Title: **Differentiating Simple Hepatic Cysts from Mucinous Cystic Neoplasms: Radiological Features, Cyst Fluid Tumour Marker Analysis and Multidisciplinary Team Outcomes**

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Abstract

Background

Differentiating hepatic mucinous cystic neoplasms (MCN) from simple hepatic cysts (SC) preoperatively is challenging. Our aim was to determine if radiological features on ultrasound (USS), computerised tomography (CT) or magnetic resonance imaging (MRI), cyst fluid tumour markers, or multidisciplinary team (MDT) outcomes could differentiate MCN from SC.

Methods

A retrospective review of radiological features, cyst fluid tumour marker levels and MDT outcomes in 52 patients was performed.

Results

There were 13 patients with MCN, 38 with SC and one ciliated foregut cyst. MCNs were more often solitary (p=0.006). Although no other individual radiological characteristic on USS, CT or MRI was predictive of MCN, MDT outcomes stating that a cyst was complex in nature were highly predictive (p=0.0007). Cyst fluid Carbohydrate Antigen 19-9, Carcino-Embryonic Antigen and Cancer Antigen 125 were unable to differentiate MCN from SC (p = 0.45, 0.49, and 0.73 respectively).

Conclusions

MDT outcomes are of greatest value when trying to differentiate MCN from SC, as well as having a solitary cyst on imaging. Conventional cyst fluid tumour markers are unhelpful. All suspicious cystic liver lesions should be discussed pre-operatively by a hepatobiliary MDT to determine the most appropriate surgical approach.

Introduction

Mucinous Cystic Neoplasms of the liver (MCN), formerly known as biliary cystadenomas, are neoplasms of the biliary duct system [1]. Although predominantly benign, they have a risk of undergoing malignant transformation with an associated mortality [2,3]. It is advocated that cystic liver lesions suspected to be MCNs should undergo complete surgical excision. Preoperative identification aims to differentiate MCN from simple hepatic cysts (SC) to prevent major resectional surgery for patients with benign lesions.

However, accurate preoperative diagnosis of MCN is challenging. Cytology is rarely helpful and microbiological analysis only of value in the rare instances when the lesion is hydatid in origin [4]. Previous research into the preoperative characterisation of cystic liver lesions has subsequently focused on the role of imaging to differentiate MCN from SC.

This study reports on our centre's experience of using preoperative imaging and intraoperative cyst fluid tumour marker analysis in determining the nature of cystic liver lesions. Our aims were to determine if MCN and SC can be distinguished by:

a) Radiological characteristics on Ultrasound Scan (USS), Computerised Tomography (CT) or Magnetic Resonance Imaging (MRI);
b) Cyst fluid Carbohydrate Antigen 19-9 (CA 19-9), Carcino-Embryonic Antigen (CEA) or Cancer Antigen 125 (CA 125); or
c) Hepatobiliary Multidisciplinary Team (MDT) assessment.

Methods

A review of the unit's prospectively maintained patient database was undertaken. All patients between January 2006 and October 2014 that underwent surgery for symptomatic or suspicious liver cysts were included. Two patients were excluded due to the absence of a confirmed histological diagnosis. Pre-procedure imaging reports were reviewed and comments relating to cyst structure were recorded (Table 1) [5-7]. Cysts were classified pathologically based on the conclusion of the reporting histopathologist. Pathology department records were searched to determine if cyst fluid aspirates had been sent for tumour marker levels intraoperatively. The Multidisciplinary Team (MDT) outcomes were reviewed to determine if the clinical context (e.g. patient-reported symptoms) in combination with the summary of the radiological findings allowed for differentiation between SC and MCN.

Demographic data were analysed using descriptive statistics. Continuous data were analysed using Mann-Whitney U test and comparison of groups was performed using Fisher's exact test.

Results

Fifty-two patients were identified, 88% of whom were female (Table 2). Patients with MCN were significantly younger at diagnosis than patients with SC (Mann-Whitney U test p=0.002). There were 13 patients with MCN, 38 patients with SC, and a single patient with a ciliated foregut cyst (Figure 1). Fifty-eight surgical procedures were performed, of which 13 were secondary procedures undertaken during another surgical procedure (10 fenestrations during cholecystectomy, one fenestration during pancreaticoduodenectomy, one fenestration of a left-sided cyst during a right hemihepatectomy and one wedge liver resection during a distal pancreatectomy for a cystic lesion suspicious for tumour). Of note, two patients with MCN

initially had fenestration performed before definitive resection and nine patients with SC underwent liver resections. In two cases of MCN fenestration was initially performed as part of another procedure. After cyst wall histology confirmed MCN both patients underwent resection. In the patients with SC who had liver resections, three had symptomatic polycystic liver disease, two patients were classified as having suspicious cysts by the MDT, two patients had cyst excision during radical resection of other hepatobiliary malignancies and one patient had previously undergone a laparoscopic fenestration that had inconclusive histology. In one case, the indication for radical surgery was not known.

