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Guidelines

Benign liver lesions 2022: Guideline for clinical practice of Associazione Italiana Studio del Fegato (AISF), Società Italiana di Radiologia Medica e Interventistica (SIRM), Società Italiana di Chirurgia (SIC), Società Italiana di Ultrasonologia in Medicina e Biologia (SIUMB), Associazione Italiana di Chirurgia Epatobilio-Pancreatica (AICEP), Società Italiana Trapianti d'Organo (SITO), Società Italiana di Anatomia Patologica e Citologia Diagnostica (SIAPEC-IAP) – Part I – Cystic lesions

Maurizio Pompili[a,*], Francesco Ardito[a], Enrico Brunetti[b], Giuseppe Cabibbo[c], Fabrizio Calliada[d], Umberto Cillo[e], Ilario de Sio[f], Rita Golfieri[g], Mauro Grova[c], Salvatore Gruttadauria[h], Maria Guido[i,o], Massimo Iavarone[j], Tommaso Manciulli[k], Duilio Pagano[m], Irene Pettinari[g], Francesco Santopaolo[a], Maurizio Soresi[l], Agostino Colli[n]

[a] *Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Gemelli Universitario "A. Gemelli" IRCCS, Università Cattolica del Sacro Cuore, Largo A. Gemelli, 8, Roma 00168, Italy*
[b] *Dipartimento di Scienze Cliniche, Chirurgiche, Diagnostiche e Pediatriche, IRCCS Fondazione Ospedale San Matteo, Università di Pavia, Unità di Malattie Infettive e Immunologia, Pavia, Italy*
[c] *Sezione di Gastroenterologia e Epatologia, Dipartimento di Promozione della Salute, Materno-Infantile, di Medicina Interna e Specialistica di Eccellenza "G. D'Alessandro" (PROMISE) Università di Palermo, Italy*
[d] *Dipartimento di Radiologia, Fondazione Policlinico San Matteo IRCCS, Università di Pavia, Italy*
[e] *Chirurgia Epatobiliare e Trapianto di Fegato, Ospedale Universitario di Padova, Italy*
[f] *Epatogastroenterologia, Facoltà di Medicina e Chirurgia, Università della Campania Luigi Vanvitelli, Napoli, Italy*
[g] *Dipartimento di Radiologia, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy*
[h] *Dipartimento per la cura e lo studio delle Patologie Addominali e dei Trapianti Addominali, IRCCS-ISMETT-UPMCI, Dipartimento di Chirurgia e Specialità Medico-Chirurgiche, Università di Catania, Palermo, Italy*
[i] *Dipartimento di Anatomia Patologica, Azienda ULSS2 Marca Trevigiana, Treviso, Italy*
[j] *Divisione di Gastroenterologia ed Epatologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy*
[k] *Dipartimento di Medicina Sperimentale e Clinica, Università degli Studi, Firenze, Italy*
[l] *Medicina Interna, Dipartimento di Promozione della Salute, Materno-Infantile, di Medicina Interna e Specialistica di Eccellenza "G. D'Alessandro" (PROMISE) Università di Palermo, Italy*
[m] *Dipartimento per la cura e lo studio delle Patologie Addominali e dei Trapianti Addominali, IRCCS-ISMETT-UPMC, Palermo, Italy*
[n] *Dipartimento di Medicina Trasfusionale ed Ematologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy*
[o] *Dipartimento di Medicina - DIMED, Università di Padova, Italy*

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ABSTRACT

Benign liver lesions are increasingly diagnosed in daily clinical practice due to the growing use of imaging techniques for the study of the abdomen in patients who have non-specific symptoms and do not have an increased risk of hepatic malignancy. They include simple or parasitic cysts and solid benign tumors which differ widely in terms of prevalence, clinical relevance, symptoms and natural history and often lead to significant clinical problems relating to diagnosis and clinical management. Following the need to have updated guidelines on the management of benign focal liver lesions, the Scientific Societies mainly involved in their management have promoted the drafting of a new dedicated document. This document was drawn up according to the present Italian rules and methodologies necessary to produce clinical, diagnostic, and therapeutic guidelines based on evidence. Here we present the first part of the guideline,

* Corresponding author.
E-mail address: maurizio.pompili@unicatt.it (M. Pompili).

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concerning the characterization of focal hepatic lesions detected by ultrasound, and the diagnosis and clinical management of simple and parasitic hepatic cysts, and of polycystic liver disease.

1. Introduction

This report is a summary of Clinical Practice Guidelines for the management of benign liver lesions promoted by the following scientific societies: Associazione Italiana Studio del Fegato (AISF), Società Italiana di Radiologia Medica e Interventistica (SIRM), Società Italiana di Chirurgia (SIC), Società Italiana di Ultrasonologia in Medicina e Biologia (SIUMB), Associazione Italiana di Chirurgia Epatobilio-Pancreatica (AICEP), Società Italiana Trapianti d'Organo (SITO), Società Italiana di Anatomia patologica e Citologia Diagnostica (SIAPEC-IAP).

