

Rare cystic liver lesions: A diagnostic and managing challenge

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Author contributions: All authors contributed equally to this work; Bakoyiannis A and Delis S designed the research; Bakoyiannis A performed the research and wrote the paper; Triantopoulou C contributed regarding diagnostic work up and imaging modalities; and Dervenis C analyzed the data and reviewed the paper before submission.

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Received: May 23, 2013 Revised: September 10, 2013

Accepted: September 16, 2013

Published online: November 21, 2013

Abstract

Cystic formations within the liver are a frequent finding among populations. Besides the common cystic lesions, like simple liver cysts, rare cystic liver lesions like cystadenocarcinoma should also be considered in the differential diagnosis. Thorough knowledge of each entity's nature and course are key elements to successful treatment. Detailed search in PubMed, Cochrane Database, and international published literature regarding rare cystic liver lesions was carried out. In our research are included not only primary rare lesions like cystadenoma, hydatid cyst, and polycystic liver disease, but also secondary ones like metastasis from gastrointestinal stromal tumors lesions. Up-to date knowledge regarding diagnosis and management of rare cystic liver lesions is provided. A diagnostic and therapeutic algorithm is also proposed. The need for a multidisciplinary approach by a team including radiologists and surgeons familiar with liver cystic entities, diagnostic tools, and treatment modalities is stressed. Patients with cystic

liver lesions must be carefully evaluated by a multidisciplinary team, in order to receive the most appropriate treatment, since many cystic liver lesions have a malignant potential and evolution.

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Key words: Liver cyst; Cystic tumor; Hepatic lesion; Gastrointestinal stromal tumors; Metastases; Cystadenoma; Cystadenocarcinoma; Hydatid cyst; Polycystic liver disease; Caroli; Echinococcus

Core tip: This paper reviews diagnosis differential diagnosis and management of rare cystic liver lesions which should be considered when a cystic hepatic lesion is identified. A diagnostic and therapeutic algorithm is provided. Patients with cystic liver lesions must be carefully evaluated by a multidisciplinary team, in order to receive the most appropriate treatment, since many cystic liver lesions have a malignant potential and evolution.

Bakoyiannis A, Delis S, Triantopoulou C, Dervenis C. Rare cystic liver lesions: A diagnostic and managing challenge. *World J Gastroenterol* 2013; 19(43): 7603-7619 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v19/i43/7603.htm> DOI: <http://dx.doi.org/10.3748/wjg.v19.i43.7603>

INTRODUCTION

Cystic lesions within the liver have been reported to occur in up to 5% of the population^[1]. Most of them are common and benign, but the possibility of a rarer cystic liver lesion, such as hepatobiliary cystadenoma (HC) or hepatobiliary cystadenocarcinoma (HCA), should not be overlooked. They can present with general or specific symptoms depending of the nature of the lesion, or they

can be silent and discovered accidentally^[2]. In fact, most are found incidentally on imaging studies and tend to have a benign course, but a minority may cause symptoms, and rarely may be associated with serious morbidity and mortality^[2]. The aim of our review is to focus upon the diagnostic and therapeutic algorithm of rare cystic lesions, including cystadenomas/cystadenocarcinomas, hydatid disease, polycystic liver disease, and metastatic neoplasms from the view of surgeons specialized in hepatobiliary surgery.

CYSTADENOMA AND CYSTADENOCARCINOMA

It is estimated that cystic neoplasms constitute approximately 5% of liver cysts, among which the malignancy is about 5%^[2,3]. The overall incidence among hepatic malignant tumors is lower than 0.41%^[2,3]. About 200 cases of HC, and a little more than half as many HCa, have been reported in the literature^[4].

More than 85% of HC are reported in women, and typically in middle-aged persons in the fifth decade of life. HC is an unusual cystic lesion accounting for less than 5% of all biliary neoplasms^[2,4]. The incidence of HCa is approximately 1 per 10 million patients. Malignant transformation is known to occur from HC to HCa. Older patients in the sixth decade of life are more likely to present with malignant tumors^[2,4].

The histogenesis of HC is unknown, although a congenital origin is generally favored. A reactive process to some focal injury is still debated^[5,6]. Pathologically, HC are multiloculated cysts with a stratified or pseudo-stratified non-ciliated columnar or cuboidal epithelium that contains mucous-producing cells. Papillary infolding is frequently present, and the mesenchyma underlying the tumor is usually hyper cellular, often with ovarian-appearing cells (85%-90%)^[7-9]. The pre-malignant progression of HC is based on the histologic presence of intestinal metaplasia (IM), characterized by the presence of numerous goblet cells^[10,11]. HC can easily be distinguished histologically from HCa, where a loss of epithelial nuclear stratification and a tubulo-papillary architecture with nuclear pleomorphism and atypia predominates. The malignant epithelium is multilayered with numerous papillary projections, and the confirmation of an invasion of the stroma confirms the diagnosis of HCa.

Regardless of the various diagnostic modalities, such a lesion (HC) may be difficult to distinguish preoperatively from an HCa^[12].

The majority of HC is asymptomatic and discovered incidentally during radiographic studies, or they can present with symptoms related to tumor compression of adjacent organs due to their large size^[2]. Patients presenting with symptoms generally complain of abdominal pain, abdominal distension, or a palpable mass. Less common presentations include intra-cystic hemorrhage, rupture, and fever from secondary bacterial infection. Any patient presenting with recurrence of liver cysts after treatment

should be suspected of having a neoplastic cyst until proven otherwise^[12].

HC and HCa should be differentiated from benign cystic hepatic lesions, including simple hepatic cyst, hepatic abscess, and echinococcal (hydatid) cyst. Simple hepatic cysts usually lack septa. Though hepatic abscesses and echinococcal cysts may appear similar to cystadenocarcinoma on diagnostic imaging, both infectious diseases are easily diagnosed through clinical and laboratory findings. Improvements in imaging techniques have helped to identify HC and HCa.

Ultrasound is an excellent modality that may delineate a simple cyst from other cystic lesions. Additionally, needle aspirates can be performed under ultrasound guidance. Simple cysts appear as anechoic unilocular fluid-filled space with imperceptible walls and posterior acoustic enhancement. A simple cyst is defined as a well-demarcated water attenuation lesion that does not enhance after the administration of intravenous contrast^[2,4].

Contrast enhanced ultrasound (CEUS) is useful in assessing the vascularity of a mural nodule and making a distinction between a mural or septal nodule and intracystic debris^[13]. In conventional ultrasound cystic lesions with solid components (septa, wall, mural nodule), this represents a wide range of rare entities like HC and HCa, as well as more common entities like simple liver cysts (after bleeding or with cell detritus), liver abscesses, or necrotic liver tumors^[13]. CEUS can be informative regarding the vascularity of solid parts of a cystic lesion. Simple cysts, which are unclear in conventional ultrasound, might be identified in CEUS^[13]. A cystic liver lesion without vascularization is most probably benign. CEUS is helpful in evaluating nodule vascularity and facilitates the final diagnosis^[13].

On conventional ultrasound, a HC typically appears hypoechoic, with thickened irregular walls and occasional internal echoes. Xu *et al*^[13], Lin *et al*^[14], and Anderson *et al*^[15] describe it as a well-defined unilocular, or more typically multilocular, cystic mass with mural or septal nodules in rare cases. On CEUS, a HC presents with septa enhancement during the arterial phase and hypo-enhancement during the portal and late phases^[13,14]. Cystadenocarcinoma, on the other hand, appears as a multilocular cystic mass with mural or septal nodules with thick and coarse calcifications on the septa on conventional ultrasound, while appearing on CEUS with septa enhancement during the arterial phase, mural or septal nodules enhancement and hypo-enhancement during the portal or late phase^[13,14]. Xu *et al*^[13] reported that on CEUS there is no significant difference between cystadenoma and cystadenocarcinoma regarding enhancement pattern and extent. Simple cysts, unlike HC, are virtually never septated^[2,4]. Ultrasonography (US) is a very useful initial investigation in these patients as it demonstrates cystic lesions with thin internal septations, debris, projections, or mural nodes, and it can in most cases accurately distinguish simple from neoplastic cysts (Figure 1A).

Differential diagnosis between HC and HCa is dif-

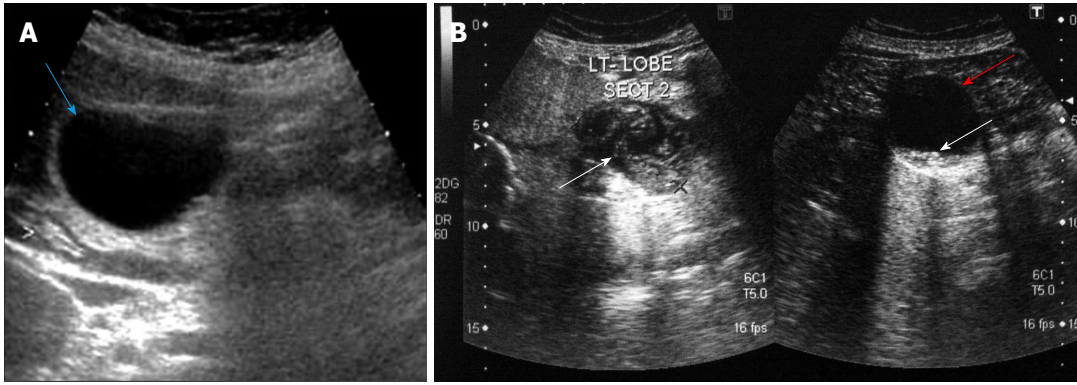


Figure 1 Ultrasound image. A: Showing an anechoic mass in the liver (light blue arrow), with a rather thin capsule (cystadenoma); B: Showing two echinococcal cysts. The first on the right (red arrow-right image) appears as an anechoic mass with hydatid sand (type CE1) (white arrow-right image), while in the second (on the left), the detached and folded endocyst membrane is obvious (type CE3) (white arrow-left image).

ficult. Although the presence of mural nodularity is not pathognomonic for cystadenocarcinoma, the absence of mural nodularity is suggestive of cystadenoma^[15,16]. The diameter of the mural nodule (when it exists) in cystadenomas is much smaller (less than 1.0 cm) than mural or septal nodules in cystadenocarcinomas (larger than 1.0 cm)^[13]. It seems that the presence of the internal septations and a mural or septal nodule, as well as the nodule diameter, might be diagnostic clues for differentiation between cystadenoma and cystadenocarcinoma^[13]. The other differential-diagnostic characteristic between HC and HCa is that cystadenomas are more typically multilocular cystic lesions and cystadenocarcinomas more typically unilocular cystic or solid lesions^[13].

Computed tomography (CT) is another useful modality to evaluate a cystic lesion of the liver. On a CT scan, a cystadenoma may be unilocular, multilocular, or may have septations. In a study from Vogt *et al*^[3], all patients demonstrated septations within the cyst at the CT scan. The cyst wall is usually thickened or irregular, in contrast to a simple cyst. A cystadenoma may also have a smooth external surface and a thin wall (Figure 2A).

Magnetic resonance imaging (MRI) is very useful, as it demonstrates a well-defined lesion that does not enhance after the administration of intravenous gadolinium. On T1 images, the cyst shows a low signal; conversely on T2 weighted images, a very high intensity signal is observed. However, no specific information is gained towards pseudo-ovarian stroma detection^[17].

Despite the various diagnostic modalities, it remains difficult to distinguish HCs from HCa on preoperative imaging; however, a significant solid component on the cystic wall suggests invasive malignant disease. Furthermore, HC can evolve into HCa after long periods lasting more than 10 years^[18,19].

Liver enzymes and bilirubin are usually normal unless the biliary tree is compressed. The elevation of alkaline phosphate and bilirubin occurs in cases of bile duct obstruction. Carbohydrate antigen 19-9 may be elevated, but CEA and α -fetoprotein are usually normal^[3,20]. It has been reported that most patients with cystadenocarcino-

ma have normal serum concentrations of CEA and CA 19-9. Moreover, the serum concentrations of these tumor markers can be elevated in patients with HCa as well. Therefore, these serum tumor markers cannot distinguish HCa from HC.

