showed denudated epithelium, leading to a false CLC diagnosis. Obvious malignant clinical evolution seven years later led to a revised pathological diagnosis of initially benign IPNB.

Postoperative course

Immediate and late postoperative course (Table 4) was complicated in five out of nine patients (56%). Their complications were graded as Dindo–Clavien type II (2 patients) and type IIIa (3 patients), none required surgical reoperation. Biliary complications were more frequent (though not significantly so) after enucleation procedures (3/4 patients) than

Table 4. Pathology, details of surgical procedures and postoperative outcome.

N	Presence of ovarian stroma	WHO 2000 pathological diagnosis	WHO 2010 pathological diagnosis	Cyst fluid analysis	Procedure	Short-term complications	Follow-up (FU) (months)	Final status at FU
1	No	Cystadenoma	IPNB LG	NA	LH	None	151	A&W
2	Yes	Cystadenoma	MCN LG	NA	LH	None	124	A&W
3	No	Cystadenoma	IPNB LG	NC	Unroofing	Pneumothorax	82	DOD
4	Yes	Cystadenoma	MCN LG	NC	Enucleation	Biloma	74	A&W
5	Yes	Cystadenoma	MCN LG	NC	Enucleation	None	281	A&W
6	Yes	Cystadenoma	MCN LG	NC	Enucleation	Biloma	6	A&W
7	Yes	Cystadenocarcinoma	MCN HG + focal invasion	NC	Enucleation	Liver abscess 5 months later	77	A&W
8	No	Cystadenocarcinoma	IPNB invasive	C	LH	None	12	DOD
9	No	Cystadenocarcinoma	IPNB HG + invasive	C	Extended LH	Biloma	202	DOC

IPNB: intraductal papillary neoplasm of the bile duct; MCN: mucinous cystic neoplasm of the liver; LG: low grade; HG: high grade; NA: not available; NC: not contributive; C: contributive; LH: left hepatectomy; A&W: alive and well with no evidence of disease; DOD: died of disease; DOC: died of other causes.

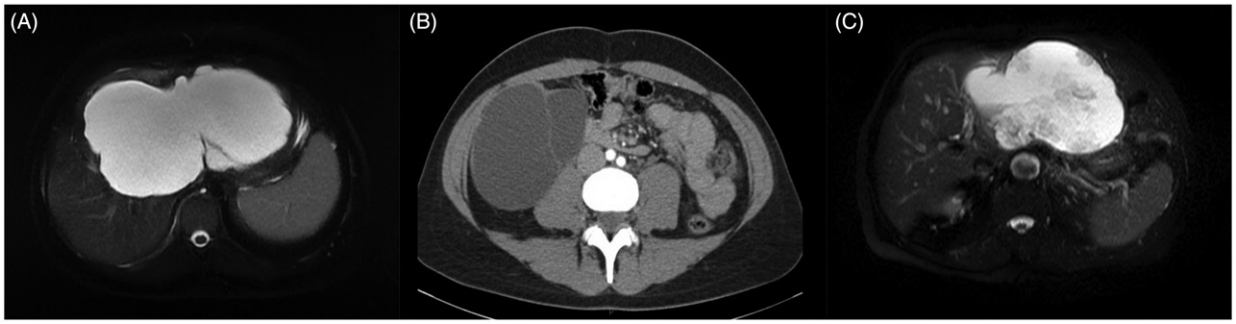


Figure 1. Representative computed tomography (CT) and magnetic resonance imaging findings. (A) patient 6, MRI T2 fat-sat, 18 cm benign MCN, demonstrating thin septae and homogenous content. (B) patient 4, contrast-enhanced CT, 9 cm benign MCN, demonstrating thin septae and homogenous content. (C) patient 8, MRI T2 fat-sat, 15 cm malignant IPNB, demonstrating mural nodule, heterogenous content and papillary projections.

after formal hepatectomy (1/4), despite using methylene blue tests during surgery.

Long-term follow-up

All benign MHCN patients treated by resection (4 MCN, 1 IPNB) were alive without recurrence after a median postoperative follow-up of 104 months (range: 6–281 months). Misdiagnosed/Mismanaged case 3 was lost to follow-up for seven years then readmitted at our centre with peritoneal carcinomatosis. The patient refused further treatment and died soon after admission. One of two malignant IPNB died from disease progression (patient 8: 12 months postoperatively). One died from other cause (patient 9). Finally, focally invasive MCN (patient 7) was alive and without evidence of disease, 77 months postoperatively. Overall survival rates were 87.5% ± 11.7% at 1 year, 70.0% ± 18.2% at 5 years.

Discussion

This 32-year series of surgical management of rarely encountered MHCN at Cliniques universitaires Saint-Luc, Brussels, showed firstly that adequate diagnosis is not always easy, potentially leading to fatal mismanagement. Secondly, preoperative diagnosis of malignancy is almost impossible, particularly in cases of micro-invasion or in situ carcinoma. Thirdly, a complete cure is possible in most patients by radical surgical excision.