Current knowledge on diagnosis and management of benign liver lesions is translated into relevant practical recommendations following the rules and the methodology suggested in Italy by the Centro Nazionale per l'Eccellenza delle cure (CNEC) and Istituto Superiore di Sanità (ISS).

1.1. Clinical epidemiology of benign liver lesions

Benign focal liver lesions are increasingly diagnosed due to the use of imaging techniques in patients with non-specific symptoms and without increased risk of liver malignancy. Therefore, in most cases they are incidental findings [1] including liver cysts and solid benign liver tumors. The latter are a heterogeneous group of lesions among which the most common are hemangioma, focal nodular hyperplasia, and adenoma, with different prevalence, clinical relevance, symptomatology, and natural course. The prevalence of benign liver lesions in the general population is approximately 15% [2–4]. Their management is a relevant clinical issue: a definition of the appropriate use of imaging, follow -up, and treatment is needed [5].

Based on these considerations, the problem of diagnosis and treatment of benign liver lesions was considered a priority and evaluated as such in the GRADEpro Evidence to Decision (EtD) GDT tables [6].

1.2. Methods for developing the guideline

The above mentioned scientific societies whose members are primarily involved in the management of benign liver lesions selected a committee of 16 experts to draw up the guideline. This document was prepared according to the rules of the National center for clinical excellence, quality and safety of care (Centro Nazionale per l'Eccellenza Clinica, la Qualità e la Sicurezza delle Cure - CNEC) [7]. The committee defined the objectives and key issues. The most relevant questions were developed following the PICO format (Population, Intervention, Comparison, Outcomes), selected by discussion and voted by the whole committee. For each PICO question, the literature on MEDLINE database was systematically searched with both pertinent string and free text. A further hand-search was performed on previously published guidelines. The evidence profiles were developed applying the GRADE Evidence to Decision (EtD) framework [6] according to the CNEC manual [7,8]. All aspects concerning questions, assessment of evidence, and conclusions were discussed among panel members and voted. The online GRADEpro GDT tool was used to develop questions and make decisions [9]. The quality of the studies was assessed applying the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklist for diagnostic accuracy questions [10], the revised tool for Risk of Bias in randomized trials (RoB 2) [11], and the Risk Of Bias in Non-randomized Studies - of interventions (ROBINS-I) tool [12] for randomized clinical trials and non-randomized studies, where applicable.

PICO questions and recommendations

Focal liver lesions detected in patients without chronic liver disease or neoplastic disease

PICO 1 - In adults without history of chronic liver disease and cancer, and with ultrasound evidence of anechoic focal liver lesions, should ultrasound with contrast agent, magnetic resonance with contrast agent, or computed tomography with contrast agent be used for an accurate diagnosis?

Detecting hepatic cysts by ultrasound (US) or computed tomography (CT) or magnetic resonance imaging (MRI) is generally incidental. US shows a diagnostic accuracy >90% for hepatic cysts [13,14] and is able differentiating simple from complex cysts [15–17]. Simple cysts show typical characteristics: anechoic content, round or oval shape, lack of intralesional septa, thin walls, and posterior acoustic reinforcement [16–18]. Only one single case of oncocytic bile duct cystic adenoma misdiagnosed as a simple cyst at US was reported [19]. Accordingly, contrast-based imaging techniques are not recommended for further characterization of simple cysts. Atypical cystic lesions, characterized by multiple or thick septa, calcifications, fenestrations, daughter cysts, irregular wall, solid papillary projections, and echo-structural heterogeneity, should be evaluated by contrast enhanced techniques, favoring MRI for lower biological risk and a probably higher diagnostic accuracy than CT [13–17].

Recommendation

a. **In asymptomatic adults without chronic liver disease and cancer and with ultrasound evidence of anechoic focal liver lesion with the simple cyst characteristics, we suggest avoiding further evaluation with contrast-enhanced ultrasound, magnetic resonance, or computed tomography. Very low quality of evidence (D); strength of recommendation 2 (conditional)**
b. **In symptomatic patients or in case of ultrasound characteristics suggesting complex cysts (presence of multiple and/or thick septa, calcifications, fenestrations, daughter cysts, irregular wall, solid papillary projections, echo-structural heterogeneity) we suggest performing a contrast-enhanced imaging technique, favoring magnetic resonance. Very low quality of evidence (D); strength of recommendation 1 (strong)**

PICO 2 - In adults without history of chronic liver disease and cancer and with ultrasound evidence of hyperechoic focal liver lesion, should magnetic resonance or computed tomography or ultrasound with contrast agent be used for an accurate diagnosis?

