Chapter 6

Mucinous Cystic Neoplasms of the Liver and Extrahepatic Biliary Tract

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Abstract

Mucinous cystic neoplasms of the liver and extrahepatic biliary tree have recently been re-defined by WHO as epithelial cystic tumours with ovarian-type mesenchymal stroma. Correct recognition of these tumours can be difficult because of their rarity and, consequently, lack of awareness by the medical team. Radiological evaluation, including ultrasonography, computed tomography, magnetic resonance imaging and, upon necessity, positron emission tomography, can yield the correct diagnosis. Radical surgical resection with tumour-free margins is the mainstay of treatment. Adequate treatment approach can be very rewarding, bringing prolonged survival. Here we discuss the up-to-date concepts of definition and classification, theoretical views on tumour origin along with practical issues of clinical presentation, diagnostics, treatment and prognosis.

Keywords: mucinous cystic neoplasm, liver, liver tumour, biliary cystadenoma, biliary cystadenocarcinoma

1. Introduction

Mucinous cystic neoplasms of the liver [1], formerly known as bile duct/biliary cystadenoma and biliary cystadenocarcinoma [2], represent an enigmatic entity, characterised by unknown origin and peculiar morphology including the presence of ovarian-type stroma. Clinically, these tumours are important albeit rare. Mucinous cystic neoplasms of the liver can be diagnostically challenging because of several reasons, including (1) prolonged clinical course suggesting a benign disease or even harmless liver cyst; (2) controversial radiologic presentation;

and (3) insufficient experience of the involved medical team. Consequently, it might be difficult to select the best treatment. Lack of awareness of these unusual tumours is an important cause of diagnostic and surgical mistakes. To enhance the knowledge of medical society on the mucinous cystic neoplasms of the liver, here we aim to summarise contemporary data on these tumours, including the current definition and classification [1], the recent molecular genetic findings [3, 4] as well as the practical issues of clinical presentation, diagnostic approach, treatment and prognosis.

2. Definition and evolution of the concept

Currently, mucinous cystic neoplasms of the liver are defined as epithelial cystic tumours associated with ovarian-type mesenchymal stroma. They are further subclassified by (1) presence or absence of invasion and (2) in non-invasive tumours—by the highest grade of epithelial atypia [1]. Thus, four entities are obtained (**Table 1**). Although intrahepatic location predominates, mucinous cystic neoplasms with true ovarian-type stroma can primarily develop in extrahepatic biliary ways [5, 6] or show extrahepatic extension [7].

The previous classification by WHO (2000) included bile duct cystadenoma/cystadenocarcinoma, defined as cystic tumours, that were lined by mucus-secreting or, less frequently, serous epithelium [2]. Stroma was not set as a diagnostic criterion.

Considering the current WHO definition [1] in the context of preceding classifications and morphology, three aspects must be kept in mind.

2.1. Diagnostic importance of the ovarian-type stroma

Mucinous cystic neoplasms of the liver were formerly referred to as bile duct/biliary cystadenoma and cystadenocarcinoma. However, the presence of ovarian-type stroma was not mandatory in the preceding entities. It was present in the mucinous type of benign cystadenomas, but was absent from the serous type of biliary cystadenomas [2] as well as from a subfraction of cystadenocarcinomas [8]. In contrast, currently only tumours with ovarian-type subepithelial stroma are classified as mucinous cystic neoplasms [1]. The cases lacking the specific stroma could represent intraductal papillary neoplasms of bile ducts with marked

Biologic potential	Diagnosis	ICD-O code
Non-invasive mucinous cystic neoplasms of the liver	Mucinous cystic neoplasm with low-grade intraepithelial neoplasia	8470/0
	Mucinous cystic neoplasm with intermediate-grade intraepithelial neoplasia	8470/0
	Mucinous cystic neoplasm with high-grade intraepithelial neoplasia	8470/2
Mucinous cystic neoplasms of the liver with an invasive component	Mucinous cystic neoplasm with an associated invasive carcinoma	8470/3

Table 1. Classification of the mucinous cystic neoplasms of the liver [1].

cystic changes [1]. The rearrangement of classification is in accordance with the previously well-known observation that biliary cystadenocarcinoma without ovarian-type stroma has distinctly worse prognosis [8–10] (it must be noted that contrary and neutral reports also have been published: see [11, 12], respectively) and is more frequently observed in males [8, 11].

2.2. Extent of mucus secretion

The neoplastic epithelium in fact may lack mucus production [1, 4]. Still, neoplasms showing ovarian-type stroma are not classified as serous cystadenomas [1].

2.3. Criteria to identify malignant cases

In the current classification, invasive and non-invasive tumours are clearly separated. In contrast, the preceding diagnostic criteria of biliary cystadenocarcinoma included invasion, cellular atypia, and mitotic activity to recognise a malignancy. Although invasion was underlined as the hallmark of malignant course, presence of cell atypia and mitoses also justified the diagnosis of carcinoma [2]. Currently, non-invasive cases showing anaplastic cell morphology would be classified as mucinous cystic neoplasms with high-grade intraepithelial neoplasia [1].

Unfortunately, terminological controversies and disagreements still remain. Although the current WHO classification redefined mucinous cystic neoplasms already on 2010, the preceding terms of biliary cystadenoma and cystadenocarcinoma are still in use [5, 13–15]. Ovarian-type stroma has been neglected as a diagnostic criterion, e.g., in a recent (2015) multicentric study only 33.3% of the evaluated biliary cystic tumours actually had this feature [11]. Some research teams have expressed disagreement with the present classification [5]. There are repeated discussions on cases lacking both ovarian-type stroma and communication with biliary ducts—a separate entity has been hypothesised [16].

3. Epidemiology

Mucinous cystic neoplasms of the liver are rare tumours. Previously, incidence of biliary cystadenoma was estimated to range between 1:20,000 and 1:100,000, while incidence of biliary cystadenocarcinoma was reported to be 1:10 million [10]. Considering, that cases of biliary cystadenocarcinoma without ovarian-type stroma are reclassified as intraductal papillary neoplasms and non-invasive tumours showing cell anaplasia—as mucinous cystic neoplasms with high-grade intraepithelial neoplasia, the true incidence of malignant mucinous cystic neoplasms of the liver is even lower. The incidence of benign tumours also might change in accordance to the current (2010) WHO classification. Non-invasive mucinous cystic neoplasms of the liver that were previously diagnosed a biliary cystadenocarcinomas on the basis of cell atypia and mitotic activity, would be transferred to the benign group, increasing it, albeit slightly [1, 2]. On the contrary, the rare [10] serous type of biliary cystadenoma, defined by the previous WHO classification (2000), was known to lack ovarian-type stroma and nowadays would be excluded from the group of mucinous cystic neoplasms of the liver [1, 2]. Considering the whole group of mucinous cystic neoplasms with ovarian-type stroma, 25% of cases that were previously diagnosed as hepatobiliary cystadenoma/cystadenocarcinoma were reclassified as other entities according to the current WHO classification [15].