Cyst characteristics on imaging

One-hundred-and-seventeen imaging investigations were performed prior to the 58 procedures. The most common combination of pre-procedure imaging was USS and CT, with no significant difference noted in the likelihood of having a particular combination of pre-procedure imaging modalities between MCN and SC. There was no significant difference in average cyst size and no individual cyst feature was associated with MCN more frequently (Table 3). However, patients with MCN were more likely to have a single hepatic cyst on imaging (23.7% vs. 69.2%, Fisher's exact test p=0.0059).

MDT outcomes

All 52 patients were discussed at least once at the hepatobiliary MDT. Six of the 38 (16%) patients with SC were initially classified as complex by the MDT, compared to nine of the 13

(69%) cases of MCN. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value of MDT assessment in determining a diagnosis of MCN was 69.2%, 84.2%, 60.0%, and 88.8% respectively).

Cyst aspirate tumour marker levels

Thirty-five patients had cyst fluid aspirate sent for one or more tumour marker levels (Figure 2). There was no significant difference in the median values observed for CA 19-9, CEA or CA 125 levels between SC and MCN (Mann Whitney U test p = 0.45, 0.49, and 0.73 respectively). All MCNs had raised tumour markers in cyst aspirates. However, all simple cysts also had one or more abnormally raised tumour markers, making a raised value poorly predictive of MCN (PPV of 12.8%, 15.2% and 12.9% for CA 19-99, CEA and CA 125 respectively).

Discussion

Mucinous Cystic Neoplasms (MCNs) are rare tumours of the biliary duct system that usually (80-85%) arise in the liver and are most commonly found in middle-aged women [1,8,9]. MCNs have a reported incidence of one in 20,000 – 100,000 and account for 4.6% of intrahepatic cysts of biliary origin [8-11]. Due to a lack of disease-specific biochemical or radiological features, accurate pre-operative diagnosis is often challenging. The differential diagnosis includes parasitic cysts, mucinous and degenerative metastatic tumours, haemangiomas, hamartomas, teratomas, ciliated foregut cysts and congenital cystic dilatations as well as SC [8]. The importance of accurate pre-operative characterisation relates to the choice of surgical

intervention; symptomatic SC can be safely and effectively treated with laparoscopic fenestration, whereas MCN should undergo complete surgical excision due to the risk of malignant transformation. Current diagnostic algorithms to determine the most appropriate surgical intervention rely on the presence of complex features on radiological imaging and raised tumour markers in cyst fluid aspirate [10].

No imaging modality in standard clinical practice can differentiate between MCN and SC[4]. MCNs are classically described on imaging as low density, thick-walled, multilocular cystic masses with internal septa that occasionally contain mural nodules [1]. SCs characteristically have thin, regular walls with homogenous content, and are often multiple [4]. SCs can be mistaken for complex lesions if they have bled internally, giving a heterogenous appearance. In addition, MCNs that have undergone malignant transformation will have the same radiological features as benign MCNs [10,12-15]. Although USS, CT and MRI can be complementary and provide a wealth of information regarding cyst characteristics and their relationship to surrounding structures for preoperative planning, they are unable to confirm a diagnosis of MCN [1,16].

In this study, none of the three imaging modalities investigated were able to differentiate between MCN and SC, which is consistent with a recent literature review [1,17]. Irrespective of the imaging modality used, a solitary cyst on imaging was more predictive of MCN than any other feature. The classic features expected in such lesions (septa, increased echogenicity, wall thickening, irregularity, calcification and vascular or biliary deviation), although detected in at least one case of MCN by at least one of the three modalities, were nevertheless absent in the majority of cases of MCN. Moreover, one or more of these features were present in over half of images in histologically-proven cases of SC. The presence of septa on CT or MRI showed a trend

towards being predictive of MCN, but did not reach statistical significance. This may be due to the small number of cases of MCN in this study.