At US examination, hemangiomas typically present as homogeneously hyperechoic focal lesions with well-defined margins, posterior acoustic reinforcement, and diameter < 3 cm [20,21]. Atypical characteristics are more common in larger lesions and include hyperechoic rim delimiting a hypo- or isoechoic nodule, iso- or hypoechoic homogeneous appearance, heterogeneous echogenicity with hypoechoic areas (due to necrosis, bleeding or thrombosis) and/or calcifications [22–25]. In patients without chronic liver disease and cancer, the US evidence of hyperechoic lesion < 3 cm with typical characteristics of hemangioma is considered sufficient

for the diagnosis, despite the lack of adequate studies and based solely on common practice [15,17,26–29]. In case of atypical US features, using MRI, CT or contrast-enhanced ultrasound (CEUS) is suggested to characterize the lesion. A retrospective study in patients with histological diagnosis of hemangioma showed similar accuracy for CEUS and MRI [30]. The very high sensitivity (88% and 93% respectively) and specificity (99% for both methods) appear overestimated for evident patient selection bias. Accordingly, since the quality of the studies is low, there is no evidence to choose one of the two imaging techniques [31–35]. After contrast agent administration, hemangiomas typically show peripheral globular enhancement followed by slow, progressive, and centripetal filling which appears complete in the late phases [24]; about 16% of hemangiomas (especially the smaller ones) show an immediate and intense contrast filling (a.k.a. flash-filling hemangioma). Rarely, hemangiomas show centrifugal filling, or absent early peripheral enhancement and very slow or absent filling (sclerotic hemangiomas). Lesions with atypical enhancement often simulate neoplastic lesions, and histology is usually required to confirm the diagnosis [24,36].

Recommendation

a. **In adults without history of chronic liver disease and cancer, in case of ultrasound evidence of hyperechoic focal lesion smaller than 3 cm with typical ultrasound characteristics of hemangioma, we suggest avoiding the use of contrast-enhanced ultrasound, magnetic resonance or computed tomography. Very low quality of evidence (D); strength of recommendation 2 (conditional)**
b. **In case of atypical ultrasound characteristics or lesions > 3 cm, we suggest performing contrast-enhanced techniques for proper characterization. Very low quality of evidence (D); strength of recommendation 2 (conditional)**

PICO 3 - In adults without history of chronic liver disease and cancer and with ultrasound evidence of hypo- or isoechoic focal liver lesion, should magnetic resonance or computed tomography or ultrasound with contrast agent be used to obtain an accurate diagnosis?

The US detection of isoechoic or hypoechoic focal lesions does not allow a definitive diagnosis requiring a correlation with clinical-laboratory data [15]. All benign lesions can appear as hypo- or isoechoic: more frequently focal nodular hyperplasia (FNH) and hepatocellular adenoma (HCA), less frequently hemangiomas. Particularly, the US pattern of FNH is variable, most commonly homogeneously isoechoic and less frequently hypoechoic or hyperechoic [37]. A central scar may be detected (45% of cases). HCA US appearance is also variable: HCAs smaller than 3–5 cm are usually isoechoic, but their appearance may vary due to bleeding, necrosis, fibrosis, or calcifications [38]. Primary or secondary neoplastic lesions, incidentally detected in patients without liver disease or cancer, more commonly appear hypoechoic or isoechoic [15]. Due to the different pathogenesis of hypoechoic or isoechoic lesions, contrast-enhanced techniques are needed for diagnostic characterization [17]. Contrast-enhanced MRI allows differentiating FNH from HCA, although its diagnostic accuracy, reported as > 90% and assessed in high- risk-of bias studies, is probably overestimated [39–43]. CEUS differentiates benign from malignant lesions with sensitivity of 85–100% and specificity of 63–100% [44–48], although the evidence from these studies is indirect, as patients with hyperechoic lesions or chronic liver disease or cancer were also included. In a study considering HCA as a malignant lesion, CEUS correctly identified benign hypoechoic lesions in 81% of cases, and malignant hypoechoic lesions in 88% [49]. The combination of CEUS and MRI can correctly characterize 98% of liver lesions [50]. Contrast-enhanced CT has a diagnostic accuracy of 80–88% [50,51], lower than that of MRI [42].

Recommendation

In adults without chronic liver disease and cancer, in case of ultrasound evidence of hypo- or isoechoic focal lesion, we suggest performing magnetic resonance or computed tomography or ultrasound with contrast agent to obtain an accurate diagnosis. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 4 - In adults without chronic liver disease and cancer and with a solid focal liver lesion not definitively characterized by contrast-enhanced imaging techniques, should a percutaneous biopsy of the lesion be performed to obtain an accurate diagnosis?