Some authors have reported that fine needle aspiration cytology of the cyst contents is a good method for diagnosing cystic lesions^[5,16]. In many studies, however, no malignant cells were recovered in patients with HCa who underwent intraoperative cytology examination. Thus, this procedure rarely generates a definitive diagnosis and carries the risk of pleural or peritoneal dissemination, and should therefore be avoided, especially when surgery is planned. The fluid of the cystic cavity often consists of a high-molecular-weight glycoprotein called mucin. However, hemorrhagic, bilious, clear, and mixed fluid contents have also been observed^[5,16]. Aspiration and cyst fluid analysis for CEA and Ca 19-9 has been proved more useful than serum analysis^[5,16]. Cyst fluid demonstrates marked, but variable, elevation in Ca 19-9 and moderate elevation of CEA^[5,16]. Elevation of these cyst fluid tumor markers has high specificity and sensitivity in distinguishing HC from simple and echinococcal cysts.

HC has been treated by marsupialization, internal Roux-en-Y drainage, repeated needle aspirations, fenestration, or partial resection. All these methods have been associated with high rates of recurrence and complications including sepsis, continued growth, and progress to malignancy. Although the rate of malignant transformation is relatively low (5%-10%), all suspected HCs must be excised^[16,21]. Liver resection with clear margins is strongly indicated due to the possibility of synchronous appearance of HCa at the borders of the cyst^[16,21]. Enucleation is also acceptable. Reports supporting resection cite the low associated mortality of the procedure and the permanent relief of symptoms^[16,21].

The majority of HC can be completely and safely excised by enucleation, including those that are centrally located. Once the cyst has been decompressed and the proper plane identified, enucleation can proceed without

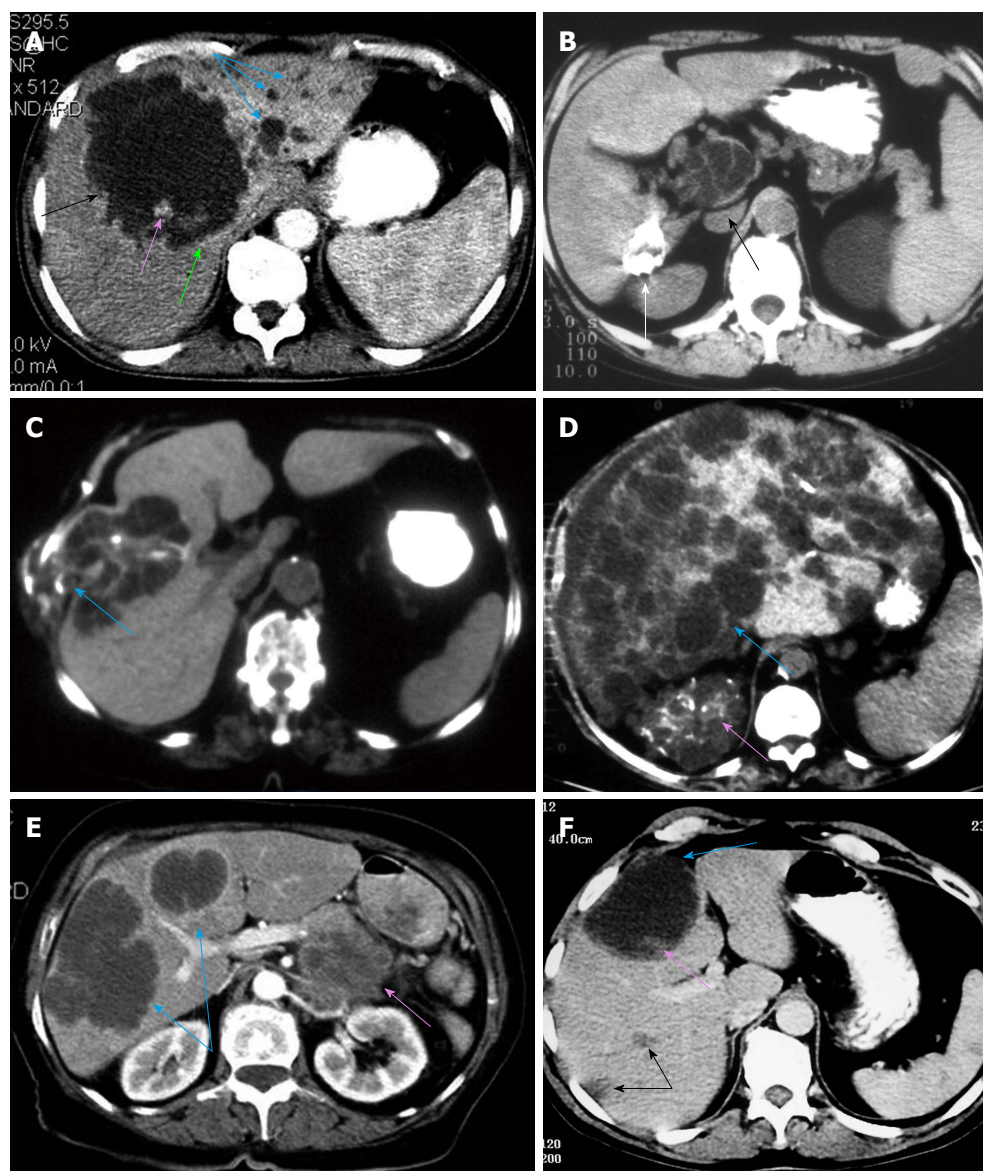


Figure 2 Computed tomography image. A: In liver segment IV there is a large cystic lesion (black arrow) causing compression with dilatation of biliary ducts (light blue arrows) in the left liver lobe. Peripheral contrast enhancement (light green arrow) as well as a nodule (pink arrow) is evident in this case of cystadenoma; B: Echinococcal disease evaluated. Two lesions are evident. The first in liver segment I appears as a multilocular cystic lesion (black arrow) and the second in liver segment VI as a calcified mass with irregular margins (white arrow); C: Demonstrates direct infiltration of a liver hydatid cyst in the adjacent peritoneal surface and abdominal wall (light blue arrow); D: A typical case of multicystic disease with liver (light blue arrow) and kidney (pink arrow) involvement were very well depicted; E: Showing two large cystic-appearing liver lesions (light blue arrows) in a case of a metastatic pancreatic cystadenocarcinoma that is also evident (pink arrow); F: A large cystic lesion (light blue arrow) with a small solid component at the periphery (pink arrow), as well as two small hypodense liver lesions (black arrows), are seen on this image, in a case of proven gastrointestinal stromal tumors metastatic lesions.

significant blood loss. If the possibility of hemorrhage is high due to adjacent major venous vascular structures, enucleation can be completed with either inflow occlusion (Pringle maneuver) or total vascular exclusion. In the era of laparoscopic surgery, a laparoscopic frozen section biopsy of the cyst wall is feasible. If the frozen section is consistent with a simple, benign cyst, laparoscopic partial excision is adequate. If the biopsy demonstrates HC, then complete excision is necessary. However, frozen section biopsies are not always accurate due to inconsistency and discontinuity of the pathological epithelium^[3,7,22]. Frozen sections cannot definitely exclude or confirm the diagno-

sis of HC, especially in the case of HCa^[3,7].

The only potentially curative treatment for HCa is complete removal, usually by a major liver resection with 1-cm margins. Reported survival rates for HCa range from 25% to 100% (87% disease free) at 5 years^[4]. It has been reported that patients with HCa who have invasion of the liver parenchyma or neighboring organs have a poor prognosis^[4]. Asahara *et al* have reported that the prognosis of patients with HCa is poor when the tumor lacks mesenchymal stroma^[2,4]. Absence of mesenchymal stroma in HCa appears to be associated with aggressive disease behavior (*i.e.*, rapid dissemination or distant metastasis)^[2,4].

HYDATID DISEASE

Human cystic echinococcosis, or hydatid cyst disease, is a zoonosis caused by the larval cestode *Echinococcus granulosus*, *Echinococcus multilocularis*, or *Echinococcus vogeli*. *E. granulosus* produces unilocular cystic lesions, whereas *E. multilocularis* and *E. vogeli* produce multilocular alveolar cysts^[23,24]. Dogs are the definitive hosts for *E. Granulosus*, with sheep being the major intermediate host (yaks, goats, and camels are other relevant intermediate hosts). Man is only incidentally infected when ingesting tapeworm eggs^[24]. The eggs penetrate the intestinal wall, with the resulting larvae infiltrating the blood and lymphatic circulation system. Then, through the portal vein into the liver, lungs, and other tissues, the larvae develop into hydatid cysts^[25,26].

The liver is the most frequent site for the cystic lesions (52%-77%) seen in hydatid disease, followed by the lung (10%-40%), brain, and other viscera^[24,26,27]. The disease may remain silent for many years before coming into medical attention as an incidental imaging finding, or it may present with complications.

The diagnosis of uncomplicated hepatic hydatid disease is based on clinical suspicion, with special attention paid to factors such as the patient's residence, place of origin and occupation in order to identify high-risk patients. The symptoms depend on the size, location, and development stage of the cyst^[26,28]. Pain in the right upper quadrant or the epigastrium is the most common symptom, whereas hepatomegaly and a palpable mass are the most common signs. Nonspecific symptoms such as fatigue, fever, nausea, or dyspepsia may also be present. Patients with complicated hepatic hydatid disease may present with fever, jaundice, or anaphylactic symptoms, depending on the complication^[26,29].

Acute cholangitis is the most common syndrome when the hydatid cysts rupture in the biliary tract. Rupture of a cyst may produce fever, pruritus, eosinophilia, or fatal anaphylaxis^[23]. Lower chest pain, a productive cough, and hemoptysis are the most frequent symptoms when there is thoracic involvement. Biliptysis is diagnostic of a biliobronchial fistula^[25].

General blood tests are not specific except in complicated disease, whereas a high white blood cell count with eosinophilia are possible findings. Hepatic parameters are normal except in the case of biliary compression^[30]. Serologic tests such as hemagglutination, latex agglutination, and enzyme-linked immunosorbent assay (ELISA), are associated with a high incidence of false-negative and false-positive results^[28]. Nevertheless, the detection of specific antigens and immune complexes of the cyst with ELISA yields a positive result in more than 90% of patients. Specific IgE antibodies are demonstrated with ELISA and the radioallergosorbent test is positive in the presence of active disease. Confirmatory tests such as arc-5 immunoelectrophoresis and immunoblotting use parasite-specific antigens. The positivity rate with arc-5 immunoelectrophoresis is as high as 91.1%^[26,29]. The Casoni and Weinberg tests are no longer used for the diag-

nostic workup, mainly due to their low sensitivity^[29].

The indirect immunofluorescence assay (IFA) first reported by Coudert *et al* is specific and sensitive, especially in cases of hepatic cystic hydatidosis. This easy-to-do assay can be achieved in less than 2.5 h and is the most sensitive test in more than 95% of patients with hepatic cystic hydatidosis^[30]. The diagnosis of hydatidosis by molecular biology is based on the polymerase chain reaction and the technique needs to be evaluated. Based on the choice of primers and probes, molecular biology can differentiate *E. granulosus* from *E. multilocularis* in clinical samples^[30].

False-positive results have been described in some patients with tumors, for which there is no explanation as yet, whereas false-negative results are observed when cysts are calcified, even if fertile and corresponding to the lack of antigenic stimulation. Serologic tests do not supplant clinical or imaging investigations but they can, however, confirm the hydatid origin of a cyst. Specific antibodies increase 4-6 wk after surgery, after which they decrease slowly for the next 12-18 mo. The decrease in specific antibodies is too irregular to be a good witness of recovery or relapse, however. Persistently high specific antibody titers or a secondary increase in the antibody titers 6 to 12 mo after surgery indicate a relapse^[30].

Standard chest and abdomen radiographs may reveal an elevated diaphragm and concentric calcifications in the cyst wall. Liver scanning was an important diagnostic tool during the 1970s. Since then, US and CT have replaced scanning and are considered the first choice in the diagnostic armamentarium. These methods are helpful for determining complications as well^[29]. MRI and endoscopic retrograde cholangiopancreatography (ERCP) can prove helpful during the diagnostic approach.

US, a noninvasive, readily available, sensitive, and cost-effective imaging technique, should be the diagnostic method of choice. US is helpful for defining the internal structure, number, and location of the cysts and the presence of complications (Figure 1B). The specificity of US is in the range of 90%. Several authors have proposed an ultrasonographic classification of hepatic hydatid disease (Table 1)^[26,31]. Classification was standardized by the World Health Organization-Infomal Working Group on Echinococcosis (WHO-IWGE) in 2001 (Table 2)^[26]. According to the five categories noted in the classification of Gharbi types: II and III are characteristic of hydatid cysts, types I and V are suggestive of hydatid cysts in endemic areas, and type IV simulates a pseudotumor^[25].