These nine cases had been classically described as biliary cystadenomas and cystadenocarcinomas, and divided into mucinous or serous according to presence or absence of ovarian-like mesenchymal stroma [1]. For our study's purpose, all nine MHCN cases were retrospectively reclassified (WHO, 2010) into Mucinous Cystic Neoplasms (MCN, with ovarian-like stroma, European mostly, almost exclusively women) and Intraductal Papillary Neoplasms of the Bile ducts (IPNB, communicating with bile ducts, mostly Asian, often men) [21,22]. All our MCN patients were indeed female, however, so was 1/4 IPNB. Surprisingly, biliary tract communications were demonstrated in 40% MCN and 75% IPNB patients.

Autopsy series report a 14% CLC occurrence rate in the general population, but MHCN are far less frequent [23]. Accordingly, only nine MHCN patients were treated surgically at our centre over a 32-year period.

Adequate MHCN diagnosis is mandatory as it carries a significant risk of malignant transformation, observed initially or during evolution after incomplete tumour excision. The only curative treatment modality is, therefore, complete resection. This differs from CLC, where treatment varies from percutaneous sclerotherapy to laparoscopic fenestration [24,25]. MHCN diagnosis is a real challenge, as shown by numbers of reported misdiagnosed lesions, mismanaged by cyst aspiration or unroofing procedures, i.e. 42–55% patients [26–29]. Similarly, four out of nine of our patients (44%) underwent erroneous treatment for presumed CLC, leading sometimes to unresectable malignancy at reoperation [30–33]. To help surgical decisions, the reliability of frozen section analysis is still debated [8]. Many authors report misdiagnosed MHCN for CLC based on frozen section leading to secondary surgery after definitive pathological analysis or early recurrence [28,31,34]. In contrast, Gigot et al. reported two cases of suspect frozen sections during laparoscopic fenestration leading to complete resection while final pathological analysis concluded to complicated cyst [25].

Hepatic cystic lesion diagnosis is influenced by patient's history (trauma, surgery, malignancy, infection, pancreatitis, etc.), clinical symptoms,

serum hydatid serology, serum and intracystic tumour markers, cytology and radiology. Differential diagnosis includes CLC, hydatid cysts, amebic abscess, pyogenic abscess, mucinous cystic neoplasm, Caroli's disease, cystic hepatocarcinoma, cystic metastases, embryonal sarcoma, cavernous hemangioma, melanoma, bilioma, hematoma, posttraumatic cysts, polycystic diseases, biliary hamartomas and teratoma [5,7,8,29,35].

Abdominal pain is the most common presenting symptom of hepatic lesions. However, regarding CLC, only 10–16% will become symptomatic and/or complicated by bleeding, surinfection or spontaneous rupture [24,25]. Obstructive cholestasis may be encountered in large compressive central CLC, in intrabiliary migration of hydatid sand or daughter vesicles, or in MHCN with tumoral biliary thrombus, encountered twice in our series [4,36–40]. Large tumour volume can also cause IVC obstruction, as in two of our patients. Clinical presentation is thus nonspecific, unable to guide towards a correct diagnosis.

Serum tumour markers such as CEA and CA 19-9 have both been reported normal or elevated in MHCN [7,10,11,13,26,32]. In our series, only three out of nine patients presented elevated CA 19-9 serum level. Furthermore, elevated serum CA 19-9 was also reported in simple or haemorrhagic CLC [41,42]. Serum tumour markers cannot, therefore, be used as diagnostic tools for MHCN. Cystic fluid analysis, helpful in MHCN diagnosis, cannot discriminate benign and malignant MHCN. Our series' intracystic tumour markers were indeed mostly elevated, irrespective of malignancy [5,43,44]. However, high intracystic CA 19-9 is also described in CLC and polycystic liver diseases [45–47]. Thus, nor CEA neither CA19-9 can help discriminate MHCN from other hepatic cystic lesions. Interestingly, Fuks et al. reported tumour-associated glycoprotein (TAG) 72 as a marker with high sensitivity and high specificity for the diagnosis of mucinous cysts as it is not expressed by normal biliary cells as opposed to CA19-9 and CEA. Percutaneous measurement of TAG 72 is reported to be useful for preoperative diagnostic of MHCN [48]. False negatives of fine needle aspiration (FNA) cytology are frequent, FNA's sensitivity for diagnosing malignant MHCN is reportedly 66% [7,29,49,50]. However, FNA could lead to needle tract dissemination or peritoneal carcinomatosis [51] and is therefore not usually recommended [7,32].

