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RESEARCH ARTICLE

MUCINOUS CYSTIC NEOPLASM OF LIVER - PEELING SIGN MITIGATES A DIAGNOSTIC CONUNDRUM

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Abstract

Background: Mucinous cystic neoplasms (MCN) are rare primary cystic neoplasms of the liver. It is commonly misdiagnosed for other cystic SOL's of liver. Clinical management of MCN is challenging due to scant literature on pre-operative and per-operative indices to distinguish MCN from other cystic SOL's of liver. Imprecise diagnosis leading to suboptimal surgical management results in recurrence and progression to malignancy.

Methods: A retrospective analysis of cystic SOL's from July 2019 to July 2023 was analyzed in our centre. Data collection included demographics, clinical presentations, imaging characteristics, surgical techniques, intra-operative observations, complications, histopathology, post-operative follow-up, morbidity, and mortality.

Results: Between July 2019 and July 2023, six patients were diagnosed and treated for MCN at our centre. Female patients were predominant (5 out of 6) with average age of 45.5yrs (Range 26-53). Abdominal discomfort was the commonest symptom (50%). All patients underwent abdominal ultrasounds and CT scans, while MRI was done in one patient. Two were misdiagnosed with non-neoplastic liver cysts and one had an ambiguous diagnosis. Four patients underwent liver resection and two had enucleation. All were MCN by HPE. In 3 patients, with ambiguous pre-op diagnosis, our recommended pre-operative and per-operative strategy including "THE PEELING SIGN" was helpful in diagnosing MCN. No recurrences were observed at 43 months of follow up.

Conclusions: Liver MCNs are infrequent and often mistaken for other hepatic cystic conditions. By applying our pre-operative and per-operative indices, patients with MCN of liver can be diagnosed with precision and offered radical surgery.

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Introduction:-

Cystic space-occupying lesions (SOLs) of liver are frequently discovered due to increased cross-sectional imaging use [1]. The most typical cystic tumors originating in the liver are known as mucinous cystic neoplasm (hepatobiliary

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cystadenoma). Liver is the most common site in 83% to 94% of patients, [2, 3, 4]. There are myriad of differential diagnoses, and those challenging the recognition of mucinous cystic neoplasms are simple cysts and hydatid cysts (CE1, CE3, CE4). Geographic location can influence the differential diagnosis. Since the treatment modality differs it is essential to differentiate simple/Hydatid cyst from biliary cystadenomas. Mucinous cystic neoplasms (MCN), are rare, with estimated incidences of 1 in 20,000-100,000 for non-invasive MCN and 1 in 10,000,000 for cystadenocarcinoma [5]. They may present with non-specific abdominal symptoms, as incidental findings, or during surgery for presumed benign cysts. The natural history of MCN remains uncertain, but complete excision is often recommended due to the risk of post-operative recurrence and malignant progression [6][7]. With this background, we reviewed our experience in a single tertiary-care centre, with patients who underwent surgery for MCN, and suggest pre operative and intra operative strategies to aid in the diagnosis which facilitates complete excision of MCN liver.

Materials and Methods:-

After permission from the institutional ethical committee, a retrospective analysis of all consecutive patients admitted with hepatic cysts and who had undergone a surgical procedure, with a final histopathological confirmation of biliary mucinous cystic neoplasm from July 2019 to July 2023 was analyzed. [Figure 3]. Pre-operative data (demographics, symptoms, examination features, imaging findings), operative data (type of procedure, intra-operative findings, operative time), and post-operative data (length of stay, histopathology, complications, and follow-up, morbidity and mortality) were extracted from the patient's records. All patients were evaluated with Ultrasound and a dedicated CT scan. MRI scans were taken in cases when CT imaging was uncertain, or when MCN was strongly suspected. Patients with a well-defined preoperative diagnosis of MCN underwent surgical resection and/or complete enucleation. In patients with inconclusive diagnosis, and in those with a high suspicion of MCN, we utilized our pre-operative and intra-operative diagnostic strategies to offer liver resection/enucleation. Follow-up data were obtained from outpatient clinic records.