The decision to biopsy a focal liver lesion not definitively characterized with imaging techniques in patients without chronic liver disease or cancer is not supported by the available data. Indeed, no study was found reporting the frequency of non-diagnostic results of imaging techniques. A multidisciplinary team might better evaluate the decision, considering potential complications and benefits of lesion characterization. Patient data (age, gender, risk factors, clinical picture, laboratory tests) and lesion data (imaging findings, size, visibility, accessibility for US or CT-guided biopsy) influence the choice between biopsy, imaging surveillance, or immediate surgery [52]. Percutaneous liver biopsy does involve risks. The risk of mortality is 0.02% [53], and the bleeding risk 0.1%−1.7% [54]. The risk of needle tract seeding of malignant lesions has been estimated 2.3%−2.7% in patients with HCC [55,56], 6% in metastatic colon cancer patients and 0% in metastatic breast cancer patients [57]. A retrospective study showed that CEUS guidance is more effective than US guidance for diagnosing malignancy in indeterminate lesions (100% vs 74%) [58]. Fusion image-guided techniques of US with CT or MRI for poorly visualized lesions showed technical success rate of 96% [59].

Fig. 1 shows a proposed flow-chart for the characterization of focal liver lesions detected by ultrasound in patients with negative history of chronic liver disease or cancer.

Recommendation

In adults without chronic liver disease and cancer and with solid focal liver lesions not characterized by imaging techniques, we suggest a multidisciplinary discussion to assess if biopsy could influence the therapeutic decisions. Very low quality of evidence (D); strength of recommendation 2 (conditional)

Simple cyst

Simple hepatic cysts are congenital lesions arising from aberrant bile duct, not communicating with the biliary tree, in which endoluminal fluid secretions progressively accumulate [60]. Most of them are < 3 cm, but larger cysts can reach 30 cm in diameter [16,61]. Multiple cysts are common in the same patient, but this condition is distinguished from polycystic liver disease (PLD), which is characterized by more than 20 cysts. The incidence is higher in adults over 40–50 years, with female/male ratio of 4:1 [16]. The prevalence ranges between 2.5% and 18% in adults [4,18,62] with a clear trend to increase with age [4,63].

PICO 5 - In asymptomatic adult patients with an imaging diagnosis of simple cyst is follow-up required?

The incidental detection of simple cysts in asymptomatic patients without history of neoplastic disease requires no treatment nor follow-up. Indeed, it has been shown that there is no risk of malignant transformation [64], The benefit of surveillance cannot be demonstrated and does not justify the costs. The recommendation is based on the opinion generated by clinical practice rather than systematic follow-up studies [16,27].

Recommendation

In asymptomatic adults with simple cysts and negative history of malignancy we suggest avoiding follow-up. Very low quality of evidence (D); strength of recommendation 2 (conditional)