Feature	Mucinous cystic neoplasms of the liver[1]		Biliary cystic tumours[2]	
	Non-invasive	Invasive	Cystadenoma	Cystadenocarcinoma
Gender: proportion of female patients	Almost all [1]	Unclear proportion [1]	84.2% [22]	0% [22]
			96% [8]	33.3% [23]
			100% [15, 23, 24]	56% [8]
				71.4% [24]
				100% [15]
Mean age, years	45 [1]	59 [1]	40.6; range, 30–51 [24]	51.3; range, 41–63 [24]
			45; range, 2–87 [8]	59; range, 24–90 [8]

[1]According to WHO Classification of Tumours of the Digestive System, 2010 [25].

[2]According to World Health Organisation Classification of Tumours: Pathology and Genetics of Tumours of the Digestive System, 2000 [26].

Table 2. Demographic characteristics of mucinous cystic neoplasms of the liver.

Geographic differences have been highlighted by Zen et al. [17]. Comparing the numbers of intraductal papillary neoplasm of bile ducts and mucinous cystic neoplasm of the liver in medical institutions of Seoul, Seattle and London, the ratios were 5.7:1; 1:3.0 and 1:6.3, respectively. In Eastern countries, intraductal papillary neoplasms are significantly more frequent [17].

In a recent large study, mucinous cystic neoplasms with ovarian-type stroma accounted for 11% of resected cystic liver lesions in a single institution [15]. However, this proportion should not be applied to all liver cysts found by radiologic investigation as only a small fraction of liver cysts needs surgical treatment [9, 18, 19]. Even the frequently cited assessment that mucinous cystic neoplasms constitute 5% of cystic liver lesions [13, 19, 20] is known to be an overestimate [18] otherwise the incidence of biliary mucinous cystic tumours would exceed the occurrence of cholangiocarcinoma which is not observed. Instead, mucinous cystic neoplasms might represent 5% of symptomatic liver cysts referred for surgical treatment. In 1996–1997, biliary cystadenocarcinoma accounted for 0.18% of all liver tumours registered by Japanese Liver Cancer Study Group [9]. However, it has been noted that mucinous cystic neoplasms are rare in Japan [21]. Currently, invasive mucinous cystic neoplasms constitute 0.41% of hepatic carcinomas [19].

Although the demographic characteristics of the patients vary slightly depending on the classifications (**Table 2**), there are some essential general trends, including a strong female preponderance, predominant occurrence in middle-aged people and earlier age of diagnostics in benign/non-invasive cases.

4. Tumour origin and tissue structure

The presence of ovarian-type mesenchymal stroma raises questions on the origin of mucinous cystic neoplasms of the liver. The correct hypothesis should explain both the presence of this unusual feature and the structural similarity with mucinous cystic tumours of the pancreatic

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gland and retroperitoneal space showing similar stroma [27]. During embryogenesis, ectopic ovarian rests might develop in the liver, along biliary tree, in the pancreas or retroperitoneal tissues and stimulate the proliferation of adjacent biliary or pancreatic ducts by synthesis of growth factors [9, 28]. Indeed, during embryonic development, gonads initially are located directly under the diaphragm, dorsally to the liver and pancreatic tail, and only later they descend to the typical anatomic location seen in adults. The local morphologic appearance of embryonic peritoneal lining with swollen, activated-looking cells is also suspected to be an evidence of interaction between gonadal primordia and developing liver/pancreas, situated just across peritoneal cavity [29].

Origin from intrahepatic peribiliary glands has been preferred by some authors, based on morphological similarity, presence of endocrine cells both in mucinous cystic tumours and in peribiliary glands, and a huge autopsy investigation on 938 livers [1, 30]. In the given autopsy study reported by Sato et al., cystic and micropapillary changes in peribiliary glands were sought for and subjected to morphological and immunohistochemical analysis. Cystic glands were found in 4% of the examined livers while micropapillary lesions were present in 1%, but showed association with an invasive adenocarcinoma in a single case. Micropapillary areas exhibited marked mucus secretion, up-regulation of cyclin D1 and higher proliferative fraction by Ki-67, suggesting that these cell groups possessed a premalignant potential [30].

The peribiliary origin of mucinous cystic neoplasms of the liver seems to be the preferable explanation for the parallels with analogous pancreatic tumours. Biliary tract along with peribiliary glands has considerable structural similarity with pancreatic ducts and acini. Indeed, the biliary tree has even been designated as "incomplete pancreas". The structural similarity is reflected in several pathologies (**Table 3**), not limited to mucinous cystic neoplasms [27]. The peribiliary glands could also eventually receive stimulation by ectopic ovarian stroma—thus, both the aforementioned theories fuse together.

However, not all scientists support the hypothesis of ectopic ovarian tissues. Although the morphology of the specific mesenchymal component closely resembles ovarian stroma, there is also a remarkable similarity to embryonal tissues that are destined to form gallbladder or foregut [10]. The stromal immunophenotype is largerly unspecific, characteristic for myofibroblasts. Hormone receptor expression, including both oestrogen and progesterone receptors, has been found in human embryonic stem cells [33] as well as in abdominal fibromatosis [34], not only in the stroma of ovaries. Thus, according to Ockham's razor, simpler explanation might include origin from peribiliary glands influenced by embryonal-like fibroblasts. Such view allows considering not only congenital but also acquired origin as proposed by Cruickshank and Sparshott [35], possibly a response to a focal injury or oestrogen-containing oral contraceptives [10, 18]. Indeed, a significant fraction of patients has history of obesity, heavy alcohol use, or hormone-related therapy [36].

Research team of D'Errico found that biliary cystadenocarcinomas co-expressed high levels of biliary cytokeratins (by immunohistochemistry) and albumin mRNA (by *in situ* hybridisation). This might indicate either tumour origin from pluripotent stem cells or re-acquisition of embryonal features. *In situ* hybridisation for albumin mRNA was proposed to distinguish between cystadenomas and cystadenocarcinomas; the association with malignancy might rather indicate dedifferentiation and not an evidence of the origin of biliary mucinous cystic neoplasms [37].

Pathogenesis and characteristics	Biliary diseases	Pancreatic diseases
Pre-invasive flat intraepithelial neoplasia, representing a precursor of a solid invasive tumour	**Biliary intraepithelial neoplasm: the precursor of nodular sclerosing cholangiocarcinoma**	**Pancreatic intraepithelial neoplasm: the precursor of pancreatic ductal adenocarcinoma**
Grossly visible, mass forming, primarily intraductal neoplasms that can lead to duct obstruction with papillary tumour masses and secondary cystic dilation of obstructed ducts, followed by intracystic tumour growth. Invasive component can develop	**Intraductal papillary neoplasm of bile ducts**	**Intraductal papillary mucinous neoplasm of pancreas**
Presence of gross cysts	Frequent, secondary to duct dilation	Frequent, secondary to duct dilation
Involvement and dilation of ducts	Frequent	Frequent
Mucus secretion	Frequent	Frequent
Ovarian-type stroma	Absent	Absent
Prognosis	Can progress to an aggressive invasive cancer	Can progress to an aggressive invasive cancer
Patients	Males and females	Males and females
Mucinous cystic neoplasms: cystic tumours with subepithelial ovarian-type stroma	**Hepatobiliary mucinous cystic neoplasm**	**Pancreatic mucinous cystic neoplasm**
Presence of gross cysts	Always	Always
Involvement and dilation of ducts	Rare or absent	Rare or absent
Mucus secretion	Frequent but variable	Frequent but variable
Ovarian-type stroma	Always	Always
Prognosis	Good after complete surgical resection	Good after complete surgical resection
Patients	Mostly: middle-aged females	Mostly: middle-aged females
IgG4-related autoimmune inflammation with mass (pseudotumour) development	**IgG4-inflammatory pseudotumour**	**Mass-forming type 1 autoimmune pancreatitis**

Table 3. Biliary diseases with pancreatic counterparts [9, 27, 31, 32].