Results:-

Six patients underwent surgery for MCN liver between 2019 and 2023. Demographic data and primary clinical manifestations are detailed in Table 1. All patients were less than 60 years of age, with abdominal pain as the predominant symptom. Liver function tests were normal, and CA 19-9 was performed in all patients. Imaging characteristics are documented in Table 2, Figure 1, the cysts were located most commonly in the left hemi liver (84%) [Lateral segment S2, 3(50%), central/left paramedian segments S4a, b (16%)], and least commonly in right liver [S6, 7 (16%)]. Cyst diameter ranged from 7-26 cm. Operative procedure and details are presented in Tables 3&4. All central or paramedian cysts were treated with enucleation (n = 2), and liver resection was done in 4 patients (n= 4). Laparoscopic liver resection (segmentectomy) and enucleation was done in 3 cases which also reflects the current literature on the minimally invasive possibility in MCN [10]. Post-procedural outcomes are documented in Table 5. There were two post-operative complications. There was no 90-day mortality. Final pathology revealed non-invasive MCN in all 6 patients. The median follow-up was 19.5 months. None of the patients who underwent enucleation or resection experienced a recurrence.

Discussion:-

In this review, we have analyzed on the management of intrahepatic MCN and believe in contributing to a relatively limited body of literature concerning this uncommon condition. Historical literature reviews have indicated the reporting of fewer than 300 cases [6, 7, 8–15]. Lesions described in our study as MCN (mucinous cystic neoplasm, previously hepatobiliary cystadenomas) are as per the recent WHO classification [16]. These lesions typically exhibit single multilocular cysts of varying sizes, lacking communication with the bile ducts. Microscopically, they display well-defined pseudocapsule (Figure 2C), a single-layered epithelium (simple cuboidal, columnar), and a basement membrane (Figure 2D). Additionally, beneath the basement membrane, a layer of highly cellular mesenchymal tissue is typically present, resembling normal ovarian stroma [18] (Figure 2D). The presence of a pseudocapsule separating the hepatic parenchyma from the cyst wall is a notable feature (Figure 2C) which we believe to be strong predictor of favoring a diagnosis of MCN. While MCNs are typically mucinous, a serous variant lacking ovarian-like stroma is also recognized. Notably, our study specifically focuses on MCN, excluding cases recently described as a cystic variant of Biliary-IPN [14, 17]. Cystic Biliary-IPN is often associated with clinically significant cyst formation, usually due to ductal dilation and mucin blockage. Distinguishing it from MCN can be based on communication with the biliary tract on imaging or pathologically by the absence of ovarian-type stroma in histological examination.

Nevertheless, a rare variant of MCN without ovarian-type stroma, occasionally observed in men, adds complexity to this differentiation [17].

Our data revealed that MCNs predominantly present as large cysts, primarily in young or middle-aged females, consistent with findings from existing literature [20-23]. While some authors have suggested that MCNs occur exclusively in women [15], our data, along with previous studies, suggests that males can account for 0-10.5% of cases when excluding cystadenocarcinoma [6, 7, 8, 9, 12–15]. The average maximum cyst diameter in our study was approximately 12.6 cm, similar to previous research papers, where cysts typically exceeded 10 cm in size [6, 7, 8, 9, 12, 13, 15]. Our study also found that the majority of cysts (5 out of 6) were situated in the anatomical left lobe of the liver or in central/paramedian regions near the confluence of portal or hepatic veins, consistent with patterns observed by Vogt et al. and Wang et al. [7, 15]. The underlying cause of this distribution is not immediately apparent but could be linked to the location of embryonic tissue normally found in the adult gallbladder [19]. Recent reviews recommend considering a diagnosis of MCN for inconclusive cysts which occur exclusively in the left paramedian (Seg 4a, 4b) sector of liver.

In this series, intraoperative frozen section analysis was not attempted to rule out MCN. This omission was due to challenges related to non-representative surgical material, insufficient pathological sampling, or intricate histological interpretation. Other groups have suggested pre-operative cyst fluid analysis for CA 19-9 and carcinoembryonic antigen, but the results have been mixed [10, 12].

The natural progression of this lesion is not well-understood, and malignant transformation likely occurs over several years [17, 18]. The rate of malignancy in comparable surgical or pathological series of MCN has shown significant variability, ranging from 3.4% to 42% [6, 7, 8, 9, 11, 13, 15, 19]. Due to the associated risk of malignancy, many experts advocate complete excision of all intrahepatic MCNs [6, 7]. In our study, all patients underwent complete excision, with no observed progression to malignancy during follow-up periods ranging from 1.5 to 43 months.