Radiology is the cornerstone for differential diagnosis between hepatic cystic lesions, with reported sensitivity and specificity of 81% and 21%, respectively [6]. It enabled 89% preoperative MHCN and two out of three malignancy diagnoses in our series [7]. Typical MHCN imaging features include smooth-walled low-density cystic structures, with internal septations and calcifications, mural nodules and/or intracystic papillary projections in malignancy [5,15–17,26]. Intracystic septations were identified in seven out of nine in our series. However, septae can be present in CLC also [45]. Thomas et al. considered septations were not pathognomonic of MHCN but suggested their vascularization was more relevant [26]. In our series, enhanced septae were identified in only 55% MHCN. Finally, CLC usually lack nodularity and septations but can mimic MHCN when complicated by infection or haemorrhage [13,25,49,52]. Uniloculated MHCNs are uncommon [15,21,53,54]. However, this led to misdiagnosing one of our patients [15].

Ultrasound is the more powerful imaging method for detecting septations and calcifications that can be missed on CT or MRI [6,15,35]. Contrast-enhanced CT scan can demonstrate vascularized septae, wall enhancement and mural nodules and is better than ultrasound in demonstrating the extent of the lesion [8]. Contrast-enhanced MRI is helpful to analyse the lesion's relationship with the biliary tree and hepatic vessels. MRI is also powerful to define the character of the lesion thanks to increased contrast resolution compared to CT [55]. MRCP is useful to show the communication with the bile ducts even upstream to an obstruction [5,16,43,56]. The cyst can demonstrate variable MRI signal due to variable composition (serous, mucinous, bilious, hemorrhagic fluid) [57]. Imaging modalities are all mutually complementary in the evaluation of MHCN [28,29,56]. Wang et al. recommend using both US and CT for preoperative evaluation as they show in their study that only a small number of specific features were detected by both modalities [10]. Contrast-enhanced ultrasound (CEUS) was not used in our centre for this series. It is a quite novel technique that provides information on the enhancement pattern of a lesion and helps characterize it. Its advantages are that it lacks ionizing radiations, is portable and can be used in renal failure patients [58]. In malignant MHCN, hyperenhancement of the septa during the arterial phase and hypoenhancement during the portal venous phase is characteristic [59].

Diagnosing malignancy radiologically is also a real challenge. Indeed, malignant changes may be observed in benign MHCN, thus supporting that malignant MCHN can arise from benign lesions over time [54,60–63]. Craig et al. reported malignant transformations in 25% benign MHCN [2]. Accordingly, the detailed pathological examination of the whole resected cyst wall is mandatory for the definitive diagnosis of benignity [9,32]. Peroperative frozen section examination of cystic walls does not fulfil this requirement [32]. Similarly, malignant recurrence of an initially benign MHCN has been reported, as encountered in one of our patients [64]. It is thus almost impossible to predict a microinvasive MHCN. There are, however, several clinical features in favour of invasive MHCN: older patients' age, male gender, shorter symptom duration, tumour size and right hemiliver tumour location [6,7,10,32,60]. Radiologically, mural nodules and nodular septa with thick, irregular walls with strong contrast enhancement are in favour of malignant MHCN, whereas thinner septae and regular walls are in favour of benign MHCN [5–7,15–17,26,55,57]. In line with others, our series found unilocularity ($p < .031$), greater cystic lesions ($p < .05$) and mural nodules ($p < .049$) to be significantly more frequent in invasive MHCN.

On suspicion of MHCN, treatment of choice is total tumour excision, in view of its premalignant nature and difficulties in differentiating benignity from malignancy preoperatively [8,16,28,31,63,65,66]. Indeed, partial resection or local treatment are associated to almost constant disease persistence or recurrence [6,7,9,26,27,29,43,50,54,60]. In addition, disease recurrence may take several years, as demonstrated by the 7-years lapse before malignant recurrence in our misdiagnosed MHCN patient.

Anatomical parenchymal resection or enucleation (4/9 in present series), can be safely performed with low postoperative morbidity. Complete enucleation is indicated in centrally located lesions, bilateral tumour extension, close contact with major vascular or biliary trunk, or underlying liver cirrhosis, as selectively used in the present series [32,56]. Both procedures achieve effective long-term outcomes, with 5-year overall survival rates of 60–84% in whole MHCN, 92–100% in benign and 57–74% in malignant MHCN [6,9,32,56,60]. Similarly, our series' overall survival rates were 87.5% at 1 year and 70% at 5 years. Laparoscopy could be used in selected patients [29,56]. Finally, IPNBs are reportedly more aggressive than MCNs, particularly in men, and carry a worse prognosis [6,56,63]. Indeed, ZEN reported malignancies in only 10% MCNs versus 100% IPNBs [21], and the three disease fatalities in our series were similarly IPNB.

Conclusions

Accurate differential diagnosis of MHCN from other hepatic cystic lesions is not easy. Ultrasound of a liver lesion demonstrating septations, calcifications, irregular walls or intracystic nodules should prompt further evaluation (CT, MRI, CEUS). Serum tumour markers are not helpful in the diagnosis. FNA is not recommended but, if performed, intracystic TAG-72 measurement is of high sensitivity for MHCN. Misdiagnosis and mismanagement can be fatal. As benign MHCN can become malignant, initial complete resection, which carries a favourable prognosis, is the treatment of choice.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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