5. Morphology: from gross findings to the molecular landscape

5.1. Gross structure

Grossly, the tumours represent a single cyst or a multilocular cystic lesion: a dense group of several cysts recognised by the cyst-in-cyst appearance or the presence of internal septations [1, 21]. Multilocular structure (see **Figure 1**) predominates, in contrast to (1) simple cysts lacking internal septations and (2) intraductal papillary neoplasms exhibiting multicystic appearance: a grape-like cluster of adjacent cysts [21]. Thus, among 20 mucinous cystic neoplasms of the liver and extrahepatic bile ducts, there were 2 unilocular and 18 multilocular neoplasms [5].

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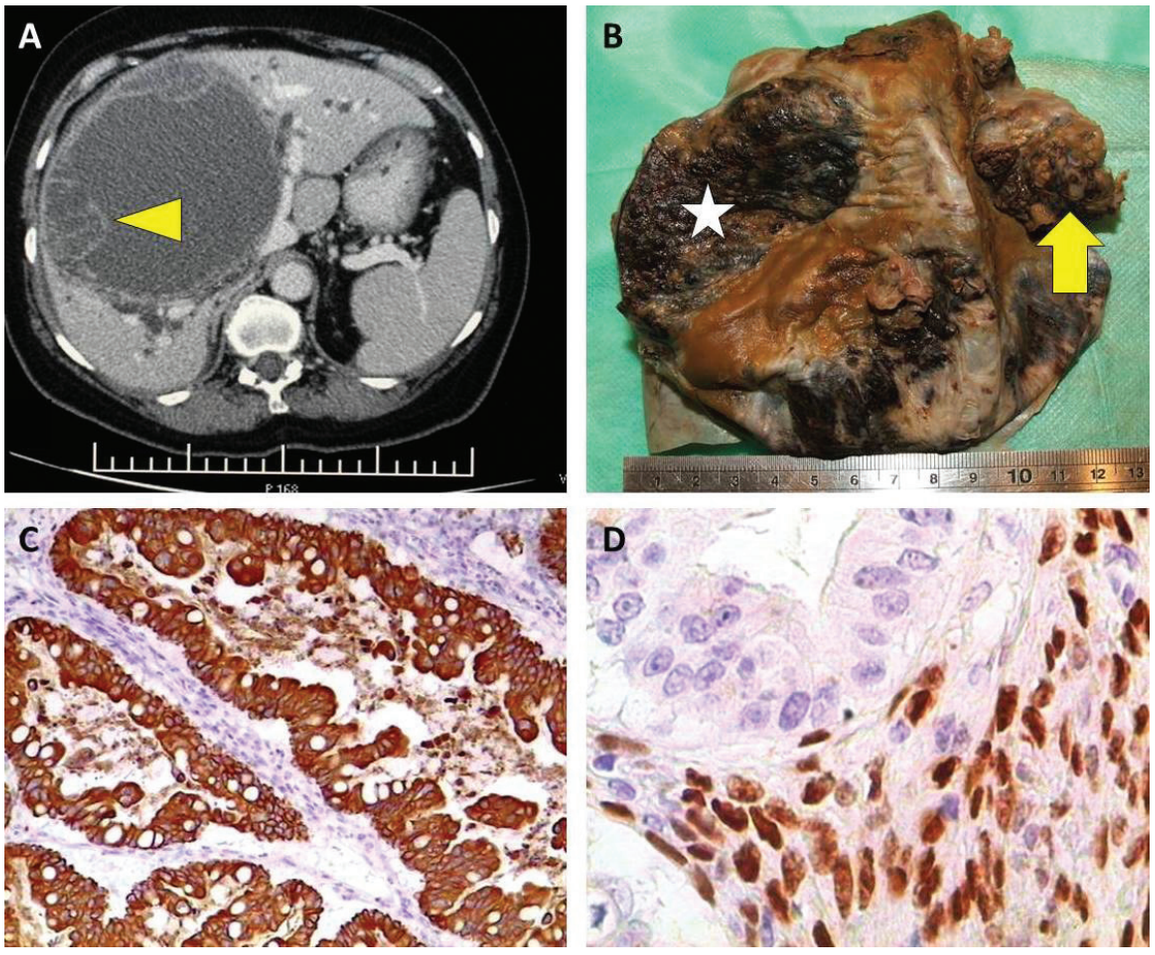

Figure 1. Mucinous cystic tumour of the liver. A, computed tomography findings. Note the huge cyst with internal septations (arrowhead). B, gross view. Note the nodule (arrow) harbouring invasive malignancy. Widespread haemorrhage (star) also is present. C, intense expression of cytokeratin 20 in an area of intestinal differentiation, showing rich presence of goblet cells. Immunoperoxidase (IP), original magnification (OM) 100×. D. Intense nuclear expression of progesterone receptors in the ovarian-type stroma. Note the absence of reactivity in the epithelium. IP, OM 400×.

The frequency of multilocular tumours is estimated to be 84%. In non-invasive cases, fibrous capsule delineates the whole tumour. Even invasive tumours mostly show only a limited spread within the fibrous pseudocapsule [38]. Extrahepatic development is less frequently seen, e.g., in a series of 20 cases, only 4 patients had an extrahepatic tumour [5]. The frequency of extrahepatic mucinous cystic neoplasms of biliary tree has been variably estimated to range between 3 and 20% [5, 39], averaging 10% of all mucinous cystic neoplasms of liver [13].

The cysts usually contain clear fluid, but occasionally thick mucus or haemorrhagic content can be found [1]. The tumour size is variable, reported to range from 1.2 to 40 cm in diameter [38]. A grossly evident communication with larger bile ducts is not typical. If present, such feature may suggest the diagnosis of an intraductal papillary neoplasm of bile ducts [31]. Papillary areas and mural nodules (**Figure 1**) should be identified grossly, described in the surgical pathology report and sampled extensively as these foci are suspicious for malignant change [1]. In contrast, trabeculation of the inner surface can be seen even in cystadenomas [10].