Our observation has identified 10 decisive strategies, four preoperative and six intra operative, which differentiates MCN and Hepatic hydatid disease. The preoperative imaging findings that favored MCN are summarized in **Table 6**. The intra operative findings are summarized in **Table 7**. The intra operative findings more specific for MCN were, 1. The absence of parieto-capsular adhesions, which are dense string-like adhesions extending from the capsule of the liver segment involved, to the adjacent parietal wall (absent in all cases of MCN), 2. Presence of clear serous, mucinous, haemoserous, and absence of white viscous, bilious fluid in the cyst (positive in all cases of MCN- hence we recommend visual inspection of the cyst fluid after aspiration), 3. Absence of pearly white inner lining and absence of endocyst – (positive in all cases of MCN- hence we recommend intra cavitory inspection of the cyst cavity after aspiration), and 4. **“THE PEELING SIGN”** (Figure 2A)- Probably the most definitive finding and hence described as a **“SIGN”**- is the ability to easily peel off the cyst wall from the surrounding liver parenchyma which is present in all cases of MCN but is impossible in all hepatic hydatid cysts. Hence we recommend a trial peel of the cyst wall from the adjacent parenchyma which when easily accomplished, definitively favors a diagnosis of MCN. **“THE PEELING SIGN”** is based on the pathology of the cyst which has a pseudocapsule (Figure 2C) that is densely hyalinised and surrounds the cyst, and also separates it from the adjacent liver parenchyma making it possible to be enucleated. If all the preoperative and intra operative strategies are fulfilled, definitive operative decision with formal resection or enucleation can be planned based on the location of the cyst. The most advantageous aspect of the intraoperative decisive strategies recommended is that, in this minimally invasive era these can be assessed in both open and laparoscopic platforms.

The current study has clear limitations. It is retrospective with a small sample size. When compared to the existing literature on this topic, the current series contributes to literature especially in hepatic hydatid endemic areas.

Conclusion:-

Liver MCNs are infrequent and often mistaken for other hepatic cystic conditions, leading to suboptimal surgical interventions. Any atypical liver cystic lesion should raise the suspicion of hepatobiliary cystadenomas. In the current series, MCN (hepatobiliary cystadenomas) of the liver presented as large central/left-sided cysts in young or middle-aged women. Implementing targeted pre-operative and intra-operative decision-making strategies can elevate diagnostic accuracy, facilitating comprehensive resection to mitigate the risk of relapse and malignancy.

Table1:- Patient Data. (n=6).

Patient demographics	
Gender, F:M	5:1
Female: Male (%)	80:20
Age, years, mean, SD	45.5, +/- 11.4, range 26-53
Presenting symptoms	
Abdominal pain	3 (50%)
Asymptomatic	2 (34%)
Abdominal distension	1 (16%)
Physical examination findings	
Nil detected	4 (68%)
Abdominal fullness	1 (16%)
Abdominal (epigastria) tenderness	1 (16%)

Table2:- Imaging Characteristics.

Imaging performed	
Ultrasound	6/6
CT (contrast enhanced)	6/6
MRI	1/6
Cyst location	
Left lateral segments (seg2,3)	3 (50%)
Central/Left paramedian segments (seg4a,b)	2 (34%)
Right posterior segments (seg 6,7)	1 (16%)
Definitive preoperative diagnosis	
Definitive of MCN	3 (50%)
Hydatid cyst	2 (34%)
Inconclusive	1 (16%)
Imaging findings	
Single cyst	6
Multiloculated cyst	6
Internal septations	6
Well defined capsule	6
Enhancing cyst wall	5
Absence of biliary communication	6
Maximal cyst diameter, in cm, SD	12.6 +/- 6.7 cm, range7-26

Table3:- Operative Procedures.

Pre operative Cyst location	Preoperative Diagnosis	Procedure done	Open / Lap
Seg 2,3	MCN	Left lateral segmentectomy	Lap
Seg 2,3,4	MCN	Left hepatectomy	Open
Seg 6,7	MCN	Nonanatomical resection	Lap with open conversion
Seg 4b	Inconclusive ^a	Enucleation	Lap
Seg 4ab	Hydatid cyst ^a	Enucleation	Lap with open conversion
Seg 2,3	Hydatid cyst ^a	Left lateral segmentectomy	Lap

^a preoperative and intra operative decision strategy applied.

Table 4:- Operative details.

1. Operative time, mins	Median 179, range 108-348	
Left hepatectomy(open)	1	348
Left lateral segmentectomy (lap)	2	108,126
Enucleation (lap)	1	166
Enucleation (open conversion)	1	192
Nonanatomical resection (open conversion)	1	212

Table 5:- Procedural outcomes.