CT is a helpful tool for confirming the diagnosis, essentially when an ultrasound examination shows a type IV sonographic pattern^[25]. It provides information equivalent to that derived by US, but it shows the location and depth of the cyst within the liver more accurately (Figure 2B and C). Moreover it can reveal calcified cystic walls^[28], daughter cysts, and exogenous cysts, as well as evaluate their volume and density. CT is essential for planning surgical treatment, especially when a minimally invasive approach is to be used^[26,29]. Imaging findings on CT depend on the stage of cyst growth and the *Echinococcus* species

Table 1 Gharbi classification of cystic hydatid disease

Type	Ultrasonographic features and patterns
I	Pure fluid collection
II	Fluid collection with a split wall (water-lily sign)
III	Fluid collection with septa (honeycomb sign)
IV	Heterogeneous echographic patterns
V	Reflecting thick walls

Table 2 World Health Organization-Informal Working Group on Echinococcosis

Type	Ultrasonographic features and patterns
CL	Unilocular cystic lesion with uniform anechoic content, cyst wall not visible
CE1	Unilocular cystic lesion with uniform anechoic content, cyst wall visible, snowflake sign
CE2	Multivesicular, multiseptated cysts, daughter cysts present, honeycomb sign
CE3	Unilocular cyst containing liquid with a floating membrane inside, daughter cysts may be present, water-lily sign
CE4	Cysts with heterogeneous hypoechoic or hyperechoic degenerative contents, no daughter cysts
CE5	Cysts characterized by a thick calcified wall, which is arch-shaped, producing a cone-shaped shadow; degree of calcification varies from partial to complete

involved. Hepatic involvement by *E. multilocularis* is characterized by a different appearance than *E. granulosus*, consisting of an infiltrating solid mass composed of multiple cysts and indistinct margins. Infection by *E. granulosus* usually forms a single cyst, with or without daughter cysts^[23].

Although MRI can be helpful for demonstrating the lesion in the liver (Figure 3), it does not provide additional information in hepatic lesions and is not cost-effective when compared with either US or CT^[26,29]. However, both CT and MRI have high specificity and sensitivity in the detection and differential diagnosis of hepatic cysts and extracapsular (satellite) cysts^[28].

The ideal treatment for hepatic hydatid disease should completely eliminate the parasite and prevent recurrence of the disease with minimum morbidity and mortality. There are three available therapeutic modalities for hepatic hydatid cysts; systemic chemotherapy, surgery, and the treatment known as “puncture, aspiration, injection, reaspiration” (PAIR). Chemotherapy and PAIR are recommended as alternatives to surgery, especially for patients who cannot tolerate or refuse surgery. However, surgery is still the first choice of treatment for hepatic hydatid cysts. Selection of the most appropriate treatment depends on the patient’s health status, the nature of the cyst(s) (considering number, size, location, and presence of complications), and the available resources and expertise^[26].

Mebendazole (MBZ) was the first benzimidazole carbamate agent found to have *in vivo* activity in hydatid disease. The drug interferes with mechanisms of glucose absorption through the wall of the parasite, leading to

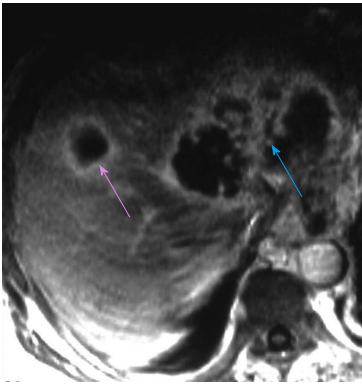


Figure 3 Magnetic resonance T1-w image shows an echinococcal cyst as a multiloculated cystic liver lesion, indicative of the presence of daughter cysts (light blue arrow). A second smaller unilocular lesion with peripheral contrast enhancement is also seen (pink arrow).

glycogen depletion and subsequent degenerative changes in the mitochondria and endoplasmic reticulum of the germinal cells^[32]. Albendazole (ABZ) is more active *in vitro* than MBZ and has improved gastrointestinal absorption and bioavailability, as well as reports of better clinical results^[32]. Although orally administered, ABZ results in high serum concentrations and penetration into cyst contents is erratic. Currently, ABZ chemotherapy as the primary treatment may be considered for patients who are not acceptable candidates for surgery, have inoperable, recurrent, peritoneal or multiple liver cysts within the whole liver, have multiple cysts in several organs, refuse surgery or percutaneous drainage, and perhaps, for asymptomatic individuals^[32].

Both drugs may decrease the size of hydatid cysts and lead to the sterilization of cyst contents in some cases; however, without concomitant drainage, clinical and radiographic resolution is unpredictable and occurs in less than half of treated patients^[24]. Hepatic and hematologic toxicities are the most frequent serious adverse effects of ABZ and MBZ. Treatment of hepatic cystic echinococcosis with MBZ or ABZ alone is not as effective as a combined chemotherapy-drainage approach^[24,33]. Clinical and radiographic improvement (in most studies defined as a > 25% reduction in cyst size, membrane separation, or cyst calcification) is seen frequently, but complete cure (*i.e.*, cyst disappearance) generally occurs in less than half of patients treated with anti-parasitic monotherapy^[24,33].

According to the WHO guidelines, chemotherapy is indicated for inoperable primary liver or lung echinococcosis, for patients with multiple cysts in two or more organs, and for peritoneal cysts. Another important indication for chemotherapy is the prevention of secondary echinococcosis. Preoperative use of ABZ or MBZ can reduce the risk of recurrence of cystic echinococcosis and facilitate the operation. Concomitant chemotherapy is also recommended for PAIR. Chemotherapy is contraindicated for large cysts that are at risk of rupture (superficially situated, infected cysts) and for inactive or calcified cysts^[34].

The usually recommended oral dosage of ABZ is

10-15 mg/kg per day in two divided doses for several 1-mo courses separated by 14-d intervals. The usual oral dosage of MBZ is given as 500 mg tablets in daily doses of 40-50 mg/kg (in three divided doses) for at least 3-6 mo. Better intestinal absorption of benzimidazole compounds is gained by administering it with a fat-rich meal or by combining it with cimetidine. Medical and laboratory examinations for adverse reactions are initially necessary every 2 wk and then monthly^[35].

A third antiparasitic agent, praziquantel, has had limited use in the treatment of hydatid cysts of the liver. The drug increases the permeability of the parasite's cell membrane to calcium, resulting in strong contractions and paralysis of the musculature leading to detachment from host tissue. In humans, it has favorable pharmacokinetics when given in a dose of 50 mg/kg either once weekly or every two weeks. There are few clinical studies documenting the efficacy of praziquantel in humans, however several of these have suggested that the use of praziquantel in combination with MBZ or ABZ is more effective and perhaps, more rapid than with benzimidazole alone (47.4% *vs* 36.4%) after only 2-6 mo of drug therapy^[24].

Surgery was defined as the only definitive and curative modality by the WHO-IWGE in 1996^[33]. The goals of surgery in hydatid disease are to inactivate the cestode parasites, evacuate the cyst cavity, remove the germinal layer, and obliterate the residual cavity. Surgical interventions consist of open conservative, radical, and laparoscopic approaches^[24]. Conservative techniques involve drainage, marsupialization, capitonnage, deroofting, partial simple cystectomy, and open or closed total cystectomy with or without omentoplasty^[24]. The conservative procedures are safer and easier to perform^[25]. Radical procedures include total pericystectomy, partial hepatectomy, or lobectomy^[24]. Although it seems logical that radical operations would be associated with higher intra- and postoperative morbidity but less frequent recurrence, recent studies have shown that radical surgery is not associated with a high complication rate^[26].

Laparoscopic drainage of hepatic hydatid cysts is a "minimally invasive" surgical technique that appears safe and effective. It has the theoretic advantages of a shorter hospital stay, lower incidence of wound infection, and less postoperative pain, but the disadvantages of difficult accessibility to the various locations, increased risk of cyst content spillage, and the difficulty of aspirating the cyst content of the thick, degenerated cyst contents, especially in some WHO-IWGE CE3 and CE4 cysts. Thus, choosing the best candidates for the laparoscopic approach requires careful evaluation of the cystic disease^[25,26]. Whichever technique is used, a benzimidazole agent is best administered before any surgery in an attempt to sterilize the cyst contents and reduce the risk of anaphylaxis and dissemination^[24].

Meticulous packing of the operative field is necessary irrespective of the surgical technique employed, as is the use of solutions that kill the infective scoleces and

protoscolices of the parasite residing within the hydatid cyst, or potentially leaking from the cyst during surgical manipulation. Various scolicidal solutions used in surgical (and percutaneous) approaches include: hypertonic saline (3%-20%), povidone-iodine, hydrogen peroxide, iodine, formalin, silver nitrate, ethyl alcohol, and ABZ. These scolicides can be used alone or in combination^[24].

Potential major complications associated with the surgical treatment of hepatic hydatid cysts include postoperative hemorrhage, bile exudation from the residual cyst cavity, incisional fistula formation, cholangitis, wound infection, sepsis, incisional fistulae, pulmonary complications such as pneumonia and pulmonary embolization, complications of anesthesia, and death^[24].

ERCP is used as a diagnostic and therapeutic tool in the management of biliary tract-complicated hepatic hydatid cysts. Preoperatively, ERCP defines biliary tract-related complications and allows the assessment and management of acute conditions, including acute cholangitis and biliary obstruction, so that elective surgery can be performed later. When combined with sphincterotomy, this drains the cyst cavity and helps prevent postoperative biliary fistula. Postoperatively, ERCP allows visualization of distorted anatomy in recurrent cases, helps clarify the etiology of ongoing or recurrent biliopancreatic symptoms and biochemical abnormalities, allows endoscopic management of a biliary fistula, and enables treatment of secondary biliary strictures by stenting^[26].

The treatment modality that we prefer using in our department with optimal results is the evacuation of the cavity with careful removal of the laminated membrane and the daughter cysts in order to avoid spillage. The cyst cavity is obliterated by omentoplasty or capitonnage, and the site is drained externally by suction catheter. Partial cystectomy and internal drainage with a Roux-en-Y intracystic hepaticojunostomy is performed when large ducts had been disrupted due to large cysts. Preoperative ERCP is performed when communication between the cyst cavity and biliary tree is suspected, and endoscopic sphincterotomy is performed in cases of obstruction.

The minimally-invasive technique of puncture, aspiration of cyst, injection of hypertonic saline and/or absolute alcohol, and re-aspiration (PAIR), described initially by Voros *et al*^[28] and Falagas *et al*^[32], is an alternative to major interventional procedures. PAIR treatment satisfies all the goals of surgery in hydatid disease, but substitutes germinal membrane sclerosing and separation using scolicides for surgical removal. PAIR drainage is best performed under continuous ultrasonographic or CT guidance.

Patients undergoing PAIR typically receive oral ABZ that is administered 24-4 h before intervention and 15-30 d after intervention according to cyst size^[34]. Different scolicidal solutions can be used in PAIR, although hypertonic saline is most commonly employed. Hypertonic saline (in 5%-30% concentrations) exerts its scolicidal effect by creating a strong osmotic gradient across the outer cuticular membrane of the protoscolex, which

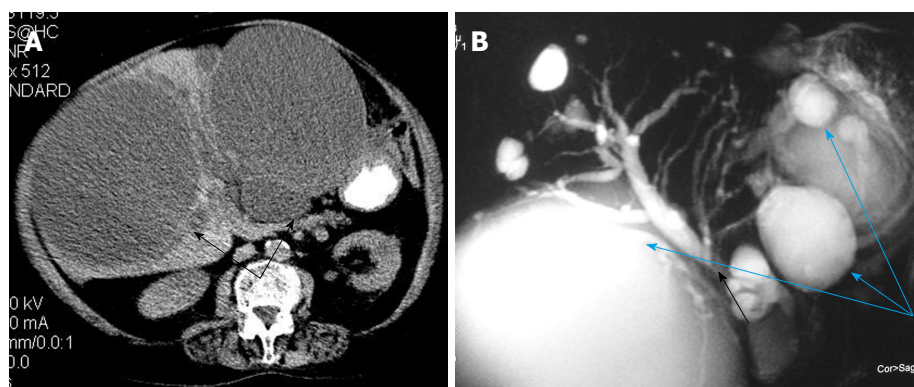


Figure 4 Image. A: Computed tomography image in a case of multicystic disease, showing two large dominant cysts causing mild intrahepatic biliary dilatation (black arrows); B: Magnetic resonance cholangiopancreatography image shows multiple hepatic cysts (light blue arrows) while the common bile duct seems compressed between the two larger cysts (black arrow).

causes its lysis. For multiseptate Type III cysts or large cysts over 6 cm in size, some authors advocate the use of absolute alcohol because it is a more effective sclerosing agent than hypertonic saline, may destroy daughter cysts not killed by saline, and may also result in a more rapid involution of the cyst cavity. Alcohol should not be used, however, if pre-existing biliary communication is suspected or documented, as the agent may cause a chemical cholangitis^[33].