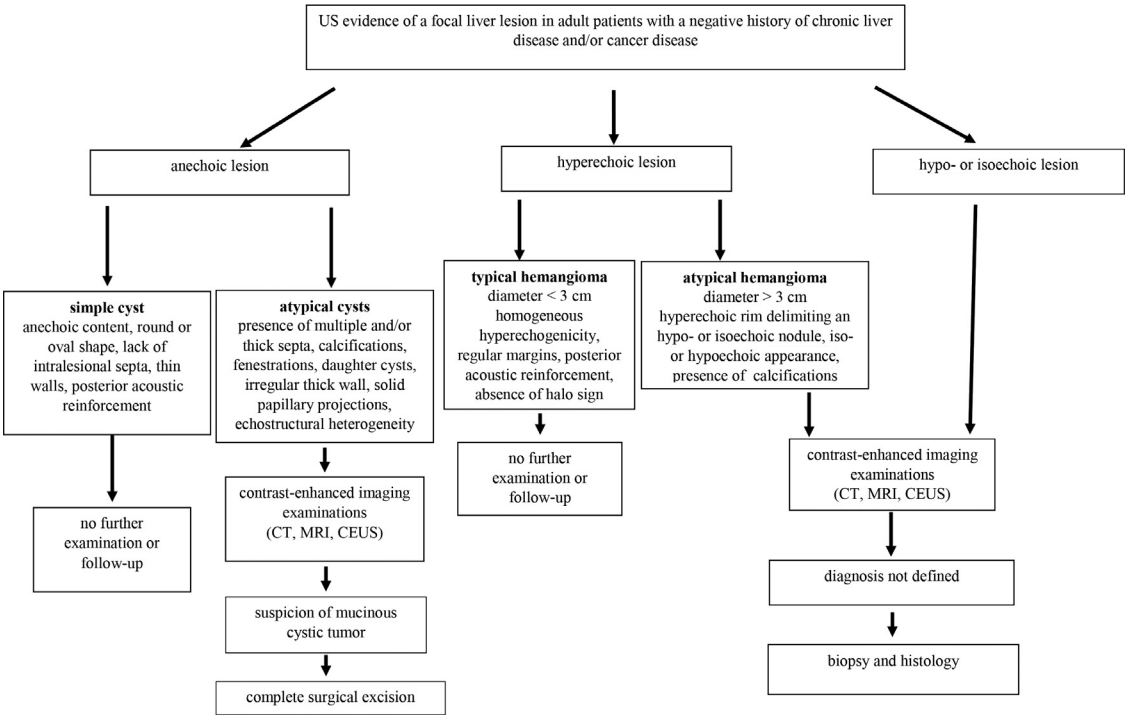

Fig. 1. Flow-chart concerning the recommended sequence of imaging and biopsy techniques to be used for the characterization of focal liver lesions detected by ultrasound in patients without chronic liver disease and/or neoplastic diseases.
Abbreviations: US: ultrasound; CT: computed tomography; MRI: magnetic resonance imaging; CEUS: contrast enhanced ultrasound.

PICO 6 - In adults with complex cysts, are cytologic or histologic examinations indicated for a more accurate diagnostic characterization?

The few available data suggest a low sensitivity of cytologic and histologic examinations [65]. The diagnosis of mucinous cystic tumor (aka biliary cystadenoma) requires the identification of the stroma which can not be obtained by cyto-aspiration; furthermore, neoplastic areas are often focally distributed with low probability of being sampled [66,67]. The same considerations apply to the differential diagnosis between intraductal papillary neoplasm and intraductal papillary neoplasm with invasive component.

Recommendation

In adults with complex cysts, we suggest not performing a cyto-aspirate or a needle biopsy due to low diagnostic sensitivity. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 7 - In adults with complex cysts, should surgical treatment versus follow-up be indicated?

Differential diagnosis of complex hepatic cysts includes mucinous cystic tumor and simple cysts with previous intra-cystic bleeding [68]. In case of radiological suspicion of mucinous cystic tumor, surgery with complete excision of the cyst is the preferred treatment as the estimated risk of malignant transformation is 25%, and simple fenestration is associated with high risk of relapse [69].

Recommendation

In adults diagnosed with complex cysts, we suggest surgical treatment. In case of preoperative radiological suspicion of mucinous cystic tumor, the complete excision of the cysts (enucleation or liver resection, depending on the site) should be performed. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 8 - In symptomatic patients with simple cysts does treatment offer better results than follow-up?

Most common symptoms are abdominal pain, nausea, vomiting, and postprandial swelling. Symptoms are rarely associated with complications such as bleeding or abscess formation. A retrospective study compared symptoms recurrence in patients undergoing surgery or conservative treatment and showed a lower rate of recurrence after surgical treatment [70]. Furthermore, a retrospective study, lacking a control arm, showed that surgery improves the quality of life in symptomatic patients with simple cysts [71].

Recommendation

We suggest treating symptomatic patients with simple cysts to improve the quality of life. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 9 - In symptomatic patients with simple cysts does surgical treatment offer better results than percutaneous treatment?

Percutaneous aspiration of the cyst is effective only when intracystic instillation of sclerosing agents (such as ethanol, minocycline, tetracycline or polidicanol) is performed after inoculation of contrast agent excluding biliary communication. Nowadays, the surgical treatment of choice is laparoscopic fenestration that is as effective as laparotomic fenestration and is associated with symptomatic relief in 90.2% of cases, symptomatic recurrence in 9.6%, and reintervention in 7.1% [72]. Concerning the comparison between percutaneous aspiration with sclerotherapy (PAS) and surgical treatment, the quality of evidence is very low due to the lack of randomized comparative studies. In a retrospective study, PAS and laparoscopic fenestration were equally effective in achieving partial or complete cyst obliteration [73]. In a systematic review, the ratio of persistent symptoms was higher after PAS compared to laparoscopic fenestration (3.5% vs. 2.1%), but major complication (1.7% vs. 0.8%) and post-treatment relapse (5.5% vs. 0%) were higher in patients treated with laparoscopic fenestration. To note, the mean size of the cysts was smaller (9.3 vs 12.7 cm) and the mean follow-up was shorter (26 vs 38 months) in the PAS group than in the surgical group [74].

Recommendation

In symptomatic patients with simple cysts, the available data fail to demonstrate superiority of surgical (laparoscopic fenestration) over percutaneous treatment (aspiration and sclerotherapy). Both treatments are effective. We suggest that the choice between the two options considers the size and location of the cyst, the experience of the center, the comorbidities, and the preferences of the patient. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 10 - a) In symptomatic patients with simple cysts does laparoscopic fenestration offer better results than liver resection? b) In symptomatic patients with recurrent simple cysts does liver resection offer better results than laparoscopic fenestration?