5.2. Microscopic characteristics of epithelium

Histologically, the cysts are lined by epithelium. The height and cytoplasmic structure of epithelial cells varies widely: from cylindrical to flat, from mucus secreting to cases in which only a small amount of mucus can be highlighted by mucicarmine stain or tumours with serous appearance of epithelium [1]. Typical epithelium is cuboidal, columnar or tall, with pale eosinophilic cytoplasm and basally located nuclei [10]. Mucus secretion is not marked in significant fraction of the considered tumours albeit the entity is designated as mucinous cystic neoplasms of the liver [4]. For instance, among 20 cases of mucinous cystic tumours of the liver and extrahepatic bile ducts, 18 tumours were predominantly composed of cuboidal or low columnar epithelium that was similar to the lining of bile ducts. Only two cases showed rich mucus secretion along with intestinal differentiation and presence of goblet cells [5]. Among 36 mucinous cystic neoplasms of the liver and extrahepatic biliary tree, non-mucinous epithelium was predominant in 50% cases [15]. Gastric, intestinal (**Figure 1**) or squamous differentiation can also occur. Basement membrane is present in non-invasive cases [1].

Enlarged, hyperchromatic, crowded nuclei, loss of nuclear polarity and presence of mitoses indicate intraepithelial neoplasia. High-grade intraepithelial neoplasia is characterised by glandular crowding, significant nuclear pleomorphism and brisk mitotic activity. The architectural disarray in high-grade intraepithelial neoplasia manifests both as papillary elevations and crypt-like invaginations into the stroma. The latter must be distinguished from true invasive growth.

Invasion is the hallmark of malignancy and must be acknowledged in the diagnosis as a mucinous cystic neoplasm with an associated invasive carcinoma [1]. The frequency of invasive carcinoma in mucinous cystic neoplasms of the liver or extrahepatic biliary ways has been variably reported to be 2 [17]; 6 [15]; 10 [4] or 15.4% [40]. In some series, invasion was not found, e.g., there were no invasive carcinomas among 29 mucinous cystic neoplasms described by Zen et al., although a single case of so-called carcinoma *in situ* was identified [21]. In contrast, the proportion of malignant cases by the preceding WHO classification (2000) was as high as 38.5% [41]. If present, invasive areas tend to be small, e.g., in the only 2 (of 36 investigated mucinous cystic neoplasms of the liver or extrahepatic biliary tree) invasive cases, the invasive areas measured merely 7–8 mm [15].

5.3. Molecular features in correlation with morphology

The amount of cytoplasmic mucus is an interesting and significant feature of neoplastic epithelium (**Table 4**). As mentioned, in a significant fraction of cystic tumours, mucinous epithelium is not the dominant type: it occupies less than 50% of surface and can be as limited as 10%. Nevertheless, such cases are still diagnosed as mucinous cystic neoplasms of the liver if ovarian-type stroma is present. Although the terminology might seem slightly confusing, sufficient experience of pathologist will easily allow overcoming the diagnostic problems. However, there is a far more important aspect: the degree of mucinous differentiation is shown to parallel the frequency of *KRAS* mutations and of invasive carcinoma [4]. Already earlier, intestinal metaplasia with the presence of goblet cells (**Figure 1**) has been acknowledged as a premalignant lesion [10].

Reference	Parameter	Total number	Mucinous differentiation	
			Marked	Weak
Shibata et al. [4]	Study group	15 mucinous cystic neoplasms of liver (2) and pancreas (13)	6	9
	KRAS mutation	6	5	1
	Invasive carcinoma	2	2	0
Albores-Saavedra et al. [42]	Study group	31 mucinous cystic neoplasms of pancreas	22	9
	Invasive carcinoma	6	6	0
Zhelnin et al. [43]	Study group	136 mucinous cystic neoplasms of liver (32) and pancreas (104)	71	58
	High-grade intra-epithelial neoplasia	8	8	0
	Invasive carcinoma	14	14	0
Albores-Saavedra et al. [5]	Study group	20 mucinous cystic neoplasms of liver (16) and extrahepatic bile ducts (4)	2[1]	18
	High-grade intra-epithelial neoplasia and invasive carcinoma	2	2	0

[1] Along with intestinal differentiation.

Table 4. Clinical and pathogenetic significance of mucinous differentiation in cystic neoplasms with ovarian-type stroma.

Thus, in a study group of 15 mucinous cystic neoplasms of the pancreas and liver, there were 6 cases with marked mucus secretion while in the remaining 9 cases less than 50% of epithelium showed obvious mucus in the cytoplasm. Invasive carcinoma was found in two cases, both from mucus-rich group. A single case of high-grade intraepithelial neoplasia also was found within the mucus-rich group. The tumours with limited amount of mucus featured only low-grade intraepithelial neoplasia [4]. Analogous findings have been reported also by Albores-Saavedra et al. [42] and Zhelnin et al. [43]. The first of these studies was devoted to pancreatic mucinous cystic neoplasms—the counterpart of hepatic tumours. Among the evaluated 31 cases, 22 showed abundant mucus production and 6 of them were associated with invasive carcinoma. In contrast, there was no invasive component in any of the nine cases presenting with non-mucinous cuboidal or low columnar epithelium [42]. Subsequently, in a large cohort comprising 136 pancreatic and hepatic mucinous cystic neoplasms, high-grade intraepithelial neoplasia (8 tumours) or invasive carcinoma (14 patients) were found only among cases with marked mucus secretion (defined as presence of microscopically visible mucus in more than 50% of neoplastic epithelial cells). There were also 58 cases with predominantly (>50%) non-mucinous epithelium, and no evidence of high-grade intraepithelial neoplasia or invasion was found among them. Both these differences were statistically significant as shown by $p = 0.007$ for high grade intraepithelial neoplasia and $p < 0.001$ for invasive carcinoma [43].

The significance of mucinous differentiation was further clarified by molecular studies. *KRAS* mutations have recently been associated with marked mucinous differentiation and malignant transformation [4]. Among 15 mucinous cystic neoplasms of the liver or pancreas, *KRAS* mutations were present in 6 cases, and 5 of them featured marked mucus secretion. Thus, the frequency of *KRAS* mutations in mucinous *versus* non-mucinous tumours was 83 *versus* 11%; p = 0.011. The mutations were found in both invasive cancers (2) and 4 cases of low-grade intraepithelial neoplasia [4]. *KRAS* mutations are confirmed to be the driver mutations in the mucinous cystic neoplasms of the liver and pancreas [3]. These genetic changes are uncommon in low-grade intraepithelial neoplasia (1/20; 5%) while are present in most of cases with invasion, intermediate- or high-grade intraepithelial neoplasia (4/5; 80%; p = 0.002). Interestingly, in *KRAS*-mutated cases that were diagnosed as intermediate- or high-grade intraepithelial neoplasia, identical mutations were found in adjacent areas of low-grade intraepithelial neoplasia. Thus, it seems that *KRAS* mutations precede and possibly drive the morphological changes. In comparison with wild-type tumours, *KRAS* mutated cases more frequently express mucins: MUC1 (pancreatobiliary), MUC2 (intestinal) and MUC5AC (gastric), as reflected by the corresponding p values: p = 0.04; p = 0.016; p = 0.015. By sequencing, no alterations of *GNAS*, *RNF43* and *PIK3CA* have been found in hepatic and pancreatic mucinous cystic neoplasms [3]. C-met activation is another pathogenetic event in the mucinous cystic neoplasms of the liver [44].