With PAIR, cyst fluid or operative tissue specimens are immediately subjected to cytologic, histopathologic, and parasitologic examinations after aspiration or catheter drainage in order to confirm the diagnosis and assess the success of the drainage procedure.

Complications after PAIR therapy, such as infections, are generally well tolerated and can be managed with systemic antimicrobial therapy. Leakage during drainage may lead to fever, urticaria, transient hypotension, or anaphylaxis, but these can be anticipated and effectively managed with antipyretics, IV fluids, antihistamines, and subcutaneous epinephrine. Cyst-biliary communications (biliary rupture and fistula formation) developing after PAIR and caused by cyst decompression, can usually be managed endoscopically^[24]. For patients who underwent PAIR as a primary procedure, a total complication rate of 14.7% and a recurrence rate of 1.57% have been reported^[28].

In conclusion, compared to patients undergoing surgical intervention for cystic hepatic echinococcosis, PAIR plus ABZ is associated with greater clinical and parasitologic efficacy, less major and minor morbidity whenever it is indicated (*i.e.*, for non-echoic lesion ≥ 5 cm in diameter (CE1), cysts with daughter cysts (CE2), and/or with detachment of membranes (CE3). Surgery may be reserved for patients with hydatid cysts refractory to PAIR because of secondary bacterial infection or difficult-to-manage cyst-biliary communication or obstruction^[24,34].

POLYCYSTIC LIVER DISEASE

Polycystic liver disease (PLD) is inherited as an autosomal

dominant trait presenting in adulthood and is more common in women^[36]. Autosomal dominant polycystic disease is genetically heterogeneous, with mutations in two distinct genes predisposing to the combination of renal and liver cysts (AD-PKD1 and AD-PKD2)^[36,37]. PLD is genetically linked to protein kinase C substrate 80K-H and SEC63^[38]. The cysts in PLD can also increase in size and number during pregnancy or simultaneously with the use of exogenous female steroid hormones^[39].

Most patients are asymptomatic and do not require treatment. Some patients develop massive hepatic cystic disease and become clinically symptomatic, which is associated with increased liver volume and adjacent visceral compression. Usually patients suffer from chronic dull abdominal pain, satiety, weight loss, dyspnea, physical disability, and descensus^[36,40]. Liver function tests are usually normal except for mild elevation in ALP or γ -GT^[36,40]. Liver failure or complications of advanced liver disease, such as infection or intracystic hemorrhage, are rare. Less than 5% of patients have acute medical complications. These consist of cyst hemorrhage, rupture, infection, uterine prolapse due to displacement, obstructive jaundice, portal hypertension, ascites, and Budd-Chiari syndrome^[19,36,40-42]. Even with marked hepatosplenomegaly and portal hypertension, liver function is well preserved in PLD. Ascites may be present and usually results from hepatic venous flow obstruction. Diagnosis is confirmed with US and CT imaging (Figure 2D), which along with MRI provides the surgeon with valuable preoperative information, such as the location of infected or hemorrhagic cysts that may be responsible for symptoms^[40] (Figure 4). Treatment should be considered in cases of persistent symptoms or associated complications.

Cyst aspiration with sclerosis, open or laparoscopic cyst fenestration, combined hepatic resection and fenestration, liver transplantation, and recent medical treatment with somatostatin analogues, are possible therapeutic options based on the type of PLD^[19,36,40,42-46]. Aspiration, combined with ethanol instillation to induce sclerosis of the cyst lining epithelium, can be effective in patients with a few dominant cysts (Type I PLD - few large cysts

greater than 7 cm). Open or laparoscopic cyst fenestration with omentoplasty is another modality of treatment that can be performed in patients with more diffuse PLD (Type II -multiple medium cysts 5-7 cm in diameter). Patients with small cysts throughout the liver have a greater risk of persistence and/or recurrence of symptoms^[19,42]. Postoperative morbidity consists of temporary ascites, pleural effusion, and rarer biliary leakage^[40].

Combined hepatic resection and fenestration is more effective for reducing the hepatic mass and relieving gastric compression. This procedure has an advantage in the case of massive hepatomegaly with associated gastric compression^[40,47,48]. Resection addresses the problem of liver mass, but poses significant risk of bile duct injury, vascular compromise, and liver insufficiency, as cysts markedly distort intrahepatic anatomy. In particular, ascites has been troublesome due to continued cyst secretion from residual fenestrated cysts, disruption of intrahepatic lymphatics, and partial venous outflow obstruction. Candidates for combined resection/fenestration should have at least two adjacent liver segments not affected by cysts and have normal liver function. Furthermore, these patients should be managed by experienced hepatobiliary surgeons at institutions with advanced intensive care, as well as interventional radiological and gastroenterology support.

Liver transplantation has been performed in rare cases, especially when the above-mentioned interventions are not an option. In patients who harbor diffuse PLD, orthotopic liver transplantation (OLT) is effective, but inherently assumes the risks of long-term immunosuppression and rejection. OLT is indicated for patients with progressive PLD after resection/fenestration, patients with concurrent liver dysfunction and renal failure, and patients with diffuse PLD without segmental sparing. Although symptomatic relief from hepatomegaly occurred in all surviving patients, long term follow up addressing quality of life, hepatorenal function, immunosuppressive complications, and survival is limited^[42,49].

Regarding the results of invasive methods, in case series it is noted that aspiration and sclerosis of individual liver cysts reduced liver volume by 19% in patients with 1 or more large dominant liver cysts^[50]. Reduction of liver volume is reported to be as high as 12.5% when laparoscopic fenestration is used, but the complication rate reported is also high (0%-33%)^[51-55].

The drawbacks of invasive procedures in treating PLD are their partial effectiveness, their related morbidity and mortality and, most importantly, the fact that they do not change the natural course of the disease as symptoms recur due to growth of new cysts or re-growth of treated ones^[41].

Several studies have reported the positive effects of somatostatin analogues in decreasing liver and kidney growth in PKD and ADPLD over a treatment period of minimum 6 mo^[43-46].

Somatostatin may reduce cyst development through

several mechanisms^[45]: (1) by inhibiting secretin release from the pancreas^[56]; (2) by inhibiting secretin-induced cAMP generation and fluid secretion in cholangiocytes^[57-59]; (3) by vasopressin-induced cAMP generation and water permeability in collecting ducts^[60-63] by its effects on Gi protein-coupled receptors; and (4) by suppressing the expression of IGF-1, vascular endothelial growth factor, and other cystogenic growth factors and downstream signaling from their receptors^[60-64].

Ruggenti *et al.*^[43] in 2005 showed that kidney volume increased by 2.2%-3.7% during active treatment with octreotide LAR compared with 5.9%-5.4% ($P < 0.01$) while on placebo. Octreotide LAR (40 mg intramuscularly every 4 wk) was given for 6 mo in 12 adult polycystic kidney disease (ADPKD) patients with advanced renal disease (mean total kidney volume 2435 mL, mean serum creatinine 1.9 mg/dL)^[43].

In 2009, van Keimpema *et al.*^[44], tested lanreotide for treating PLD (120 mg subcutaneously every 4 wk) for 6 mo in 54 patients with PLD (32 ADPKD and 22 AD-PLD). He concluded that liver volume decreased by 2.9% (from 4606 to 4471 mL) in the lanreotide group, whereas it increased by 1.6% (from 4689 to 4895 mL) in the placebo group ($P < 0.01$)^[44]. In the 32 patients with ADPKD, total kidney volume decreased by 1.5% (from 1000 to 983 mL) in the lanreotide group, whereas it increased by 3.4% (from 1115 to 1165 mL) in the placebo group ($P < 0.02$)^[44].

The results of the clinical trial reported in 2010 by Hogan *et al.*^[45] showed that administration of octreotide LAR for 1 year induced a moderate but significant reduction in liver volume, inhibited the growth of polycystic kidneys, and improved quality of life in patients with ADPKD and/or ADPLD, with low toxicity and few side effects.

In 2012, Hogan *et al.*^[46] reported their results in treating patients with PLD with Octreotide LAR for 2 years. He concluded that his study further substantiates the positive effects of somatostatin analogs in reducing TLV (6.08% overall reduction in TLV in the first year), demonstrating their safety and efficacious over a 2-year period in individuals with ADPKD or ADPLD, many of whom had chronic renal insufficiency^[46]. While OctLAR inhibited renal enlargement within the first year of treatment, it appeared to lose effectiveness during Year 2. While the results of OctLAR therapy on TLV were clearly positive and results on TKV may show some benefit, he did not detect any positive effect of OctLAR on GFR^[46].

The administration of octreotide or lanreotide has been generally well tolerated in all studies, with mostly mild, predictable, and dose-dependent gastrointestinal side effects. Patients undergoing long-term octreotide treatment should be monitored for cholelithiasis symptoms or signs; a known complication^[45,65]. Alopecia, symptomatic bradycardia, and steatorrhea are other known adverse events associated with somatostatin analogue treatment^[66-73].

CYSTIC METASTASES

Many cystic tumors may metastasize to the liver (*e.g.*, pancreatic or ovary cystadenocarcinomas) (Figure 2E). Other liver metastatic lesions which can appear cystic usually originate from rapidly growing hypervascular tumors (sarcoma, melanoma, and neuroendocrine tumors) and appear so due to necrosis and cystic degeneration^[74]. Despite the fact that these metastatic sites often show cystic characteristics, in most cases the differential diagnosis between them and benign liver cysts is easily made with the contribution of computed tomography.

Of particular interest are the liver metastases from gastrointestinal stromal tumors (GIST) that may appear cystic even before treatment (Figure 2F).

GIST is the most common mesenchymal tumor of the gastrointestinal tract, accounting for 1%-3% of all gastrointestinal malignancies^[75-77]. GIST can arise anywhere along the GI tract, but is most common in the stomach (50%-70%) and small bowel (25%-35%)^[78].

Despite its less aggressive pathologic nature, GIST can metastasize after a long remission period. When GIST originates in the small bowel it behaves in a more aggressive manner. The most common site for metastases is the liver and the peritoneal cavity^[76,77,79], but it can also occur in bones, lungs, skin, and lymph nodes. Data from the MD Anderson Cancer Center report 18% of patients presented with metastatic disease^[80]. Liver metastases are commonly multiple, distributed in both lobes, and more frequently detected synchronously with the primary tumor than metachronously. Case reports showed further metachronous liver metastases being detected after more than 10 years (13 years after gastrectomy for gastric GIST, 17 years after resection for retroperitoneum GIST, and 12 years after surgery for rectal GIST)^[77].

GIST mostly affects males between the ages 40 and 70 and are usually found incidentally. Features at clinical presentation depend on tumor size. Large or advanced lesions may present with a variety of clinical findings, including bleeding, abdominal pain, early satiety, bowel obstruction, or perforation. Bowel obstruction is reported in up to 30% of clinical series, but accounts for less than 10% of presentations in most reports^[81].

The initial workup should include history and physical examination, appropriate imaging (*i.e.*, chest, abdominal and pelvic CT with contrast and/or MRI), endoscopy in selected cases of primary gastric mass, endoscopic ultrasound, liver function tests, full blood counts, and surgical assessment of tumor resectability. On CT scans, metastases within the liver developed lower attenuation than that of the normal surrounding parenchyma. Liver metastases are hypervascular in 92% of patients, and rapidly become cystic following therapy with imatinib.