Hospital stay, median, days	9.5, range 7-20
Complications	Biliary leak (2), SSI (1)
Follow-up, median, months	19.5, range 1.5-43
Recurrence	
Post resection	0/6
Post enucleation	0/6

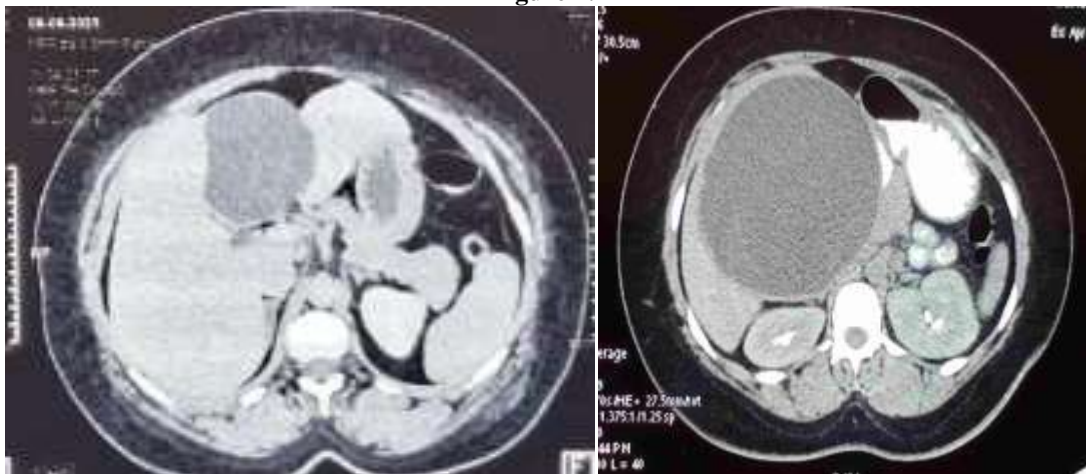
Table6:- Preoperative strategy.

Female gender	FAVOURS MCN LIVER
Left lobe / Paramedian or central cyst	
Single & Multilocular cyst	
Absence of biliary communication	

Table 7:- Intraoperative strategy.

Intraoperative findings	
Appearance of blue domed cyst (2/2)	Surface cysts
Thin-walled cyst (4/6)	Intra parenchymal cyst
Absence of parietocapsular adhesions (6/6)	Adhesions between the liver capsule & parietal wall
Cyst fluid aspiration and inspection of fluid (6/6)	Presence of serous, mucinous, hemoserous fluid. Absence of white viscous, bilious fluid – both favoring MCN
Intra cavitory inspection (6/6)	Absence of pearly white inner lining, absence of endocyst – both favoring MCN
‘THE PEELING SIGN’ (3/3)	Easily peelable cyst wall from the surrounding hepatic parenchyma.