An MDT outcome stating that the cyst was complex in nature was more predictive of MCN than any individual imaging modality. Four cases (31%) of MCN were initially classified as being benign lesions by the MDT, which is a similar false negative rate to a previously published case series comparing pre-operative diagnoses with histology [18]. The MDT at our unit consists of hepatobiliary surgeons, hepatologists, oncologists, gastrointestinal radiologists, histopathologists and a cancer nurse specialist. Because the MDT does not review images in isolation but in combination with the clinical context, this may explain the high predictive value of MDT outcomes. For example, even though septations in isolation were not found to be predictive of MCN in this study, septations in the context of the clinical history and cyst progression over time may be more predictive of MCN and may account for the MDT's ability to identify suspicious cystic lesions correctly.

In the 13 patients where the procedure for the cyst was secondary to another surgical procedure, the primary diagnosis is likely to have significantly altered the management of those cysts. For example, the three patients with hepatobiliary malignancies were all discussed preoperatively at the MDT and a decision made then on how best to treat the cyst (two were fenestrated and one was resected based on pre-operative imaging, although all three were subsequently found to be SC). In the 10 patients who underwent cholecystectomy as their primary procedure, the decision to fenestrate an incidental cyst was likely made intra-operatively and MDT discussion only occurred after the histology of the cyst wall was available. This would explain why two MCNs were diagnosed following cholecystectomy with secondary cyst fenestrations, and MDT discussion occurred only after the first procedure. This highlights

the value of preoperative MDT discussion, even when the primary diagnosis being treated is not the cyst.

We did not find evidence that CA 19-9, CEA or CA 125 were able to differentiate between MCN and SC, which is consistent with previous studies [4,11,19]. However, it is important to note that the patients with SC in this study represent a selected group of patients with large cysts causing symptoms or displaying suspicious radiological features. These patients may represent a subgroup of SC that are more aggressive or rapidly growing in their natural history. This may explain why many of our cases of SC had a high number of septa and wall abnormalities identified on CT.

This study has several limitations. Firstly, the MRI imaging protocol changed during the nine year period of data collection in our hospital. Since 2010 the MRI liver protocol used liver-specific contrast agents and also provided diffusion-weighted (DW) MRI images which can improve the characterisation of liver lesions [20]. In addition, none of our cases underwent contrast-enhanced USS, which can increase the detection rate of septa and nodularity [21]. The histological reports were not directly compared with imaging reports to determine if the absence of complex features on imaging was confirmed histologically. Finally, this study only used five sets of cyst fluid tumour marker levels from four cases of MCN, none of which had evidence of malignant transformation.

In conclusion, this study found that a pre-operative MDT outcome stating that a cystic lesion is suspicious in nature is of greatest value when trying to differentiate SC from MCN. The most significant radiological finding is a solitary cyst present on imaging. Other radiological characteristics on USS, CT and MRI are unable to differentiate between SC and MCN. The authors

advocate that all symptomatic or radiologically suspicious cystic liver lesions should be discussed pre-operatively at a hepatobiliary MDT to determine both the likely nature of the lesion and the most appropriate surgical approach. Advanced imaging techniques such as contrast-enhanced USS and diffusion-weighted MRI should be considered in the future to try to improve the preoperative characterisation of cystic liver lesions.

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Conflicts of interest

The authors have no conflict of interest to declare.

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Table and Figure Titles and Legends

Table 1

Title — Study definitions of radiological features and histology for simple hepatic cysts and mucinous cystic neoplasms of the liver

Table 2

Title — Demographic data and surgical interventions performed on 13 patients with mucinous cystic neoplasms of the liver and 38 patients with simple hepatic cysts

Legend — IQR = Interquartile range

Figure 1

Title — The ultrasound, CT and MRI findings of three patients with mucinous cystic neoplasms of the liver, with corresponding histology

Legend — *Haematoxylin and eosin staining displaying ovarian-type stroma and mucinous epithelial lining

Table 3

Title — A comparison of radiological characteristics in 38 patients with simple hepatic cysts and 13 patients with mucinous cystic neoplasms of the liver

Legend — IQR = Interquartile range, USS = Ultrasound scan, CT = Computerised Tomography, MRI = Magnetic Resonance Imaging

Figure 2

Title — Cyst fluid aspirate CA 19-9, CEA and CA 125 levels in four patients with mucinous cystic neoplasm of the liver and 30 patients with simple hepatic cysts

Legend — Median SC vs. MCN: CA 19-9 48,082 vs. 8134 U/ml, CEA 25.6 vs. 12.5 ng/ml, CA 125 351 vs. 417 U/ml