GIST and GIST liver metastases are soft and fragile, and biopsy may cause tumor hemorrhage or dissemination. The decision to obtain a biopsy should be based on data regarding the stage of the disease and the clinician's suspicion of other malignancies. If the diagnosis is in doubt, neo-adjuvant therapy using IM is put under con-

sideration, but if there is synchronous metastatic disease, then biopsy is essential^[77].

Before 2001, the only effective therapy was surgery alone. The development of clinically effective inhibitors targeting the trans-membrane receptor tyrosine kinase KIT radically changed the management of advanced (locally advanced and metastatic) disease. IM, a selective inhibitor of tyrosine kinase, has revolutionized the management of this disease in recent years. Laboratory studies revealed significant molecular heterogeneity among GIST^[82-84]. In 2010, a meta-analysis showed that most patients with different genotypes of GIST and KIT exon 11-mutants benefit from the individualized treatment of imatinib^[85].

Imatinib has become the first line treatment for recurrent and/or metastatic disease^[79]. Another meta-analysis comparing the efficacy of imatinib given either once (400 mg) or twice daily, revealed that the higher dose offers a progression-free survival advantage among patients with exon 9 mutations^[86], but that the overall survival was the same in the two groups of patients.

Nowadays imatinib therapy and surgical intervention are combined to give patients better disease free and survival rates. Surgical intervention in patients responding to medical therapy may provide a complete cure^[87,88]. Complete pathological response to imatinib alone occurs in less than 5% of patients^[87,88]. Surgery has the best results when offered to patients with lesions responsive to 6 mo imatinib therapy. CT with or without PET can be used to assess the therapeutic effect. MSKCC patients with lesions responsive to imatinib in one study had a 2-year progression free survival of 61% and a 2-year overall survival of 100% after surgical resection. In contrast, the 2-year survival was 36% in patients resistant to imatinib therapy^[89]. Raut *et al.*^[90] also reported that debulking surgery may prolong survival in patients who are either responsive to imatinib or have limited radiographic progression, but it has poor or no result in patients with progressive metastatic disease. Gronchi *et al.*^[91] reported in 2007 that surgery may be of value to patients who develop responsive or stable disease while on preoperative imatinib therapy.

Regarding the timing of surgical resection, Suzuki *et al.*^[92] reported a complete resection rate of 31.4% after IM therapy for a period of 6.9-37.5 mo (mean 10 mo). They also emphasized that surgical resection for IM- responsive recurrent or metastatic disease should be considered as early as possible before the development of progression and secondary resistance to IM^[92]. Surgical resection 6-12 mo after the start of IM treatment is recommended among responders^[79]. However a large tumor may prohibit resection because of the risk of postoperative liver failure. An option to counteract this phenomenon is the use of portal vein embolization (PVE). In general, the median time for detection of further metastases following resection of liver metastases, is 12 mo after the initial hepatectomy^[77,79]. Therefore, careful evaluation of the liver is critical during the first year post-hepatectomy.

Radio-frequency ablation, microwave ablation, and

hepatic artery embolization are other treatment modalities that can normally be used in patients with unresectable disease or in those who cannot undergo surgical excision due to co-morbidities.

CYSTIC HEPATOCELLULAR CARCINOMA

Rarely hepatocellular carcinoma (HCC) can have a cystic appearance, due to necrosis and cystic degeneration in cases of rapidly growing tumors. Co-existing liver cirrhosis and specific HCC imaging characteristics, such as hypervascularity of solid components and tumor invasion of the portal and hepatic veins, can help to reach the correct diagnosis^[74]. Typically the conventional ultrasound would reveal a heterogeneous echogenic lesion with a hypoechoic rim and peripheral or internal arterial flow signals in a liver cirrhosis background. The CEUS would reveal a heterogeneous hyper-enhancement during the arterial phase and hypo-enhancement during the portal and late phases^[14].

CAROLI DISEASE

Caroli disease (CD) is a benign congenital disorder, characterized by unilobular or bilobular segmental cystic dilatation of the intrahepatic biliary tract. The first report was by Todd in 1818, but Jacques Caroli in 1958 defined the disease precisely with its different types^[93]. The estimated incidence of Caroli disease is 1 in 1000000, with males and females being equally affected and more than 80% of patients presenting before 30 years of age^[94].

There are two forms of the disease, one associated with congenital hepatic fibrosis, also called Caroli syndrome, and the other a simple form occurring alone. Recent studies suggest that the simple form may be as common as congenital hepatic fibrosis^[95,96]. It is characterized by segmental cystic dilatation of the intrahepatic ducts, increased incidence of biliary lithiasis, cholangitis, and liver abscesses. Absence of cirrhosis and portal hypertension is typical^[94]. Various renal disorders have been described in association with this liver disease, including autosomal polycystic kidney disease, medullary sponge kidney, and medullary cystic disease^[93,95].

Mode of inheritance is still unclear, but in the majority of cases it is transmitted in autosomal recessive fashion^[93]. Caroli disease is associated with an increased risk of cholangiocarcinoma, with the reported incidence of malignancy ranging from 5% to 10%. The estimated risk is 100 times greater than that of the general population and is triggered by long-standing inflammation and chronic injury of the biliary epithelium^[94,97]. Although present from birth, the disease usually remains asymptomatic during the first 20 years, and may also remain so throughout life^[94]. However when symptomatic, a significant number of these patients present significant loss in their quality of life and clinical course.

The disease is frequently noted by recurrent fever, jaundice, and/or pain in the right hypochondrium^[97]. A

literature review found recurrent acute cholangitis as the main mode of presentation in 64% of patients^[94] and the most life-threatening complication of CD. Usually caused by gram-negative bacilli, it has a recurrent course and, despite different antibiotic associations, medical treatment is often not satisfactory^[93]. Patients with Caroli syndrome, on the other hand, usually present early in life, with complications of portal hypertension, mainly variceal bleeding, hypersplenism, or portal hypertension in 20%-50% of cases^[97].

Laboratory studies typically show an elevation of serum alkaline phosphatase, direct bilirubin, and a leukocytosis with a predominance of neutrophils. Hepatic synthetic function is well-preserved initially, but may be affected by progressive liver damage due to recurrent cholangitis and biliary obstruction. Coagulopathy from vitamin K malabsorption may occur in cholestatic patients^[94].

Histologically, the main macroscopic and microscopic features of CD are: non-obstructive, localized dilatation of the bile ducts; intraluminal bulbar protrusions of the ductal wall and intra ductal vascular tracts containing patent portal venous; and hepatic arterial channels that traverse the true lumen and terminate within the lumen^[94]. The diagnosis of CD therefore rests on demonstrating that the cystic lesions are in continuity with the biliary tree. This can be done by imaging studies such as isotope scan, MRCP, CT scan, US, ERCP, and PTC.

The classical finding of CD is finding that a cold area on 99mTc sulfur colloid scan becomes hot on 99mTc DISIDA scan^[94]. MRCP presents advantages in depicting the entire biliary tree. Three main patterns of CD are identified in MRCP: (1) multiple cystic ectasias connected with fusiform dilatations; (2) isolated fusiform dilatations with multiple calculi; and (3) solitary dilatation of the left bile ducts with cysts and multiple calculi^[93] (Figure 5).

A CT scan shows central dot signs in CD patients. The fibrovascular bundles containing portal vein radical and a branch of hepatic artery bridging the saccule appear as central dots or a linear streak. This central dot sign described on a CT scan is suggested as a pathognomonic finding in CD, and can also be demonstrated on US^[94]. ERCP is the method with the highest sensitivity in the diagnosis of CD. The cholangiographic features of Caroli disease are well established as saccular or fusiform dilatation of the intrahepatic bile ducts. Irregular bile duct walls, strictures, and stones may be present. Therefore, direct cholangiography is considered the method of choice for an accurate diagnosis of CD^[94]. With PTC, the diagnosis can be made confidently when the large intrahepatic branches have focal or segmental involvement with cystic outpouchings in which the contrast medium collects. False-positive findings are rare when PTC is used^[93].

The treatment of CD depends on the clinical features and location of the biliary abnormalities. It seems more than justified to advocate a rather aggressive surgical strategy in symptomatic patients who have had several

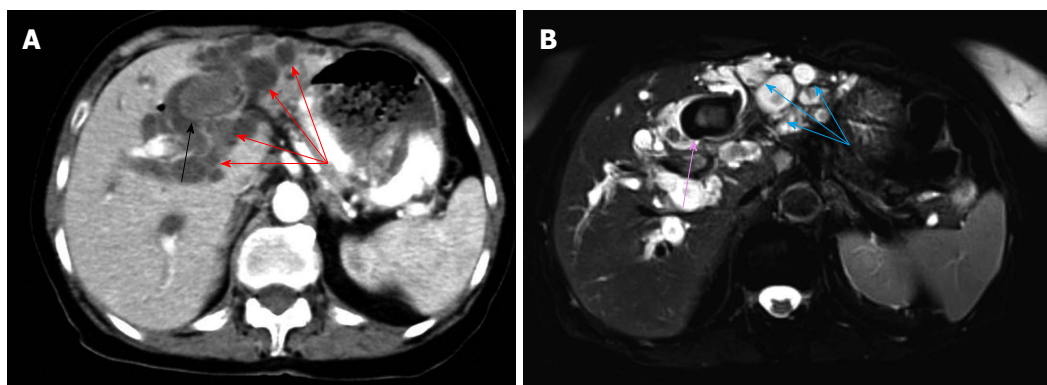


Figure 5 A case of Caroli disease. A: On computed tomography. A large intra-biliary stone (black arrow) is evident in the dilated ducts (red arrows); B: On magnetic resonance imaging. A large intra-biliary stone (pink arrow) is evident in the dilated ducts (blue arrows).

futile conservative treatment attempts^[98]. The localized forms, which involve either the whole of the left or the right half of the liver, are curable by surgery. They should be treated by hemi-hepatectomy, left or right, with associated treatment of any problem affecting the common duct^[94]. The procedure is associated with low morbidity and virtual no mortality. There is no report of malignant tumors arising after surgical resection^[98].

Diffuse involvement of both lobes can be treated with conservative management in asymptomatic patients, with appropriate antibiotics for cholangitis and ursodeoxycholic acid therapy for litholysis in cases of intrahepatic cholelithiasis, endoscopic therapy (sphincterotomy for clearance of intrahepatic stones), and internal biliary bypass procedure^[94]. These patients in whom there is no indication for liver resection or transplantation should at least be followed up regularly on an outpatient basis to detect any kind of deterioration or malignant transformation as early as possible^[98].

Bilateral disease complicated by recurrent cholangitis, cirrhosis, or both, together with symptoms of associated hepatic fibrosis, do not find the same solution, and it is often difficult to manage. Emergency surgery in the presence of acute cholangitis and deteriorating liver function is associated with high mortality (20%–40%) and morbidity (44%–80%)^[94].

It seems that liver transplantation or living donor transplantation is an effective therapeutic option and possibly the only and ultimate management option for these patients with end-stage diffuse Caroli disease providing gratifying long-term results^[94,97,98]. OLT has become a therapeutic option which, aside from the better long-term outcome, can prevent the development of cholangiocarcinoma^[96].

DISCUSSION

Liver cystic lesions consist of a heterogeneous group of disorders. Rare liver cystic lesions such as cystadenoma, hydatid cyst, polycystic liver disease, Caroli disease, and cystic liver metastases pose several dilemmas to the practicing surgeon or physician. It is very important that

awareness and a high index of suspicion for rare diseases and HC are present, so as to provide as accurate a diagnosis as possible. Since our diagnostic tools have become more powerful and accurate, our adequate knowledge of the nature, evolution, confirmation, and treatment of all the possible pathological entities in the differential diagnosis becomes more necessary than ever.

The use of CEUS in diagnoses of liver lesions has shown promising results, providing more accurate images than conventional ultrasound^[99–102]. The discrimination between malignant and benign lesions is easier and more accurate than in a conventional ultrasound.

Complete non-enhancement throughout three phases of CEUS or sustained enhancement in the portal and late phases is noticed in most benign lesions^[14]. Conversely, hypoenhancement in the late phase is seen in malignancies^[14]. Real time CEUS improves the capability of discrimination between benign and malignant complex cystic focal liver lesions^[14]. It has been shown that CEUS can greatly improve the diagnostic accuracy of focal liver lesions compared with conventional ultrasound^[14].

Contrast-enhanced ultrasound has also been used for diagnostics of the biliary system. In 2009, Xu^[100] summarized the methodology, image interpretation, enhancement pattern, clinical usefulness, and indications for CEUS in the biliary system.