One retrospective study identified 40 consecutive patients with simple cysts treated by laparoscopic or laparotomic fenestration or liver resection. The laparoscopic fenestration group showed lower postoperative morbidity and length of hospital stay. At median follow up of 20 months, there were no recurrences in the resection group, while recurrence occurred in 22% of patients in the fenestration group; only two of these patients required a resection [75]. In another retrospective study, 67 symptomatic simple cysts were treated with laparoscopic deroofing (48 cases), open deroofing (11 cases), and resection (12 cases). Recurrence occurred in 29%, 36%, and 27% of cases, respectively, with 4% of patients who had further surgery in the laparoscopic deroofing group, 18% in the open deroofing group, and none in the resection group [76]. There are no studies comparing treatments of recurrence after fenestration, therefore resection is preferred over fenestration, based on the absence of recurrence in resected patients in the above-quoted studies.

Recommendation

a. **In patients with symptomatic simple cysts laparoscopic fenestration is preferred over liver resection. Very low quality of evidence (D); strength of recommendation 2 (conditional).**
b. **In symptomatic patients with simple cysts recurrent after fenestration liver resection is preferred over fenestration. Very low quality of evidence (D); strength of recommendation 2 (conditional)**

Polycystic liver disease

Polycystic liver disease (PLD) is a genetic condition characterized by the development of more than 20 hepatic cysts [16,77]. PLD occurs in two forms depending on the presence or absence of autosomal dominant polycystic kidney disease (ADPKD) [78]. Both conditions present a dominant autosomal pattern of inheritance. PLD associated with ADPKD is linked to mutations of the PKD1 or PKD2 gene, while in PLD not associated with ADPKD - aka autosomal dominant polycystic liver disease (ADPLD)- heterozygous mutations of the genes PRKCSH or SEC63 are present [79–84]. Both conditions are included among the hepatorenal fibrocystic diseases or ciliopathies [83,85]. ADPKD is the most common monogenetic kidney disease (with a prevalence of 1:400- 1:1000) and is associated with PLD in 20%−75% of cases [86]. The prevalence of isolated ADPLD is lower, approximately 1:100.000 [86–89].

In more than 80% of cases, PLD is asymptomatic. Typical symptoms are abdominal distension and pain, early satiety, nausea, dyspnea, lower limbs' edema, and ascites. In PLD, cysts grow slowly, and their volume increase rate is between 0.9 and 3.2% /year [60,90,91]. Gender is associated with disease severity: women account for more than 80% of symptomatic patients with PLD [92] and the large majority (> 80%) of PLD patients receiving liver transplant are women [93]. These gender-related differences can be related to the hormonal status [89,94–96]. In ADPLD liver failure and liver-related death are rare, whereas liver failure is the cause of death in 10% of ADPKD patients [86]. Cyst complications are rare and include rupture, bleeding, and infection. [97]. Liver test abnormalities (with either hepatocellular or cholestatic pattern) are common in symptomatic patients [98]. PLD patients can present with portal hypertension resulting from compression of the portal branches or hepatic veins; its development was demonstrated during follow up in 6% of cases [92] and in 40% of patients listed for liver transplantation [99,100].

Ultrasound highlights multiple fluid-containing, anechoic, round or oval, sharp-edged formations with posterior wall reinforcement [98]. The total liver volume is evaluated with CT or MRI and is a prognostic marker. Two classifications of mild, moderate and severe phenotypes based on the patient's height-adjusted total liver volume (htTLV) are available [96,101]. According to Kim classification, disease severity is classified as mild (htTLV <1600 mL/m), moderate (htTLV 1600–3200 mL/m), and severe (htTLV > 3200 mL/m) [101].

PICO 11 - In asymptomatic relatives of patients with isolated polycystic liver disease, should ultrasound screening be indicated for early diagnosis?

PLD penetrance is incomplete and 20% of mutation carriers may not phenotypically experience the disease. Genetic tests and family screening in ADPLD do not influence individual clinical management [78]. Indeed, therapy is only indicated for symptomatic patients with moderate- severe disease and reduced quality of life. In the absence of treatments able to modify the disease course in asymptomatic patients, ultrasound screening in asymptomatic relatives of PLD patients is not currently indicated.

Recommendation

In asymptomatic relatives of individuals with isolated polycystic liver disease, we suggest no ultrasound screening. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 12 - In adults with ultrasound diagnosis of polycystic liver disease, should magnetic resonance with contrast agent be indicated for staging and differential diagnosis from other diseases such as bile duct hamartomas, peribiliary cysts, and Caroli disease?