Figure 1:-



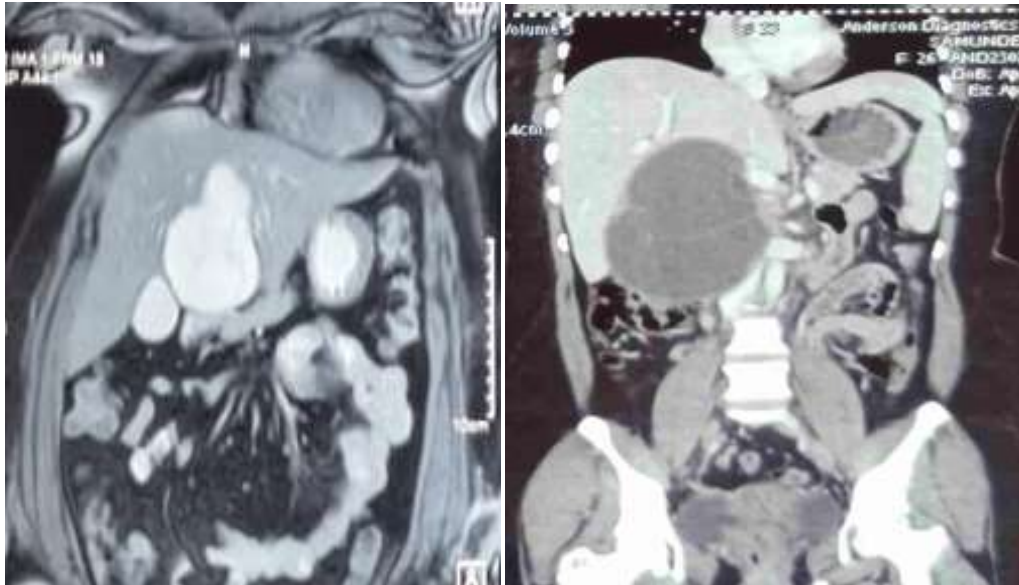


Figure 2:-

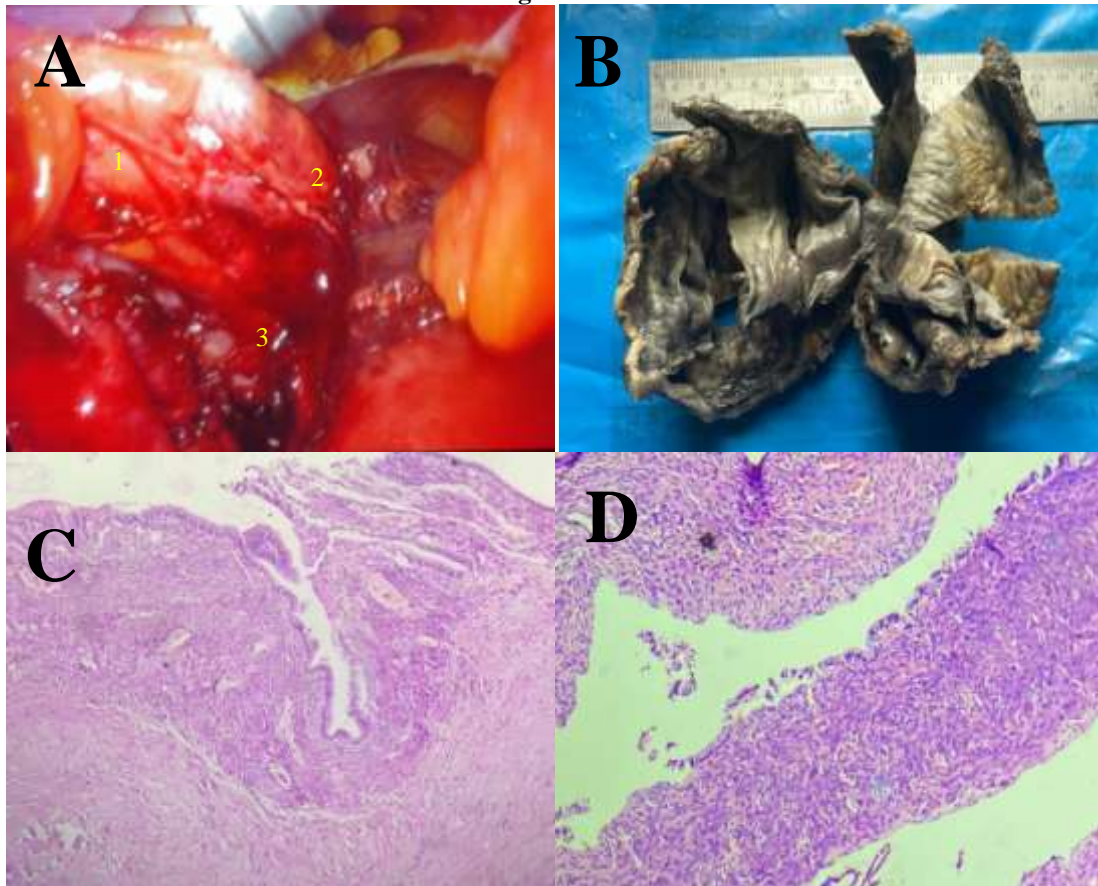


Figure legends :

Figure 1: CT scan plain axial (1A), oral and intra venous contrast axial and coronal view (1B and 1C), depicting cystic SOL liver in segments IV and V and MRI coronal view showing high signal intensity on T2-weighted images (1D).

Figure 2:A, Intra operative image depicting the peeling sign, 1)Cyst wall 2) Liver parenchyma 3) Interface between hepatic parenchyma and the cyst wall. **B**, Gross morphology of MCN liver. **C**, Hematoxylin and eosin staining (400x) showing columnar mucinous lining epithelium with cyst wall, ovarian like stroma, and the pseudocapsule. **D**, Hematoxylin and eosin staining (400x) showing mucinous lining epithelium with cyst wall showing ovarian like stroma.