Thus, there is a considerable body of evidence that mucinous epithelium is prone to develop high-grade dysplasia and progress to invasive carcinoma. *KRAS* mutations are likely to be a significant driving force within this pathway. Still, different conclusions could follow. Albores-Saavedra proposed to reclassify cystic tumours with ovarian type stroma, separating non-mucinous cystadenomas with pancreatobiliary phenotype and ovarian-like stroma in a new entity that hypothetically had no malignant potential [42]. In contrast, Zhelnin et al. viewed the mucinous differentiation as a dynamic change: a sign of tumour progression towards malignancy [43]. The observation that non-mucinous tumours are smaller [43] and found in younger patients [4, 43] is in accordance with this assumption. Consequently, evidence of marked mucinous differentiation, e.g., by *in vivo* confocal laser endomicroscopy could prompt surgery.

5.4. Immunophenotype of epithelium

Considering the immunophenotype of epithelium, expression of cytokeratins 7, 8, 18 and 19 is characteristic in accordance with the biliary differentiation [1, 5]. As was noted, *KRAS* mutated cases more frequently expressed pancreatobiliary (MUC1), intestinal (MUC2) and gastric (MUC5AC) mucins [3]. Previously, expression of MUC1 [5] was known, and presence of cytokeratin 20, CDX2 and MUC2 was reported in association with intestinal differentiation characterised by presence of goblet cells, columnar absorptive cells and Paneth cells. Notably, cases with clear-cut intestinal differentiation frequently show invasion [42, 45]. Proliferation fraction by Ki-67 is low in benign cases but increases in the areas of malignant change [45]. Epithelial membrane antigen EMA is present [8]. Carcinoembryonic antigen CEA is focally expressed in the neoplastic epithelium [8] and thus can be found also in the cyst fluid [46]. Chromogranin-positive endocrine cells are present both in benign and malignant tumours [1, 8].

5.5. Ovarian-type stroma

The morphologic appearance of stroma is among the crucial diagnostic criteria of mucinous cystic neoplasms. The specific stroma consists of densely growing spindled cells that closely resemble ovarian tissues. No cellular atypia or mitotic activity is present in contrast with biphasic malignant tumours, e.g., carcinosarcoma or mesothelioma. Sarcomatous stromal transformation has been reported in mucinous cystic tumours of the liver and pancreas but is distinctly rare [10, 47].

The immunophenotype of stromal cells discloses mesenchymal (vimentin), and myogenic (actin and desmin) differentiation along with hormone dependence reflected by expression of oestrogen (77% of cystadenomas) and progesterone (100% of cystadenomas) receptors [1, 36]. In addition, biliary cystadenomas (13 cases) displayed uniform nuclear reactivity for FOXL2, a transcription factor that was expressed in female gonads from the early stages of development to normal adult ovarian stroma [36]. Alpha-inhibin also is found [1, 44]. The landscape of oestrogen and progesterone receptor expression (**Figure 1**) along with alpha-inhibin, calretinin and CD10 can be useful in the rare but demanding cases when differential diagnosis is between endometriosis and mucinous cystic tumours [48]. Not only the mere presence, but location of positive reaction (epithelium *versus* stroma) is of utmost importance (**Table 5**).

Three additional morphologic events, occasionally seen in stroma of mucinous cystic neoplasms, include luteinisation of stromal cells [1], calcification [10] and xanthogranulomatous reaction. The latter features cholesterol crystals (seen in tissue sections as clefts) as well as foam cells and lipofuscin-containing macrophages. The outer layer of tumour wall is represented by loose fibrous tissue [1].

Some authors have emphasised the difficulties in stromal assessment, namely, the focal nature of the specific ovarian-type tissues and inter-observer variability [11]. Among 36 mucinous cystic neoplasms of the liver and extrahepatic biliary tree, only 47% of cases demonstrated diffuse ovarian-type stroma; the diffuse spread was defined as involving >75% of cyst perimeter [15]. To overcome such problems, wide sampling and increased awareness of pathologist about mucinous cystic neoplasms will be helpful. In doubt, immunohistochemical visualisation of oestrogen and progesterone receptors in the stroma can be advised. This finding is not

Antigen	Endometriosis in the liver	Mucinous cystic tumour of the liver
Oestrogen receptors	+ stroma//+ epithelium	+ stroma//− epithelium
Progesterone receptors	+ stroma//+ epithelium	+ stroma//− epithelium
Alpha-inhibin	− stroma	+ stroma
CD10	+ stroma	− stroma
Cytokeratin 7	+ epithelium	+ epithelium
Cytokeratin 19	+ epithelium	+ epithelium

Abbreviations and symbols in the table: +, positive reaction; −, negative reaction; CD; cluster of differentiation.

Table 5. Immunophenotype of mucinous cystic tumours of the liver *versus* endometriosis [1, 48].

entirely specific; endometriosis, in particular, represents another oestrogen- and progesterone receptor positive lesion. However, it is useful for the differential diagnosis with simple cyst or intraductal papillary neoplasms, both lacking stromal hormone receptor expression.

5.6. FNA, core biopsy and frozen section: findings and limitations

The efficacy of preoperative morphological diagnostics is limited, regarding both core biopsy and fine needle aspiration (FNA) for cytology. By FNA, groups of cuboidal or columnar epithelial cells can be observed against either watery or mucinous background. The cellular atypia can be variable, depending on the degree of intraepithelial neoplasia and reflecting the heterogeneity seen within a single mucinous cystic neoplasm of the liver. As the stromal cells usually are not seen in the sample, differential diagnostics with intraductal papillary neoplasm is not reliable. FNA of intraductal papillary neoplasms yields papillae with fibrovascular cores; although papillary groups can be seen in mucinous cystic neoplasms, they are abundant in intraductal papillary neoplasms. Presence of nuclear grooves is also characteristic of intraductal papillary neoplasms. In addition to problems in distinguishing between different cystic liver lesions, the focality of sampling can decrease sensitivity of FNA for the diagnosis of malignancy [1].

Core biopsy is not advised as the cystic nature of lesions precludes obtaining of a representative tissue sample. In addition, the heterogeneity represents a further obstacle as the foci of invasive growth can easily be missed. Rarely, biopsy can lead to peritoneal carcinomatosis therefore it has been advised to avoid biopsy if surgical treatment is planned [10].

For intraoperative diagnostics, the use of frozen section is controversial. The reports range from positive experience [49] to high rate (66.6%) of false negative conclusions [40]. Intraoperative scrape cytology has been informative in at least one case, revealing both biliary epithelial and mesenchymal stromal cells [50].

6. Tumour spread and staging

As was noted, malignant biliary mucinous cystic tumours usually are characterised by limited growth, invading the fibrous pseudocapsule [38]. Only in rare cases, the tumour widely infiltrates the adjacent liver, spreads to regional lymph nodes (mainly in hepatoduodenal ligament) or distant organs, such as lungs, pleura or peritoneum [1]. TNM staging is analogous to intrahepatic cholangiocarcinoma (**Table 6**).