A diagnosis of PLD can be made identifying more than 20 hepatic cysts with US, CT, or MRI. CT and MRI also allow staging by assessing: a) intrahepatic extent of disease; b) involvement of other abdominal organs; c) cyst complications. MRI cholangiography with hepato-specific contrast agent allows an appropriate differential diagnosis from other cystic diseases of the liver, such as Caroli disease, [60,102-104], bile duct hamartomas (Von Meyenburg complexes) [105–107] and hepatic peribiliary cysts [108].

Recommendation

In patients with ultrasound diagnosis of polycystic liver disease, we suggest magnetic resonance with hepato-specific contrast agent for appropriate differential diagnosis from other fibro-polycystic liver diseases (bile duct hamartomas and Caroli disease), from peribiliary cysts, and for staging the disease. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 13 - In adults with asymptomatic polycystic liver disease, does surgical (laparoscopic fenestration) or percutaneous (aspiration and sclerotherapy) treatment give better results than follow-up?

The dedicated and validated questionnaires POLCA and PLD-Q can be used to assess the symptoms burden and the need of treatment [109,110]. The Sequential Organ Failure Assessment (SOFA) has recently been developed to screen patients with PLD at risk for sepsis [111]. In rare cases treatment may be considered in asymptomatic patients with dominant cysts causing compression and distortion of intra- or perihepatic anatomical structures [112].

Recommendation

In adults with asymptomatic polycystic liver disease, follow-up with periodic administration of dedicated symptom-assessment questionnaires is suggested. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 14 - In adults with symptomatic polycystic liver disease, does treatment with somatostatin analogues give better results than follow-up?

In a randomized, double-blind, controlled trial, 54 patients with ADPLD or with PLD associated with ADPKD received lanreotide (120 mg) or placebo every 28 days for 24 weeks. Lanreotide group showed a significant reduction in liver volume compared to placebo group [91]. In a recent meta-analysis including 6 trials (592 patients), somatostatin analogues significantly reduced TLV. The same meta-analysis suggests an advantage of lanreotide over octreotide, but the small number of studies prevents to draw definitive conclusions [113]. The lanreotide dosage of 120 mg every 4 weeks was more effective than 90 mg every 4 weeks. However, the lower dose showed fewer side effects and then could be used in case of intolerance to the higher dose [114]. Finally, a summary analysis of 107 patients with PLD from 3 randomized controlled trials showed that females are the subgroup with the best response to somatostatin analogue [115].

Recommendation

In adults with symptomatic polycystic liver disease, we suggest treatment with somatostatin analogues as it provides reduction of liver volume and symptoms compared to follow-up. Low quality of evidence (C); strength of recommendation 2 (conditional)

PICO 15 - In adults with polycystic liver disease and one or more symptomatic dominant cysts, is surgical treatment more effective than percutaneous treatment for symptoms remission?

Retrospective studies showed that surgical treatment is effective in remission of symptoms in patients with PLD and dominant cysts [116–120]. A systematic review and meta-analysis of the efficacy of laparoscopic fenestration of symptomatic cysts included 15 studies with PLD patients. The postoperative complications was more frequent than in patients with solitary cysts [72]. PAS is also effective and in a recent systematic review, symptoms reduction and disappearance were observed in 72% and 59% of patients with PLD, compared with 94% and 82% in patients with solitary cysts. The most frequent side effects were post-procedural pain and bleeding [121].

Recommendation

In adults with polycystic liver disease and one or more symptomatic dominant cysts, the available data fail to demonstrate a superiority of the surgical (laparoscopic fenestration/surgical resection) over percutaneous treatment (aspiration associated with sclerotherapy preceded by contrast exclusion of communication between the treated cyst and the biliary tree). Both treatments are effective, and we suggest that the choice between the two options should consider the size and the location of cysts, the experience of the center, the presence of comorbidities, and the preferences of the patient. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 16 - In adults with polycystic liver disease and clinically relevant symptoms or measurable impairment of the quality of life, is liver transplantation more effective than other treatments?

Liver transplantation is the only curative treatment but should be considered in a minority of patients with massive hepatomegaly associated with severe malnutrition or other serious complications (recurrent cysts bleeding/infection, portal hypertension causing untreatable ascites) and when poor effectiveness of non-transplant therapies can be anticipated [78,122,123]. In addition, the indication may arise from severely and objectively compromised quality of life [124]. Survival at 1 and 5 years for combined liver and kidney transplantation is 86% and 80%, and for liver transplantation alone 93% and 92% [93]. Even more recently, 100% probability of survival at 1 year and 96% at 3, 5, and 10 years have been reported [125].