Figure 3: Flowchart of patients diagnosed with MCN liver and analyzed for the study

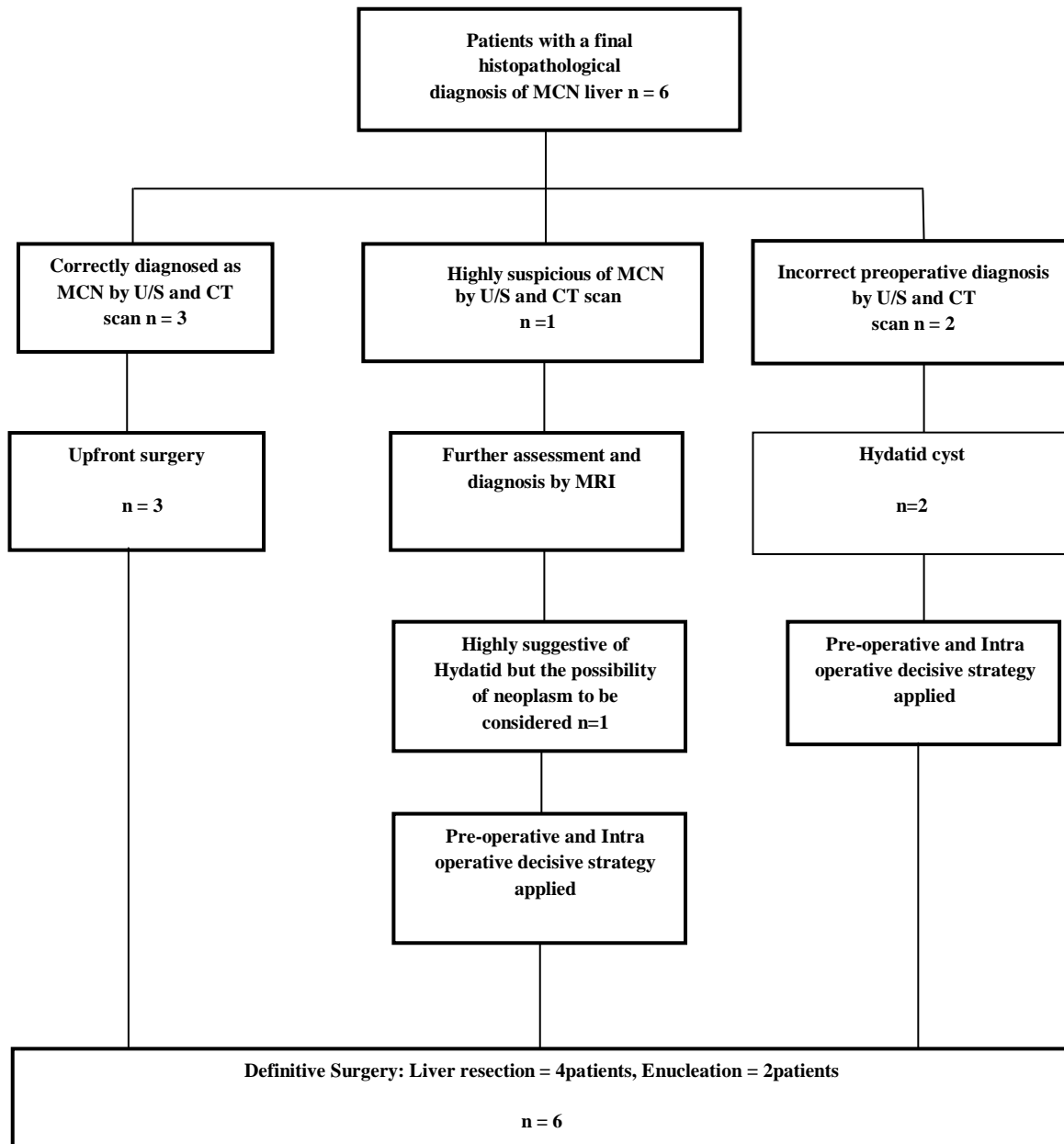


Figure 3:-

Abbreviations

MCN: Mucinous cystic neoplasm US: Ultrasonography; CT: Computed Tomography; MRI: Magnetic resonance imaging; WHO: World Health Organization; SOL: Space-Occupying lesions; Biliary-IPN- Biliary intra ductal papillary neoplasm.

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