Parameter	Definition
T—extent of local tumour spread	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary liver tumour
Tis	Carcinoma *in situ*
T1	Solitary invasive tumour lacking vascular invasion
T2a	Solitary tumour invading blood vessels

Parameter	Definition
T2b	Multiple tumours
T3	Tumour perforates visceral peritoneum or directly invades extrahepatic tissues and organs
T4	Periductal growth pattern
N—regional lymph node status in regard to metastases	
Nx	Regional lymph node status cannot be assessed
N0	No metastases in regional lymph nodes
N1	Metastasis in regional lymph nodes has been identified
M—presence or absence of distant metastases	
M0	Distant metastasis absent
M1	Distant metastasis present
Stage	
I	Stage (I) corresponds to T value (T1) in the absence of metastases in regional lymph nodes and distant locations: T1 N0 M0
II	Stage (II) corresponds to T value (T2) in the absence of metastases in regional lymph nodes and distant locations: T2 N0 M0
III	Stage (III) corresponds to T value (T3) in the absence of metastases in regional lymph nodes and distant locations: T3 N0 M0
IVA	Either highly advanced local tumour (T4) or presence of metastases in regional lymph nodes (N1) in the absence of distant metastases: T4 N0 M0 or T1–4 N1 M0
IVB	Presence of distant metastases: T1–4 N0–1 M1

Table 6. TNM staging of mucinous cystic neoplasms of the liver [25].

7. Clinical presentation and course

The symptoms and objective findings (**Table 7**) are non-specific, attributable mainly to the presence of slowly growing mass. The clinical course is characterised by insidious onset and slow progress, consistent with the gradual advancement of the tumours (but see further for exceptions). The mass can distend liver capsule, rupture, bleed, or compress stomach or duodenum [10]. Damage of biliary tree or blood vessels is possible via compression or invasion. Consequently, benign or malignant tumours can present similarly.

Abdominal pain or discomfort [10] is the most frequent complaint [22]. Pain has been reported in 74% (range in different studies: 60–80%) of patients diagnosed with biliary cystic tumours while abdominal distention is observed in 26% and nausea/vomiting in 11% [18]. Approximately 60% of patients complain about pain in right upper abdominal quadrant or epigastric area, in combination with increasing abdominal circumference or awareness of abdominal mass. The growing tumour can also lead to vague abdominal discomfort [10].

Clinical symptoms and signs				
Dominant	**Biliary**	**Vascular**	**Other**	**Absent**
60–74%	35%	Rare	Rare	30–58%
Abdominal pain Abdominal discomfort Abdominal distension Mass (objectively)	Obstructive jaundice Skin itching Biliary colic Cholangitis Steatorrhea	Portal hypertension Ascites Compression/obstruction of the inferior caval vein	Gastric/duodenal compression Tumour rupture Bleeding Peritoneal carcinomatosis Metastatic spread	Incidental finding during unrelated radiologic or surgical exploration

Table 7. The clinical manifestations of mucinous cystic neoplasms of the liver.

Bile duct compression [10] or invasion can lead to obstructive jaundice and predispose to ascending infection resulting in cholangitis. If the tumour contents are discharged into bile ducts, mucobilia is possible. Bleeding to biliary ways results in haemobilia [51]. Biliary symptoms are seen in 35% of patients with benign tumours referred to as cystadenomas by WHO classification, 2000 [10] and can be responsible for acute presentation or intermittent course, in addition to the more classical slowly progressing clinical picture.

Biliary obstruction (caused by the tumour itself, mucobilia with thick mucus or haemobilia with clots) may present as obstructive jaundice, skin itching, biliary colic, cholangitis, nausea, fever or steatorrhea. Intermitted course with repeated bouts of jaundice, biliary colic or cholangitis has been reported [10]. Notably, obstructive jaundice can be caused by benign tumour as biliary cystadenomas with ovarian-type stroma can show expansive growth with prolapse into bile duct. The prolapse is seen by endoscopic retrograde cholangiopancreatography as an oval-shaped filling defect in the bile duct. To exclude a stone, endoscopic ultrasonography and intraductal ultrasonography are useful, since multiple septa are found in tumours. At least 17 such cases have been reported in the medical literature, 2004–2015 [52].

Haemobilia denotes bleeding towards the bile ducts. In general, most cases of haemobilia are caused by trauma or iatrogenic injury from percutaneous biliary tract instrumentation. Haemobilia as a primary presentation of liver tumour is unusual. In a systematic review of 222 cases of haemobilia over 3-year period, only 14 cases were caused by tumours. Nevertheless, Philip et al. have reported a male patient presenting with anaemia (haemoglobin 6.7 g/dL) and recurrent haemobilia confirmed during duodenal endoscopy. Repeated CT and MRI scans initially could not identify liver mass. During re-bleeding episode, the mass was found radiologically, but its histogenesis remained unclear until postoperative histology [51].

Gastric or duodenal compression may present as slowly progressing upper gastrointestinal obstruction with nausea, vomiting, dyspepsia and/or anorexia [10].

Among unusual manifestations, compression of portal vein can lead to portal hypertension and ascites in the absence of cirrhosis. Compression/obstruction of the inferior caval vein with subsequent bilateral leg oedema has been reported [38].

In addition, the patients can be asymptomatic. Although it has been noted that mucinous cystic neoplasms of the liver "nearly always cause symptoms at the time of presentation" [1], this might merely reflect the cases in which diagnosis is reached at the point when patients insist on solving the diagnostic enigma after several years of controversial findings. Indeed, occasionally the patients have as long clinical history as 10 years [53]. The symptoms are likely to be size-dependant; thus, small mucinous cystic neoplasm of the liver can present as an incidental finding. Clinically silent presentation is reported in up to 42.1% of cases [22] and is expected to become more frequent with increasing availability of medical services. Indeed, the frequency of asymptomatic presentation has been noted to range between 30 and 58% [38]. The asymptomatic tumours might be revealed as an accidental finding during radiological investigation or abdominal surgery for other clinical indications [10].

At least a fraction of patients experiences lengthy diagnostics and relapse after insufficient treatment. Thus, Thomas et al., noted that the symptoms lasted in average for 3.1 years; and eight of their patients (8/19) had had 20 procedures prior to definitive ablation [18].

8. Radiological findings and differential diagnosis

Cystic neoplasms of the liver are rare while simple liver cysts are common, seen in 2.5–18% of population [54]. Radiological investigation is the mainstay of preoperative diagnostics in order to discriminate between simple liver cyst and mucinous cystic neoplasm. Estimates of the biological potential (benign *versus* malignant) and differential diagnostics with other cystic lesions, e.g., parasites, abscesses or cystic/necrotic metastases, represent other important tasks [28].

The essential methods of liver evaluation include transabdominal ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI). Positron emission tomography (PET) can be helpful in detecting malignancy. Mucinous cystic neoplasms of the liver, as the term emphasises, are cystic and usually large masses (although small tumours have been reported). To distinguish these tumours from simple liver cysts, presence and vascularity of internal septa are important. Some authors have found that vascularity of the septations is more specific than the mere presence of septa, if the differential diagnosis between a simple cyst and a mucinous cystic neoplasm of the liver is carried out [18, 24]. Other research teams emphasised the importance of finding internal septa that started perpendicularly to the outer wall and were not associated with external indentation [55]. CT can better disclose the enhanced internal septations even if they are thin; the cyst content is usually hypoattenuating [56]. By contrast-enhanced ultrasound (CEUS) imaging, biliary cystic tumours mostly (78.3%) display honeycomb enhancement pattern of the cyst wall, septa or mural nodules [14]. Prolonged enhancement in Kupffer phase is not characteristic but occasionally can be caused by rich presence of macrophages [57]. On MRI, mucinous cystic tumours are hypoattenuating on T1W1; however, high protein content in cyst fluid might increase the signal intensity. On T2W1, the fluid is hyperintense, and septations are better visible [56]. In addition, mucinous cystic neoplasms more frequently are solitary if compared with simple liver cysts [58]. Synchronous cases represent an unusual exception [59].