The first important step, regarding liver cystic lesions, is to make a definitive diagnosis of the nature of the cystic lesion. The second is determining whether the patient's symptoms are related to the cystic lesion. The third is deciding whether and when to initiate therapy for the lesion. Finally, a number of treatment options are available, leading to the fourth issue, which is deciding the appropriate therapy for the patient.

Ideally the cystic liver lesions should be handled by a multidisciplinary team familiar with liver diseases, consisting of interventional radiologist, interventional gastroenterologist, surgeon, clinical oncologist, and pathologist. In our opinion this is the way that even rare entities can be identified and treated promptly. The algorithm used in our department for managing such cystic lesions is provided in Figure 6.

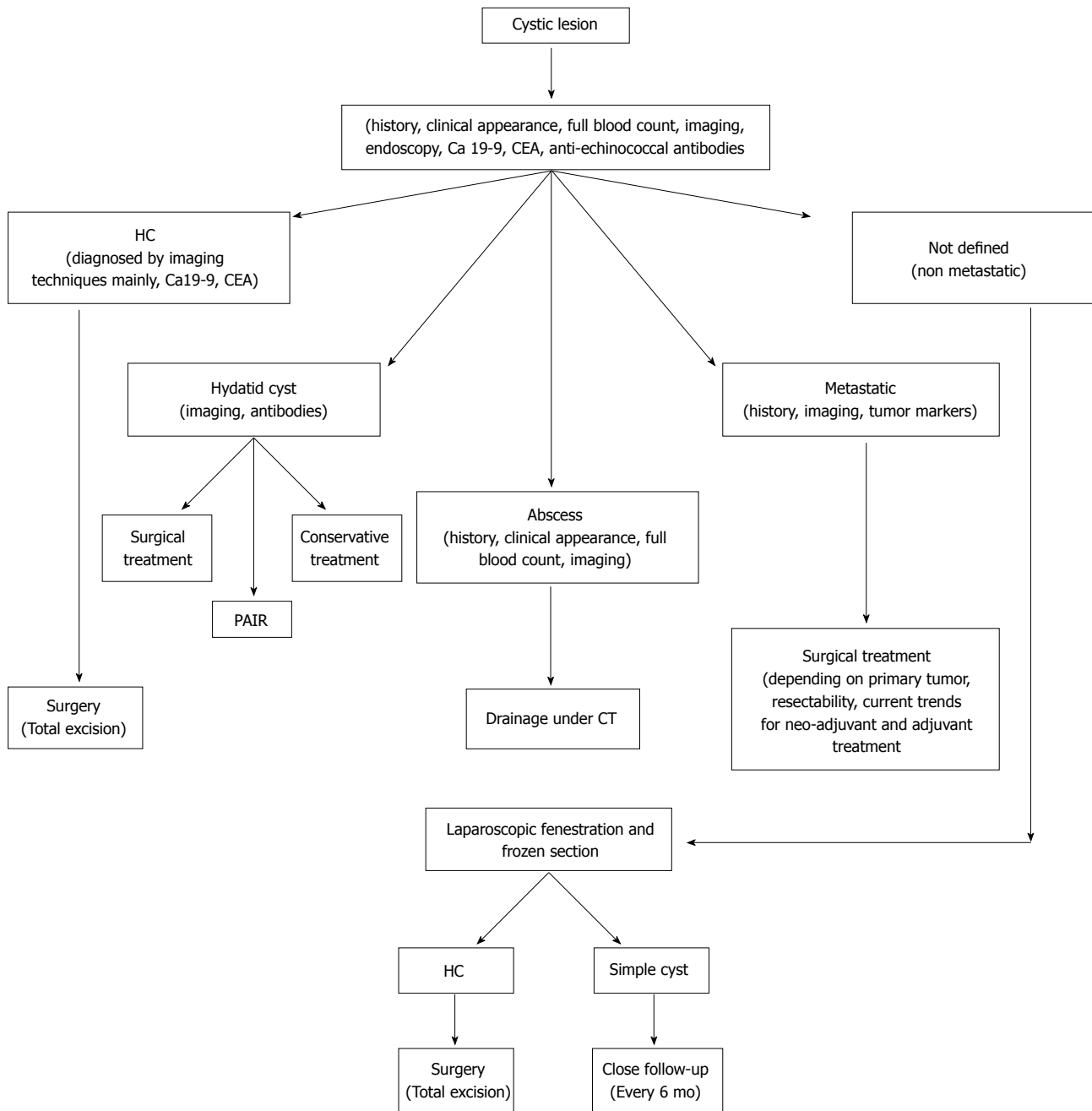


Figure 6 Liver cystic lesions management algorithm.

CONCLUSION

Cystic liver lesions require accurate pre-treatment diagnosis in order to select the appropriate therapy for each patient, as they can represent benign or malignant formations. It is best that a specialized team deals with cystic liver lesions so that diagnosis and treatment are accurate and focused. Specifically, rare entities require accurate diagnosis and management, as they can pose a malignant impact.

REFERENCES

- Caremani M, Vincenti A, Benci A, Sassoli S, Tacconi D. Ecographic epidemiology of non-parasitic hepatic cysts. *J Clin Ultrasound* 1993; **21**: 115-118 [PMID: 8381130 DOI: 10.1002/jcu.1870210207]
- Hai S, Hirohashi K, Uenishi T, Yamamoto T, Shuto T, Tanaka H, Kubo S, Tanaka S, Kinoshita H. Surgical management of cystic hepatic neoplasms. *J Gastroenterol* 2003; **38**: 759-764 [PMID: 14505130 DOI: 10.1007/s00535-003-1142-7]
- Vogt DP, Henderson JM, Chmielewski E. Cystadenoma and cystadenocarcinoma of the liver: a single center experience. *J Am Coll Surg* 2005; **200**: 727-733 [PMID: 15848365 DOI: 10.1016/j.jamcollsurg.2005.01.005]
- Carson JG, Huerta S, Butler JA. Hepatobiliary cystadenoma: a case report and a review of the literature. *Curr Surg* 2006; **63**: 285-289 [PMID: 16843782 DOI: 10.1016/j.cursur.2006.03.001]
- Ishak KG, Willis GW, Cummins SD, Bullock AA. Biliary

- cystadenoma and cystadenocarcinoma: report of 14 cases and review of the literature. *Cancer* 1977; **39**: 322-338 [PMID: 318915]
- 6 **Subramony C**, Herrera GA, Turbat-Herrera EA. Hepatobiliary cystadenoma. A study of five cases with reference to histogenesis. *Arch Pathol Lab Med* 1993; **117**: 1036-1042 [PMID: 8215827]
- 7 **Hansman MF**, Ryan JA, Holmes JH, Hogan S, Lee FT, Kramer D, Biehl T. Management and long-term follow-up of hepatic cysts. *Am J Surg* 2001; **181**: 404-410 [PMID: 11448430 DOI: 10.1016/S0002-9610(01)00611-0]
- 8 **Marcial MA**, Hauser SC, Cibas ES, Braver J. Intrahepatic biliary cystadenoma. Clinical, radiological, and pathological findings. *Dig Dis Sci* 1986; **31**: 884-888 [PMID: 3731980 DOI: 10.1007/BF01296059]
- 9 **Ferrell L**. Benign and malignant tumors of the liver. In: Odze RD, Goldblum JR, Crawford JM. *Surgical Pathology of the GI Tract, Liver, Biliary Tract, and Pancreas*. Collingwood: Saunders; 2004: 1015-1016
- 10 **Koffron A**, Rao S, Ferrario M, Abecassis M. Intrahepatic biliary cystadenoma: role of cyst fluid analysis and surgical management in the laparoscopic era. *Surgery* 2004; **136**: 926-936 [PMID: 15467680 DOI: 10.1016/j.surg.2004.06.031]
- 11 **Thomas JA**, Scriven MW, Puntis MC, Jasani B, Williams GT. Elevated serum CA 19-9 levels in hepatobiliary cystadenoma with mesenchymal stroma. Two case reports with immunohistochemical confirmation. *Cancer* 1992; **70**: 1841-1846 [PMID: 1525758]
- 12 **Delis SG**, Touloumis Z, Bakoyiannis A, Tassopoulos N, Paraskeva K, Athanassiou K, Safioleas M, Dervenis C. Intrahepatic biliary cystadenoma: a need for radical resection. *Eur J Gastroenterol Hepatol* 2008; **20**: 10-14 [PMID: 18090983 DOI: 10.1097/MEG.0b013e3282f16a76]
- 13 **Xu HX**, Lu MD, Liu LN, Zhang YF, Guo LH, Liu C, Wang S. Imaging features of intrahepatic biliary cystadenoma and cystadenocarcinoma on B-mode and contrast-enhanced ultrasound. *Ultraschall Med* 2012; **33**: E241-E249 [PMID: 23154870 DOI: 10.1055/s-0031-1299276]
- 14 **Lin MX**, Xu HX, Lu MD, Xie XY, Chen LD, Xu ZF, Liu GJ, Xie XH, Liang JY, Wang Z. Diagnostic performance of contrast-enhanced ultrasound for complex cystic focal liver lesions: blinded reader study. *Eur Radiol* 2009; **19**: 358-369 [PMID: 18795298 DOI: 10.1007/s00330-008-1166-8]
- 15 **Anderson SW**, Kruskal JB, Kane RA. Benign hepatic tumors and iatrogenic pseudotumors. *Radiographics* 2009; **29**: 211-229 [PMID: 19168846 DOI: 10.1148/rg.291085099]
- 16 **Thomas KT**, Welch D, Trueblood A, Sulur P, Wise P, Gorden DL, Chari RS, Wright JK, Washington K, Pinson CW. Effective treatment of biliary cystadenoma. *Ann Surg* 2005; **241**: 769-773; discussion 773-5 [PMID: 15849512 DOI: 10.1097/01.sla.0000161982.57360.1b]
- 17 **Dixon E**, Sutherland FR, Mitchell P, McKinnon G, Nayak V. Cystadenomas of the liver: a spectrum of disease. *Can J Surg* 2001; **44**: 371-376 [PMID: 11603751]
- 18 **Korobkin M**, Stephens DH, Lee JK, Stanley RJ, Fishman EK, Francis IR, Alpern MB, Ryttyes M. Biliary cystadenoma and cystadenocarcinoma: CT and sonographic findings. *AJR Am J Roentgenol* 1989; **153**: 507-511 [PMID: 2669463 DOI: 10.2214/ajr.153.3.507]
- 19 **Mortelé KJ**, Ros PR. Cystic focal liver lesions in the adult: differential CT and MR imaging features. *Radiographics* 2001; **21**: 895-910 [PMID: 11452064]
- 20 **Zhang M**, Yu J, Yan S, Zheng SS. Cystadenocarcinoma of the liver: a case report. *Hepatobiliary Pancreat Dis Int* 2005; **4**: 464-467 [PMID: 16109538]
- 21 **Fiamingo P**, Veroux M, Cillo U, Basso S, Buffone A, D'Amico DF. Incidental cystadenoma after laparoscopic treatment of hepatic cysts: which strategy? *Surg Laparosc Endosc Percutan Tech* 2004; **14**: 282-284 [PMID: 15492659 DOI: 10.1097/00129689-200410000-00011]
- 22 **Veroux M**, Fiamingo P, Cillo U, Tedeschi U, Brolese A, Veroux P, Basso S, Buffone A, D'Amico DF. Cystadenoma and laparoscopic surgery for hepatic cystic disease: a need for laparotomy? *Surg Endosc* 2005; **19**: 1077-1081 [PMID: 16021374 DOI: 10.1007/s00464-004-2229-9]
- 23 **Czermak BV**, Akhan O, Hiemetzberger R, Zelger B, Vogel W, Jaschke W, Rieger M, Kim SY, Lim JH. Echinococcosis of the liver. *Abdom Imaging* 2008; **33**: 133-143 [PMID: 17912581 DOI: 10.1007/s00261-007-9331-0]
- 24 **Smego RA**, Sebanego P. Treatment options for hepatic cystic echinococcosis. *Int J Infect Dis* 2005; **9**: 69-76 [PMID: 15708321 DOI: 10.1016/j.ijid.2004.08.001]
- 25 **Dziri C**, Haouet K, Fingerhut A. Treatment of hydatid cyst of the liver: where is the evidence? *World J Surg* 2004; **28**: 731-736 [PMID: 15457348 DOI: 10.1007/s00268-004-7516-z]
- 26 **Sayek I**, Tirnaksiz MB, Dogan R. Cystic hydatid disease: current trends in diagnosis and management. *Surg Today* 2004; **34**: 987-996 [PMID: 15580379 DOI: 10.1007/s00595-004-2830-5]
- 27 **Delis SG**, Bakoyiannis A, Exintabelones T, Triantopoulou C, Papailiou J, Dervenis C. Rare localizations of the hydatid disease. Experience from a single center. *J Gastrointest Surg* 2007; **11**: 195-198 [PMID: 17390172 DOI: 10.1007/s11605-006-0036-4]
- 28 **Voros D**, Katsarelis D, Polymeneas G, Polydorou A, Pistiolis L, Kalovidouris A, Gouliamos A. Treatment of hydatid liver disease. *Surg Infect (Larchmt)* 2007; **8**: 621-627 [PMID: 18171123 DOI: 10.1089/sur.2006.0070]
- 29 **Sayek I**, Onat D. Diagnosis and treatment of uncomplicated hydatid cyst of the liver. *World J Surg* 2001; **25**: 21-27 [PMID: 11213152]
- 30 **Biava MF**, Dao A, Fortier B. Laboratory diagnosis of cystic hydatid disease. *World J Surg* 2001; **25**: 10-14 [PMID: 11213147]
- 31 **Gharbi HA**, Hassine W, Brauner MW, Dupuch K. Ultrasound examination of the hydatid liver. *Radiology* 1981; **139**: 459-463 [PMID: 7220891]
- 32 **Falagas ME**, Bliziotis IA. Albendazole for the treatment of human echinococcosis: a review of comparative clinical trials. *Am J Med Sci* 2007; **334**: 171-179 [PMID: 17873530 DOI: 10.1097/MAJ.0b013e31814252f8]
- 33 **Rozanes I**, Güven K, Acunaş B, Emre A. Cystic echinococcal liver disease: new insights into an old disease and an algorithm for therapy planning. *Cardiovasc Intervent Radiol* 2007; **30**: 1112-1116 [PMID: 17533534 DOI: 10.1007/s00270-007-9081-y]
- 34 Guidelines for treatment of cystic and alveolar echinococcosis in humans. WHO Informal Working Group on Echinococcosis. *Bull World Health Organ* 1996; **74**: 231-242 [PMID: 8789923]
- 35 **Saimot AG**. Medical treatment of liver hydatidosis. *World J Surg* 2001; **25**: 15-20 [PMID: 11213151]
- 36 **Everson GT**, Taylor MR, Doctor RB. Polycystic disease of the liver. *Hepatology* 2004; **40**: 774-782 [PMID: 15382167 DOI: 10.1002/hep.20431]
- 37 **Rosenfeld L**, Bonny C, Kallita M, Heng AE, Deteix P, Bomme-laer G, Abergel A. [Polycystic liver disease and its main complications]. *Gastroenterol Clin Biol* 2002; **26**: 1097-1106 [PMID: 12520197]
- 38 **Janssen MJ**, Salomon J, Te Morsche RH, Drenth JP. Loss of heterozygosity is present in SEC63 germline carriers with polycystic liver disease. *PLoS One* 2012; **7**: e50324 [PMID: 23209713 DOI: 10.1371/journal.pone.0050324]
- 39 **Bistriz L**, Tamboli C, Bigam D, Bain VG. Polycystic liver disease: experience at a teaching hospital. *Am J Gastroenterol* 2005; **100**: 2212-2217 [PMID: 16181371 DOI: 10.1111/j.1572-0241.2005.50258.x]
- 40 **Morgan DE**, Lockhart ME, Canon CL, Holcombe MP, Bynon JS. Polycystic liver disease: multimodality imaging for complications and transplant evaluation. *Radiograph-*