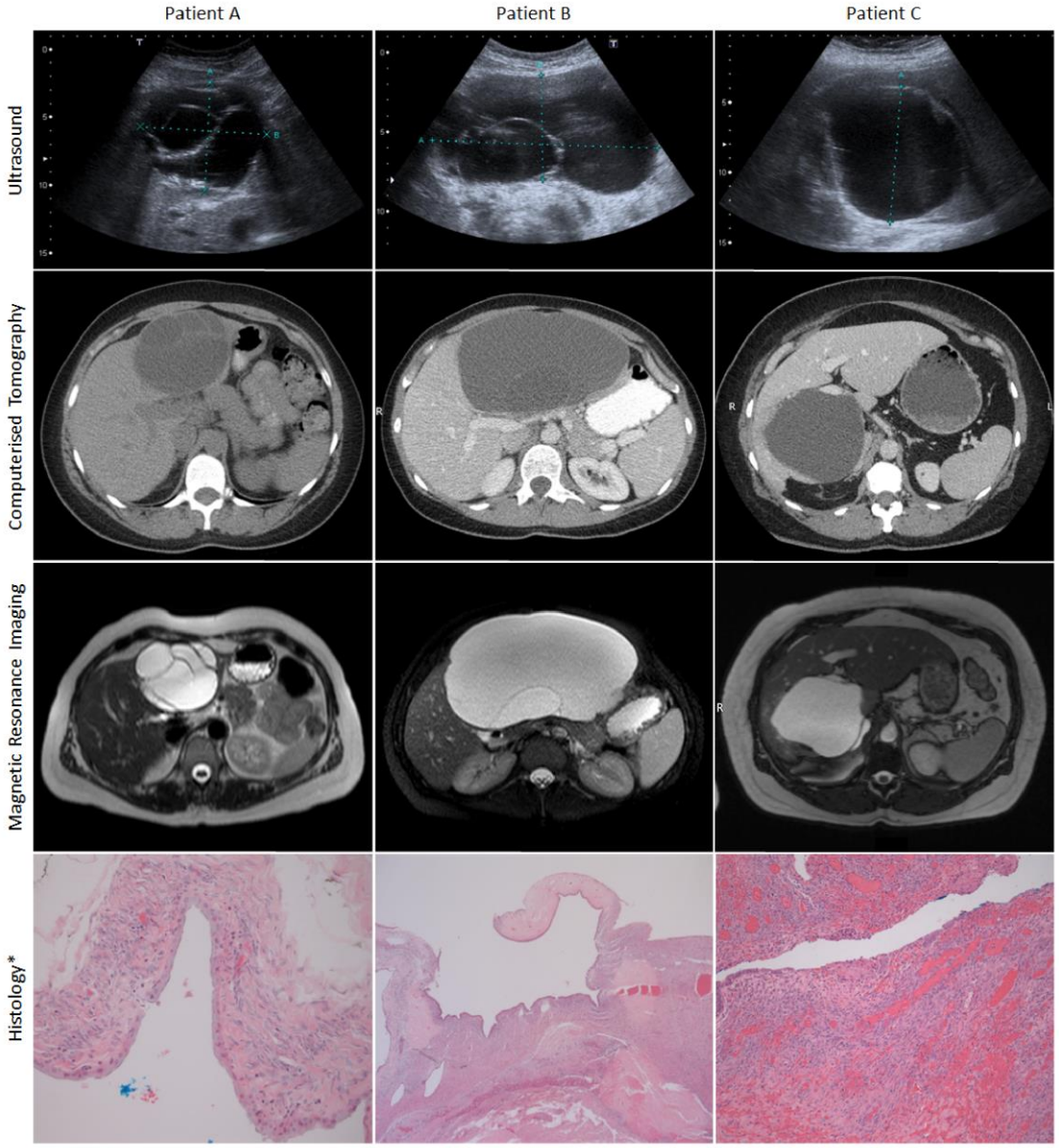
Table 1 Study definitions of radiological features and histology for simple hepatic cysts and mucinous cystic neoplasms of the liver

Definition		Description
Cyst feature	Septation	One or more septa spitting a cyst into two or more compartments
	Increased echogenicity	Cyst fluid on USS that is more echogenic than would be expected for serous fluid
	Wall thickening	Any easily visible cyst wall
	Wall irregularity	Any heterogeneity in cyst wall thickness
	Wall calcification	Calcium deposits within the cyst wall
	Biliary deviation	Distortion of the normal anatomy of the biliary tree
	Vascular deviation	Distortion of the normal anatomy of the surrounding vasculature
	Daughter cysts	Small cysts within a larger cyst
Histology	Simple hepatic cyst (SC)	Hepatic cyst lined by cuboidal epithelium
	Mucinous Cystic Neoplasm (MCN)	Hepatic cyst with epithelium ranging from columnar, cuboidal, or mucinous epithelium to malignant cells with tubulopapillary growth. There may be capsular invasion, stromal changes or ovarian-like cellular stroma