In turn, presence of enhanced mural or septal nodules is the most important sign of malignancy [38]. In contrast, benign cystic tumours have smooth and thin walls and internal septa. Calcification in the mural nodules is a controversial finding—some but not all [24, 60, 61] authors associate it with malignant tumour (in the context of mucinous cystic neoplasms of the liver). By CEUS, benign tumours are characterised by hyperenhancement of the honeycombed septa during arterial phase ($p = 0.047$) while malignant cases feature significantly ($p = 0.041$) more frequent hypoenhancement during the portal venous and late phases [14]. The experience with PET is very limited, but the reported data reflect correct identification of malignant process [18, 38].

Simple cysts are asymptomatic, single or multiple lesions with thin wall and watery contents. Thus, in CT or MRI simple cysts are seen as non-enhancing, well circumscribed, fluid-containing foci [38]. Multiple cysts can be present in patients affected by autosomal dominant polycystic liver disease, and these cases are more prone to haemorrhage. MRI can be helpful to identify it thus solving the differential diagnosis. The autosomal recessive Caroli disease represents another inherited liver disease associated with cyst development. In Caroli disease, cavernous ectasias of bile ducts develop, frequently associated with stone formation. Radiologically, communications between the cystic cavities and biliary duct system are important. "Central dot" sign is observed by CT. Bridges across the cavities are evident by MRI. Both these findings represent branches of portal vein embedded in connective tissue strands adjacent to and surrounded by dilated bile ducts [28].

Embryonal sarcoma, a rare and usually solid malignant tumour of adolescence, occasionally has cyst-like appearance on CT and MRI because of myxoid stroma. Both the age and the presence of wide solid component are helpful to exclude mucinous cystic neoplasm of the liver [28].

Other malignant tumours, especially metastases, occasionally have cyst-like appearance because of necrosis or accumulation of mucus. Necrotic metastases are seen in CT or MRI as foci with strong peripheral enhancement and irregular border; usually there are multiple lesions. Mucinous metastases most frequently represent metastatic colorectal or ovarian carcinoma. In the latter case, the characteristic transperitoneal spread by implantation can lead to development of multiple nodules within the liver capsule while mucinous cystic neoplasms of the liver are located within liver parenchyma. Neo-adjuvant treatment sometimes induces cyst-like degeneration of metastases [62]. On rare occasions, other malignant tumours develop unusual cystic appearance, e.g., angiosarcoma [63], Ewing sarcoma [64], primary or metastatic neuroendocrine neoplasm [62, 65] or hepatocellular carcinoma [66].

Multiple cystic liver lesions are seen in echinococcosis, characterised by multi-layered wall of the cysts and presence of multiple small hypoattenuating daughter cysts with thin eggshell calcifications. Serologic tests will confirm the diagnosis [28].

Liver abscess initially is seen as a cluster of small foci that later converge into an unilocular cystic lesion. It might contain gas formed by microbial flora. Later, thick, enhancing wall develops. "Double target" sign can be evident because of peripheral rim enhancement attributable to increased capillary permeability. However, invasive growth of malignant tumours

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can incite similar inflammatory response. Presence of mobile debris seen by US is characteristic of abscess [28].

History of trauma or operation is helpful to suspect a bile collection (biloma) or hematoma. Biloma is visible in CT and MRI as a well-demarcated cystic focus lacking septa, calcifications or pseudocapsule [28].

9. Assessment of cyst fluid

Regarding the analysis of cyst fluid, the diagnostic value is controversial. Promising reports have suggested that high concentrations of certain proteins in the cyst fluid might help to distinguish cystic tumours from simple cysts thus aiding in case selection for surgery. Assessment of cyst fluid would be free of problems related to sampling of heterogeneous tissues—a frequent problem in obtaining and interpretation of biopsy. Elevated levels of carbohydrate antigen CA19-9, significantly exceeding the concentration of CA19-9 in the serum, have been reported in cyst fluid [22]. Increased concentrations of CEA and CA19-9 in the cyst fluid are described in cystic tumours but not in simple liver cysts [46]. However, comparing the levels of CA19-9, CEA and cancer antigen 125, no significant differences ($p = 0.45$; $p = 0.49$ and $p = 0.73$, respectively) were found between 13 mucinous cystic neoplasms and 38 simple hepatic cysts [58]. Still, in a larger group including 32 mucinous cystic tumours and 40 simple cysts, a significantly elevated CA19-9 level in tumours was shown. The differences were demonstrated both by the median level of CA19-9 (364.8 *versus* 21.4 U/mL) and the fraction of cases in which CA19-9 exceeded the highest value of laboratory reference interval for serum assessment (46.9 *versus* 10.0%). The concentrations of CEA lacked significant difference; the median value was 6.8 mg/L in tumours *versus* 4.2 mg/L in simple cysts [67]. Tumour-associated glycoprotein (TAG) 72 has been suggested as a highly informative marker for differential diagnosis between mucinous cystic tumours and simple liver cysts. Performing ROC curve analysis, TAG-72 concentration exceeding 25 U/mL was associated with specificity and sensitivity of 0.97 and 0.79, respectively, being superior to CEA and CA19-9 and yielding area under curve (AUC) of 0.98 for the discrimination between cystic tumours and simple cysts [68].

Regarding pancreatic counterparts, attractive future research directions have appeared regarding diagnostics by cyst fluid assessment, e.g., next generation sequencing for driver mutations (e.g., *KRAS*) in the cyst content [69], combined evaluation of CEA and *KRAS* status [70]; or CEA, CA19-9, cytological and ultrasonographic findings [71]. Elaboration of combined diagnostic algorithms based on several features, including detection of tumour markers, viscosity [72], mucinous differentiation [73], *KRAS* testing, proteome analysis [74] in the cyst fluid and ultrasound or CT features, is pathogenetically substantiated, up-to-date [75] and promising direction. However, any preoperative cyst sampling involves low but not negligible risk of complications, including peritoneal or pleural dissemination, or pseudomyxoma in malignant cases [20]. In addition, the differential diagnostic background in pancreas also differs from liver—an organ, affected by simple cysts in up to 18% of the general population [54].

10. Treatment

Once the diagnosis of a mucinous cystic liver neoplasm has been established, surgery is the mainstay of the treatment. These tumours have two essential biological features: (1) capacity to recur after incomplete excision and (2) slow progression towards malignant transformation, seen with reasonable frequency [10]. Therefore complete surgical resection is strongly advised. The intent must be to remove all the neoplastic tissues. However, considering the low biological potential of these neoplasms, wide resection margin is not mandatory. Thus, enucleation or liver resection (hepatectomy, bisegmentectomy and extended hepatectomy) represent appropriate approaches while marsupialisation, internal Roux-en-Y drainage, aspiration, sclerosing or partial resection are associated with high rate of complications, mainly recurrence or sepsis [18, 20, 28]. Enucleation with clear margins is the preferable option for large central tumours, associated with/located close to blood vessels or large bile ducts [20]. Liver transplantation has been suggested in unresectable cases including recurrent or giant tumours [61, 76].