- ics 2006; **26**: 1655-168; quiz 1655 [PMID: 17102042 DOI: 10.1148/rg.266065013]
- 41 **Arnold HL**, Harrison SA. New advances in evaluation and management of patients with polycystic liver disease. *Am J Gastroenterol* 2005; **100**: 2569-2582 [PMID: 16279915 DOI: 10.1111/j.1572-0241.2005.00263.x]
 - 42 **Dransart M**, Cognet F, Mousson C, Cercueil JP, Rife G, Krause D. MR cholangiography in the evaluation of hepatic and biliary abnormalities in autosomal dominant polycystic kidney disease: study of 93 patients. *J Comput Assist Tomogr* 2006; **26**: 237-242 [PMID: 11884780 DOI: 10.1097/00004728-200203000-00013]
 - 43 **Ruggenti P**, Remuzzi A, Ondei P, Fasolini G, Antiga L, Ene-Iordache B, Remuzzi G, Epstein FH. Safety and efficacy of long-acting somatostatin treatment in autosomal-dominant polycystic kidney disease. *Kidney Int* 2005; **68**: 206-216 [PMID: 15954910 DOI: 10.1111/j.1523-1755.2005.00395.x]
 - 44 **van Keimpema L**, Nevens F, Vanslembrouck R, van Oijen MG, Hoffmann AL, Dekker HM, de Man RA, Drenth JP. Lanreotide reduces the volume of polycystic liver: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2009; **137**: 1661-8.e1-2 [PMID: 19646443 DOI: 10.1053/j.gastro.2009.07.052]
 - 45 **Hogan MC**, Masyuk TV, Page LJ, Kubly VJ, Bergstralh EJ, Li X, Kim B, King BF, Glockner J, Holmes DR, Rossetti S, Harris PC, LaRusso NF, Torres VE. Randomized clinical trial of long-acting somatostatin for autosomal dominant polycystic kidney and liver disease. *J Am Soc Nephrol* 2010; **21**: 1052-1061 [PMID: 20431041 DOI: 10.1681/ASN.2009121291]
 - 46 **Hogan MC**, Masyuk TV, Page L, Holmes DR, Li X, Bergstralh EJ, Irazabal MV, Kim B, King BF, Glockner JF, Larusso NF, Torres VE. Somatostatin analog therapy for severe polycystic liver disease: results after 2 years. *Nephrol Dial Transplant* 2012; **27**: 3532-3539 [PMID: 22773240 DOI: 10.1093/ndt/gfs152]
 - 47 **Iwatsuki S**, Starzl TE. Personal experience with 411 hepatic resections. *Ann Surg* 1988; **208**: 421-434 [PMID: 3178330 DOI: 10.1097/00000658-198810000-00004]
 - 48 **Tikkakoski T**, Mäkelä JT, Leinonen S, Päivänsalo M, Merikanto J, Karttunen A, Siniluoto T, Kairaluoma MI. Treatment of symptomatic congenital hepatic cysts with single-session percutaneous drainage and ethanol sclerosis: technique and outcome. *J Vasc Interv Radiol* 1996; **7**: 235-239 [PMID: 9007803 DOI: 10.1016/S1051-0443(96)70767-4]
 - 49 **Que F**, Nagorney DM, Gross JB, Torres VE. Liver resection and cyst fenestration in the treatment of severe polycystic liver disease. *Gastroenterology* 1995; **108**: 487-494 [PMID: 7835591 DOI: 10.1016/0016-5085(95)90078-0]
 - 50 **van Keimpema L**, de Koning DB, Strijk SP, Drenth JP. Aspiration-sclerotherapy results in effective control of liver volume in patients with liver cysts. *Dig Dis Sci* 2008; **53**: 2251-2257 [PMID: 18299984 DOI: 10.1007/s10620-007-0121-x]
 - 51 **van Keimpema L**, Ruurda JP, Ernst MF, van Geffen HJ, Drenth JP. Laparoscopic fenestration of liver cysts in polycystic liver disease results in a median volume reduction of 12.5%. *J Gastrointest Surg* 2008; **12**: 477-482 [PMID: 17957434 DOI: 10.1007/s11605-007-0376-8]
 - 52 **Fiamingo P**, Tedeschi U, Veroux M, Cillo U, Brolese A, Da Rold A, Madia C, Zanusi G, D'Amico DF. Laparoscopic treatment of simple hepatic cysts and polycystic liver disease. *Surg Endosc* 2003; **17**: 623-626 [PMID: 12574922]
 - 53 **Gigot JF**, Jadoul P, Que F, Van Beers BE, Etienne J, Horsmans Y, Collard A, Geubel A, Pringot J, Kestens PJ. Adult polycystic liver disease: is fenestration the most adequate operation for long-term management? *Ann Surg* 1997; **225**: 286-294 [PMID: 9060585 DOI: 10.1097/00000658-199703000-00008]
 - 54 **Konstadoulakis MM**, Gomatos IP, Albanopoulos K, Alexakis N, Leandros E. Laparoscopic fenestration for the treatment of patients with severe adult polycystic liver disease. *Am J Surg* 2005; **189**: 71-75 [PMID: 15701496 DOI: 10.1016/j.amjsurg.2004.03.011]
 - 55 **Robinson TN**, Stiegmann GV, Everson GT. Laparoscopic palliation of polycystic liver disease. *Surg Endosc* 2005; **19**: 130-132 [PMID: 15531969 DOI: 10.1007/s00464-004-8813-1]
 - 56 **Li JP**, Lee KY, Chang TM, Chey WY. MEK inhibits secretin release and pancreatic secretion: roles of secretin-releasing peptide and somatostatin. *Am J Physiol Gastrointest Liver Physiol* 2001; **280**: G890-G896 [PMID: 11292597]
 - 57 **Gong AY**, Tietz PS, Muff MA, Splinter PL, Huebert RC, Strowski MZ, Chen XM, LaRusso NF. Somatostatin stimulates ductal bile absorption and inhibits ductal bile secretion in mice via SSTR2 on cholangiocytes. *Am J Physiol Cell Physiol* 2003; **284**: C1205-C1214 [PMID: 12676656 DOI: 10.1152/ajpcell.00313.2002]
 - 58 **Tietz PS**, Holman RT, Miller LJ, LaRusso NF. Isolation and characterization of rat cholangiocyte vesicles enriched in apical or basolateral plasma membrane domains. *Biochemistry* 1995; **34**: 15436-15443 [PMID: 7492544 DOI: 10.1021/bi00047a007]
 - 59 **Ferjoux G**, Bousquet C, Cordelier P, Benali N, Lopez F, Rochaix P, Buscail L, Susini C. Signal transduction of somatostatin receptors negatively controlling cell proliferation. *J Physiol Paris* 2000; **94**: 205-210 [PMID: 11087998 DOI: 10.1016/S0928-4257(00)00206-0]
 - 60 **Forrest JN**, Reichlin S, Goodman DB. Somatostatin: an endogenous peptide in the toad urinary bladder inhibits vasopressin-stimulated water flow. *Proc Natl Acad Sci USA* 1980; **77**: 4984-4987 [PMID: 6107910 DOI: 10.1073/pnas.77.8.4984]
 - 61 **Friedlander G**, Amiel C. Somatostatin and alpha 2-adrenergic agonists selectively inhibit vasopressin-induced cyclic AMP accumulation in MDCK cells. *FEBS Lett* 1986; **198**: 38-42 [PMID: 2869974]
 - 62 **Winkler SN**, Torikai S, Levine BS, Kurokawa K. Effect of somatostatin on vasopressin-induced antidiuresis and renal cyclic AMP of rats. *Miner Electrolyte Metab* 1982; **7**: 8-14 [PMID: 6133212]
 - 63 **Mountokalakis T**, Levy M. Effect of somatostatin on renal water handling in the dog. *Can J Physiol Pharmacol* 1982; **60**: 655-664 [PMID: 6125252 DOI: 10.1139/y82-090]
 - 64 **Pyrionnet S**, Bousquet C, Najib S, Azar R, Laklai H, Susini C. Antitumor effects of somatostatin. *Mol Cell Endocrinol* 2008; **286**: 230-237 [PMID: 18359151 DOI: 10.1016/j.mce.2008.02.002]
 - 65 **Bigg-Wither GW**, Ho KK, Grunstein RR, Sullivan CE, Doust BD. Effects of long term octreotide on gall stone formation and gall bladder function. *BMJ* 1992; **304**: 1611-1612 [PMID: 1628089 DOI: 10.1136/bmj.304.6842.1611]
 - 66 **Jönsson A**, Manhem P. Octreotide and loss of scalp hair. *Ann Intern Med* 1991; **115**: 913 [PMID: 1952484 DOI: 10.7326/0003-4819-115-11-913_1]
 - 67 **Kwekkeboom DJ**, Bakker WH, Kam BL, Teunissen JJ, Kooij PP, de Herder WW, Feelders RA, van Eijck CH, de Jong M, Srinivasan A, Erion JL, Krenning EP. Treatment of patients with gastro-entero-pancreatic (GEP) tumours with the novel radiolabelled somatostatin analogue [177Lu-DOTA(0),Tyr3]octreotate. *Eur J Nucl Med Mol Imaging* 2003; **30**: 417-422 [PMID: 12634971 DOI: 10.1007/s00259-002-1050-8]
 - 68 **Lami MC**, Hadjadj S, Guillet G. Hair loss in three patients with acromegaly treated with octreotide. *Br J Dermatol* 2003; **149**: 655-656 [PMID: 14511007 DOI: 10.1046/j.1365-2133.2003.05478.x]
 - 69 **Nakauchi Y**, Kumon Y, Yamasaki H, Tahara K, Kurisaka M, Hashimoto K. Scalp hair loss caused by octreotide in a patient with acromegaly: a case report. *Endocr J* 1995; **42**: 385-389 [PMID: 7670568 DOI: 10.1507/endocrj.42.385]
 - 70 **Dilger JA**, Rho EH, Que FG, Sprung J. Octreotide-induced bradycardia and heart block during surgical resec-