Table 2 Demographic data and surgical interventions performed on 13 patients with mucinous cystic neoplasms of the liver and 38 patients with simple hepatic cysts

Demographic and procedural data	Simple Hepatic Cyst	Mucinous Cystic Neoplasm
Number of patients		
[n (%)]	38 (75)	13 (25)
Demographics		
Age (years) [median, IQR, (range)]	63, 14 (32-83)	46, 24 (21-73)
Female [n (%)]	33 (87)	13 (100)
Procedure		
Laparoscopic fenestration	31	2
Right hemihepatectomy	5	6
Left hemihepatectomy	3	7
Open fenestration	3	-
Wedge resection of liver	1	-
Total	43	15

Figure 1 The ultrasound, CT and MRI findings of three patients with mucinous cystic neoplasms of the liver, with corresponding histology

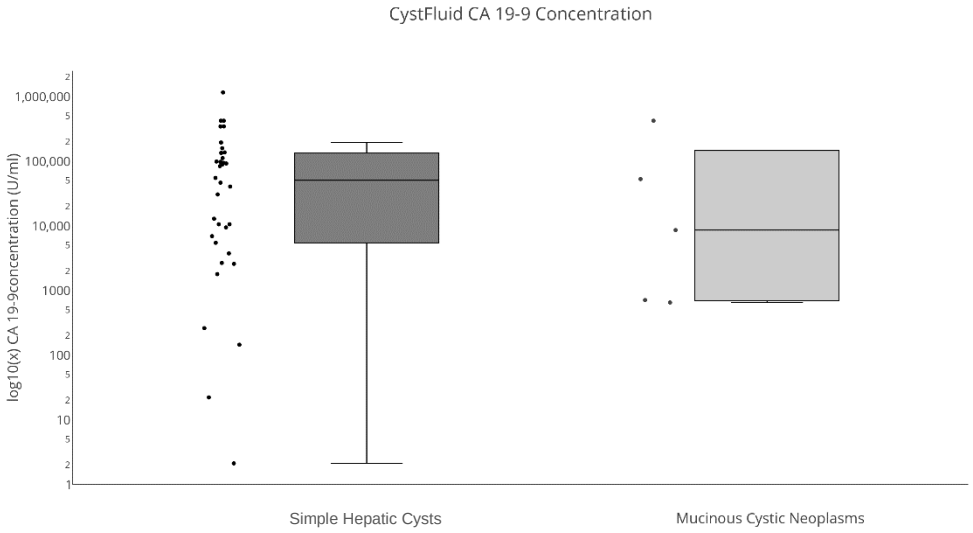


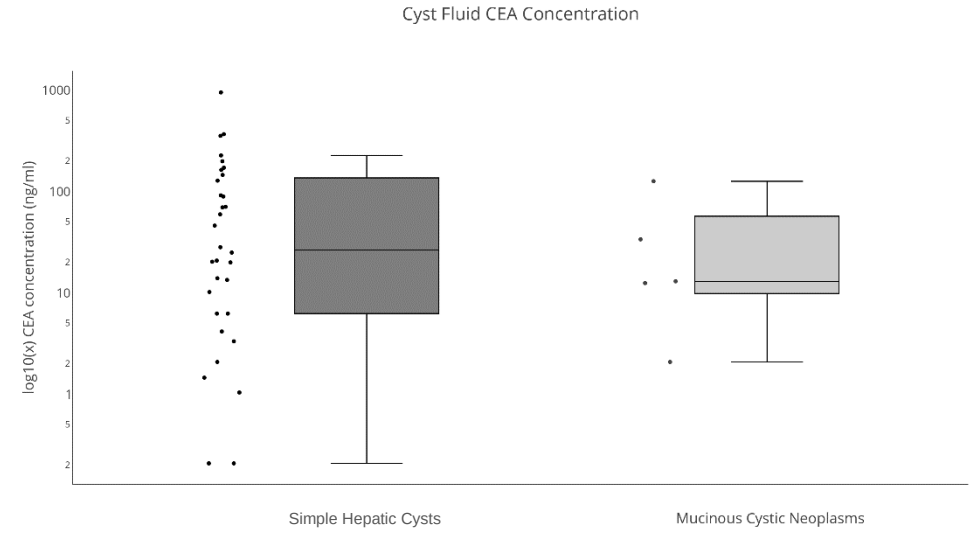
*Haematoxylin and eosin staining displaying ovarian-type stroma and mucinous epithelial lining