The recurrence rate after an incomplete resection is as high as 90% therefore an undiagnosed mucinous cystic liver neoplasm should be suspected in any patient who experiences a relapse after treatment of presumed simple liver cyst, e.g., marsupialisation (deroofing) or partial resection [20]. Although such recurrences bring the risk of malignant change, the biological potential of mucinous cystic tumours is low and recurrent patients still are amenable to surgery, even after repeated relapses and over as long time period as 10 years [18, 20, 53].

There is very limited experience with treatment other than surgery. Argon beam plasma coagulation has occasionally been used as an adjunct to surgery. A case of biliary cystadenocarcinoma has been reported in which the main focus was removed by non-anatomic liver resection while a satellite lesion underwent fulguration. The patient experienced prolonged survival and was free of disease 2142 days (5.9 years) after operation [18].

The data on the efficacy of primary or adjuvant chemo-/radiotherapy are limited to few case reports. For instance, systemic, 5-fluoruracil-based chemotherapy was reported effective in a single patient who had recurrence and multiple metastases of biliary cystadenocarcinoma 41 months after surgical removal. The patient benefitted from tumour reduction and clinical improvement [28]. In another patient, major hepatectomy was not amenable because of insufficient functional reserve of the liver, but hepatic arterial infusion of cisplatin helped to reduce the size of the tumour from 12 cm in diameter to 2 cm and to improve the general condition [77]. Three patients have received chemo-radiotherapy as a primary treatment. The 2-year and 5-year survival was 33.3% [39]. Currently, the reported experience with chemotherapy is clearly insufficient.

11. Prognosis

Exact prognostic data are difficult to obtain because of two problems: (1) rarity of mucinous cystic tumours leading to predominantly small study groups and (2) contamination of even

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these cohorts with cases lacking ovarian-type stroma. As shown further, as least a fraction of tumours lacking the specific stroma might represent intraductal papillary neoplasms that are associated with worse outcome. However, general lines still can be drawn.

The prognosis depends both on the presence or absence of invasion [78] and metastatic spread (albeit rare) as well as on the completeness of resection. After complete removal of a benign tumour, the prognosis is excellent. The overall survival is 90% over 18 years [13]. Zen et al. reported on 24 surgically treated cases; all patients were alive during follow-up of 1–132 months; median 47 months [21]. Some authors have not experienced recurrence of a benign cystic mucinous tumour after appropriate surgical treatment while others note the risk of recurrence ranging between 5 and 13% [13, 21]. Incomplete surgical removal leads to recurrence [18, 21]. In untreated cases or in patients subjected to non-radical approach, malignant change can develop; the risk is estimated to be as high as 20% [13].

Although malignant tumours can recur after surgery, the prognosis of surgically removed invasive mucinous cystic tumour of the liver is significantly better than for other primary malignant liver tumours, including hepatocellular carcinoma or cholangiocarcinoma. Prolonged survival can be expected. Even disease-free survival after radical resection of cystadenocarcinoma was 16.5 and 33 months [22]. The 5-year survival of surgically resected malignant mucinous cystic tumour of the liver is 65–70%, contrasting with 40% in hepatocellular carcinoma and 22% in cholangiocarcinoma [13]. If relapse develops, mostly it is local, but some patients (up to 20%) experience extrahepatic metastases [13].

Mucinous cystic tumours of the liver are associated with better prognosis than intraductal papillary tumours. After resection of mucinous cystic neoplasm of the liver, 5-year survival rate was 100%, contrasting with 84% in patients diagnosed with intraductal papillary neoplasm of bile duct [79]. Similarly, the 5-year survival of surgically treated hepatic mucinous cystic neoplasms (13) including malignant cases (38.5%) was 100%, exceeding the outcome of intraductal papillary neoplasms: 5-year survival rate in this group was 82% [41].

12. Conclusions

Mucinous cystic neoplasms of the liver, formerly known as biliary cystadenoma and cystadenocarcinoma in accordance with WHO classification (2000), have been redefined by WHO (2010) as epithelial cystic neoplasms with ovarian-like stroma. They are subclassified by the presence or absence of invasion. Non-invasive cases are further distinguished by the highest grade of intraepithelial neoplasia.

Although the exact incidence has to be clarified in subsequent studies, mucinous cystic neoplasms of the liver are rare. Previously, the incidence of biliary cystadenoma was estimated to range between 1:20,000 and 1:100,000, while the incidence of biliary cystadenocarcinoma was reported to be 1:10 million. Considering the whole group of hepatic and biliary mucinous cystic neoplasms with ovarian-type stroma, 25% of cases that were previously diagnosed as

biliary cystadenoma/cystadenocarcinoma might be reclassified as other entities according to the current WHO classification.

The origin of these tumours is unclear. The best substantiated hypotheses point towards peribiliary origin, possibly in association with ectopic ovarian stroma or remnants of embryonal gall bladder or foregut tissues. The most important advances in morphologic and molecular studies include mucinous differentiation as a progression phenomenon, indicating development towards malignancy and identification of *KRAS* mutations as the molecular driver force.

The clinical presentation is unspecific. Mass effects are dominant, leading to abdominal pain or discomfort. Biliary obstruction can be seen both in benign and malignant cases, being caused by expansive growth and prolapse into biliary ways or by invasion, respectively. Biliary symptoms are observed in 35% of patients and include obstructive jaundice, skin itching, biliary colic, cholangitis, mucobilia, haemobilia, nausea, fever or steatorrhea. Bile duct involvement can be responsible for acute presentation or intermittent course, in addition to the more classical slowly progressing clinical picture.

Radiological evaluation is the mainstay of diagnostics, as both FNA and core biopsy have limited informativity. The essential methods of liver evaluation include transabdominal ultrasonography, computed tomography, magnetic resonance imaging and positron emission tomography. Mucinous cystic neoplasms of the liver are cystic, usually large and solitary. To distinguish these tumours from simple liver cysts, presence and vascularity of internal septa are important. In turn, presence of enhanced mural or septal nodules is the most important sign of malignancy. Calcification in the mural nodules can indicate malignancy, but is controversial. The experience with PET is very limited, but the reported data reflect correct identification of malignant process.

In turn, radical surgery is the main treatment option. The intent is to remove all the neoplastic tissues. However, considering the low biological potential of these neoplasms, wide resection margin is not mandatory. Thus, enucleation or liver resection represent appropriate approaches while marsupialisation, internal Roux-en-Y drainage aspiration, sclerosing or partial resection are associated with high rate of complications, mainly recurrence or sepsis. After complete resection of non-invasive tumours, the prognosis is excellent. Prolonged survival can be expected even in invasive cases.

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Conflict of interest

The authors have no conflict of interest to declare.

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