- tion of a carcinoid tumor. *Anesth Analg* 2004; **98**: 318-20, table of contents [PMID: 14742361 DOI: 10.1213/01.ANE.0000097170.27056.08]
- 71 **Herrington AM**, George KW, Moulds CC. Octreotide-induced bradycardia. *Pharmacotherapy* 1998; **18**: 413-416 [PMID: 9545165]
 - 72 **Tzotzas T**, Papazisis K, Perros P, Krassas GE. Use of somatostatin analogues in obesity. *Drugs* 2008; **68**: 1963-1973 [PMID: 18778119 DOI: 10.2165/00003495-200868140-00003]
 - 73 **Nakamura T**, Kudoh K, Takebe K, Imamura K, Terada A, Kikuchi H, Yamada N, Arai Y, Tando Y, Machida K. Octreotide decreases biliary and pancreatic exocrine function, and induces steatorrhea in healthy subjects. *Intern Med* 1994; **33**: 593-596 [PMID: 7827373 DOI: 10.2169/internalmedicine.33.593]
 - 74 **Vachha B**, Sun MR, Siewert B, Eisenberg RL. Cystic lesions of the liver. *AJR Am J Roentgenol* 2011; **196**: W355-W366 [PMID: 21427297 DOI: 10.2214/AJR.10.5292]
 - 75 **DeMatteo RP**, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg* 2000; **231**: 51-58 [PMID: 10636102 DOI: 10.1097/00000658-200001000-00008]
 - 76 **Hirota S**, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M, Kurata A, Takeda M, Muhammad Tunio G, Matsuzawa Y, Kanakura Y, Shinomura Y, Kitamura Y. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 1998; **279**: 577-580 [PMID: 9438854 DOI: 10.1126/science.279.5350.577]
 - 77 **Ye YJ**, Gao ZD, Poston GJ, Wang S. Diagnosis and multidisciplinary management of hepatic metastases from gastrointestinal stromal tumour (GIST). *Eur J Surg Oncol* 2009; **35**: 787-792 [PMID: 19185444 DOI: 10.1016/j.ejso.2009.01.003]
 - 78 **Matsuoka L**, Stapfer M, Mateo R, Jabbour N, Naing W, Selby R, Gagandeep S. Left extended hepatectomy for a metastatic gastrointestinal stromal tumor after a disease-free interval of 17 years: report of a case. *Surg Today* 2007; **37**: 70-73 [PMID: 17186351 DOI: 10.1007/s00595-006-3338-y]
 - 79 **Radkani P**, Ghersi MM, Paramo JC, Mesko TW. A multidisciplinary approach for the treatment of GIST liver metastasis. *World J Surg Oncol* 2008; **6**: 46 [PMID: 18471285 DOI: 10.1186/1477-7819-6-46]
 - 80 **Pisters PW**, Blanke CD, von Mehren M, Picus J, Sirulnik A, Stealey E, Trent JC. A USA registry of gastrointestinal stromal tumor patients: changes in practice over time and differences between community and academic practices. *Ann Oncol* 2011; **22**: 2523-2529 [PMID: 21464155 DOI: 10.1093/annonc/mdq773]
 - 81 **Chen LL**, Trent JC, Wu EF, Fuller GN, Ramdas L, Zhang W, Raymond AK, Prieto VG, Oyediji CO, Hunt KK, Pollock RE, Feig BW, Hayes KJ, Choi H, Macapinlac HA, Hittelman W, Velasco MA, Patel S, Burgess MA, Benjamin RS, Frazier ML. A missense mutation in KIT kinase domain 1 correlates with imatinib resistance in gastrointestinal stromal tumors. *Cancer Res* 2004; **64**: 5913-5919 [PMID: 15342366 DOI: 10.1158/0008-5472.CAN-04-0085]
 - 82 **Heinrich MC**, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, McGreevey LS, Chen CJ, Van den Abbeele AD, Druker BJ, Kiese B, Eisenberg B, Roberts PJ, Singer S, Fletcher CD, Silberman S, Dimitrijevic S, Fletcher JA. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol* 2003; **21**: 4342-4349 [PMID: 14645423 DOI: 10.1200/JCO.2003.04.190]
 - 83 **Heinrich MC**, Corless CL, Duensing A, McGreevey L, Chen CJ, Joseph N, Singer S, Griffith DJ, Haley A, Town A, Demetri GD, Fletcher CD, Fletcher JA. PDGFRA activating mutations in gastrointestinal stromal tumors. *Science* 2003; **299**: 708-710 [PMID: 12522257 DOI: 10.1126/science.1079666]
 - 84 **Hirota S**, Ohashi A, Nishida T, Isozaki K, Kinoshita K, Shinomura Y, Kitamura Y. Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. *Gastroenterology* 2003; **125**: 660-667 [PMID: 12949711 DOI: 10.1016/S0016-5085(03)01046-1]
 - 85 **Chen P**, Zong L, Zhao W, Shi L. Efficacy evaluation of imatinib treatment in patients with gastrointestinal stromal tumors: a meta-analysis. *World J Gastroenterol* 2010; **16**: 4227-4232 [PMID: 20806443 DOI: 10.3748/wjg.v16.i33.4227]
 - 86 **Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST)**. Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. *J Clin Oncol* 2010; **28**: 1247-1253 [PMID: 20124181 DOI: 10.1200/JCO.2009.24.2099]
 - 87 **Bümming P**, Andersson J, Meis-Kindblom JM, Klingenshierna H, Engström K, Stierner U, Wängberg B, Jansson S, Ahlman H, Kindblom LG, Nilsson B. Neoadjuvant, adjuvant and palliative treatment of gastrointestinal stromal tumours (GIST) with imatinib: a centre-based study of 17 patients. *Br J Cancer* 2003; **89**: 460-464 [PMID: 12888812 DOI: 10.1038/sj.bjc.6600965]
 - 88 **Bauer S**, Hartmann JT, de Wit M, Lang H, Grabellus F, Antoch G, Niebel W, Erhard J, Ebeling P, Zeth M, Taeger G, Seeber S, Flasshove M, Schütte J. Resection of residual disease in patients with metastatic gastrointestinal stromal tumors responding to treatment with imatinib. *Int J Cancer* 2005; **117**: 316-325 [PMID: 15900603 DOI: 10.1002/ijc.21164]
 - 89 **DeMatteo RP**, Maki RG, Singer S, Gonen M, Brennan MF, Antonescu CR. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. *Ann Surg* 2007; **245**: 347-352 [PMID: 17435539 DOI: 10.1097/01.sla.0000236630.93587.59]
 - 90 **Raut CP**, Posner M, Desai J, Morgan JA, George S, Zahrieh D, Fletcher CD, Demetri GD, Bertagnolli MM. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. *J Clin Oncol* 2006; **24**: 2325-2331 [PMID: 16710031 DOI: 10.1200/JCO.2005.05.3439]
 - 91 **Gronchi A**, Fiore M, Miselli F, Lagonigro MS, Coco P, Messina A, Pilotti S, Casali PG. Surgery of residual disease following molecular-targeted therapy with imatinib mesylate in advanced/metastatic GIST. *Ann Surg* 2007; **245**: 341-346 [PMID: 17435538 DOI: 10.1097/01.sla.0000242710.36384.1b]
 - 92 **Suzuki S**, Sasajima K, Miyamoto M, Watanabe H, Yokoyama T, Maruyama H, Matsutani T, Liu A, Hosone M, Maeda S, Tajiri T. Pathologic complete response confirmed by surgical resection for liver metastases of gastrointestinal stromal tumor after treatment with imatinib mesylate. *World J Gastroenterol* 2008; **14**: 3763-3767 [PMID: 18595147 DOI: 10.3748/wjg.14.3763]
 - 93 **Lendoire J**, Barros Schelotto P, Alvarez Rodríguez J, Duek F, Quarin C, Garay V, Amante M, Cassini E, Imventarza O. Bile duct cyst type V (Caroli's disease): surgical strategy and results. *HPB (Oxford)* 2007; **9**: 281-284 [PMID: 18345305 DOI: 10.1080/13651820701329258]
 - 94 **Yonem O**, Bayraktar Y. Clinical characteristics of Caroli's disease. *World J Gastroenterol* 2007; **13**: 1930-1933 [PMID: 17461492]
 - 95 **Shedda S**, Robertson A. Caroli's syndrome and adult polycystic kidney disease. *ANZ J Surg* 2007; **77**: 292-294 [PMID: 17388839 DOI: 10.1111/j.1445-2197.2006.03659.x]
 - 96 **Wang ZX**, Yan LN, Li B, Zeng Y, Wen TF, Wang WT. Orthotopic liver transplantation for patients with Caroli's disease. *Hepatobiliary Pancreat Dis Int* 2008; **7**: 97-100 [PMID: 18234647]
 - 97 **Kassahun WT**, Kahn T, Wittekind C, Mössner J, Caca K, Hauss J, Lamesch P. Caroli's disease: liver resection and liver transplantation. Experience in 33 patients. *Surgery* 2005; **138**: 888-898 [PMID: 16291390 DOI: 10.1016/j.surg.2005.05.002]

- 98 **Bockhorn M**, Malagó M, Lang H, Nadalin S, Paul A, Saner F, Frilling A, Broelsch CE. The role of surgery in Caroli's disease. *J Am Coll Surg* 2006; **202**: 928-932 [PMID: 16735207 DOI: 10.1016/j.jamcollsurg.2006.02.021]
- 99 **Xu HX**, Liu GJ, Lu MD, Xie XY, Xu ZF, Zheng YL, Liang JY. Characterization of small focal liver lesions using real-time contrast-enhanced sonography: diagnostic performance analysis in 200 patients. *J Ultrasound Med* 2006; **25**: 349-361 [PMID: 16495496]
- 100 **Xu HX**. Contrast-enhanced ultrasound in the biliary system: Potential uses and indications. *World J Radiol* 2009; **1**: 37-44 [PMID: 21160719 DOI: 10.4329/wjr.v1.i1.37]
- 101 **Inoue T**, Kitano M, Kudo M, Sakamoto H, Kawasaki T, Yasuda C, Maekawa K. Diagnosis of gallbladder diseases by contrast-enhanced phase-inversion harmonic ultrasonography. *Ultrasound Med Biol* 2007; **33**: 353-361 [PMID: 17280766 DOI: 10.1016/j.ultrasmedbio.2006.09.003]
- 102 **Numata K**, Oka H, Morimoto M, Sugimori K, Kunisaki R, Nihonmatsu H, Matsuo K, Nagano Y, Nozawa A, Tanaka K. Differential diagnosis of gallbladder diseases with contrast-enhanced harmonic gray scale ultrasonography. *J Ultrasound Med* 2007; **26**: 763-774 [PMID: 17526608]

P- Reviewers: Cardinale V, Xu HX **S- Editor:** Wen LL
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ISSN 1007-9327