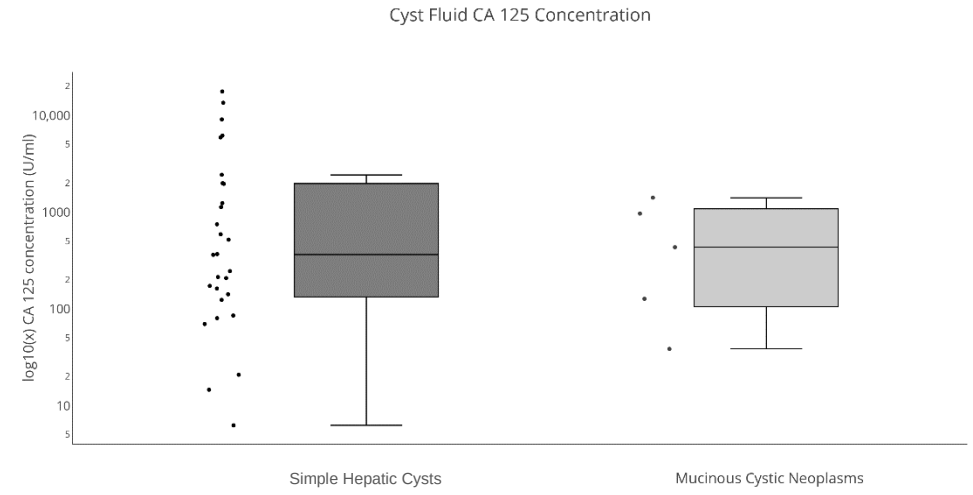
Table 3 A comparison of radiological characteristics in 38 patients with simple hepatic cysts and 13 patients with mucinous cystic neoplasms of the liver

Image feature	Simple Hepatic Cysts		Mucinous Cystic Neoplasms		p-value
	Number	Percentage (%)	Number	Percentage (%)	
Largest cyst size (cm) [median, IQR, (range)]	12, 9 (2-72)	-	13, 7 (6-18)	-	0.475
Number of hepatic cysts on imaging	(n=38)	-	(n=13)	-	
1 cyst	9	23.7	9	69.2	**0.006***
2 cysts	7	18.4	1	7.7	0.662
>2 cysts	22	57.9	3	23.1	0.052
Features identified on imaging					
USS	(n=33)	-	(n=12)	-	
Simple	13	39.4	3	25.0	0.491
Septated	10	30.3	7	58.3	0.163
Increased echogenicity	12	36.4	5	41.7	0.743
Wall abnormality	6	18.2	0	0.0	0.171
Biliary dilatation/deviation	2	6.1	1	8.3	1.000
Vascular deviation	0	0.0	1	8.3	0.267
Daughter cysts	0	0.0	1	8.3	0.267
CT	(n=37)	-	(n=13)	-	
Simple	18	48.6	4	30.8	0.339
Septated	7	18.9	6	46.2	0.073
Wall abnormality	9	24.3	5	38.5	0.474
Biliary dilatation/deviation	3	8.1	1	7.7	1.000
Vascular deviation	2	5.4	0	0	1.000
Daughter cysts	0	0.0	1	7.7	0.260
Rim enhancement	1	2.7	0	0	1.000
MRI	(n=12)	-	(n=8)	-	
Simple	4	33.3	1	12.5	0.603
Septated	3	25.0	6	75.0	0.065
Wall abnormality	3	25.0	1	12.5	0.619
Biliary dilatation/deviation	2	16.7	0	0.0	0.495
Vascular deviation	3	25.0	2	25.0	1.000
Daughter cysts	0	0.0	2	25.0	0.400
Rim enhancement	0	0.0	1	12.5	0.147

Figure 2 Cyst fluid aspirate CA 19-9, CEA and CA 125 levels in four patients with mucinous cystic neoplasm of the liver and 30 patients with simple hepatic cysts







Legend: Median SC vs. MCN: CA 19-9 48,082 vs. 8134 U/ml, CEA 25.6 vs. 12.5 ng/ml, CA 125 351 vs. 417 U/ml