Recommendation

In adults with massive polycystic liver disease (cyst/liver parenchyma volume ratio > 1) and clinically relevant symptoms such as severe malnutrition, complications of portal hypertension, severe cholestasis, recurrent cysts hemorrhage/infection, or impaired quality of life, we suggest liver transplantation. Low quality of evidence (C); strength of recommendation 2 (conditional)

Parasitic cyst

Cystic echinococcosis (CE) -aka “hydatid disease” or “hydatidosis”- is an infestation caused by *Echinococcus granulosus*, a parasite that has canids as definitive host and humans and other animals (especially cattle and sheep) as intermediate hosts [126]. Humans and ungulates are infected by ingesting embryonated eggs, shed from the feces of final hosts. CE has a global geographic distribution and cases are reported in all continents, except Antarctica [126].

After eggs ingestion by an intermediate host, the embryos hatch, penetrate the intestinal wall, enter blood or lymphatic vessels, and reach the target organs where develop to larval stage oncospheres (metacestode) and form a single chamber cyst that slowly expands and progresses from a fluid-filled unilocular cavity to a pseudo-solid, eventually calcified, lesion [127]. The liver is the organ most frequently involved (69–75% of cases). Cyst development is usually clinically silent, but abdominal pain, dyspepsia, fever, and allergic manifestations may occur. Complications of active cysts are frequent and include rupture in the biliary tree or in the peritoneum, infection, and biliary fistula [128–130].

US is the first-choice technique for diagnosing abdominal CE, with high sensitivity (93–98%) and specificity (88–90%) [131–133]. The classification of the WHO-Informal Working Group on Echinococcosis (WHO-IWGE) allows for a stage-specific treatment approach [134]. The cyst stages are the following: CE1 (active stage): uniformly anechoic cyst with wall that may consist of two hyperechoic lines separated by hypoechoic layer; fine echoes may be seen inside the cyst (“hydatid sand”); CE2 (active stage): multiple (daughter) cysts delimited by septa seen within the main cavity (“honeycomb pattern”); CE3a (transitional stage): uniform fluid collection with floating layers displaying detachment of endocyst from pericyst (“water-lily sign”); CE3b (active stage): predominantly solid cysts with embedded daughter cysts; CE4 (inactive stage): the matrix fills the cyst completely, but wavy lines (folded endocyst) confer a “ball of wool” appearance; CE5 (inactive stage): the cyst is completely solid and with an eggshell calcification. MRI allows assessing extra abdominal or abdominal cysts that cannot be visualized with US and may be used alone or in combination with CT scan for suspected complications [135,136].

To date, four treatment options are available: medical therapy, percutaneous drainage, surgery, and "watch-and-wait" approach. Albendazole (ABZ) is the drug of choice for CE treatment, its bioavailability being superior to that of mebendazole (MBZ), the first benzimidazole found to have *in vivo* activity against CE [137]. ABZ is orally administered at a total daily dose of 10–15 mg/kg [138]. When ABZ is unavailable, MBZ can be used at a total daily dose of 40–50 mg/kg. WHO-IWGE currently recommends a 3–6-month continuous regimen of ABZ without interruption [139]. ABZ alone can be considered for cysts C1 and CE3a smaller than 6 cm but is less effective for cysts C1 and CE3a larger than this size and for cysts CE2 and CE3b [140]. Elevation of liver function tests is the commonest adverse effect associated with these drugs [141].

Praziquantel 40 mg/kg/week plus ABZ has a more effective scolicidal effect than ABZ monotherapy [142]. Percutaneous techniques consist of puncture, aspiration, injection and re-aspiration (PAIR) of a scolicidal agent (ethanol or hypertonic saline) into the cyst. Cysto-biliary communications should be ruled out before the procedure which is effective in CE1 and CE3a cysts larger than 5 cm and is not effective in solid component (CE3b) or multilocular (CE2) cysts. PAIR should be performed in presence of a resuscitation team as the procedure may be complicated by the unpredictable and rare occurrence of anaphylactic shock [143]. For cysts >10 cm, PAIR is contraindicated due to the large amount of fluid to drain for obtaining a successful procedure. The surgical techniques are radical (en-bloc removal of parasitic cysts, including the pericystium) and conservative (removal of the endocyst leaving the pericyst in place) [144]. Conservative treatments are associated with lower mortality (1.2%) and both intraoperative (14.8%) and postoperative (19.4%) complications [145].

PICO 17 - In patients with uncertain imaging diagnosis of parasitic cysts, are serological tests indicated to confirm the diagnosis?

The diagnosis is based on the combination of clinical, instrumental, and serological criteria. Diagnosis is *possible* if there is a compatible clinical and epidemiological history and positive serology; *probable* if the clinical history and the instrumental and serology findings are positive; *confirmed* if there are protoscolices in the cyst fluid aspirated or components of the cyst at surgery [146]. The Western Blot method proved to be the serological test with the highest accuracy (sensitivity 83%, CI 72–91%; specificity 98%, CI 91–100%) [147]. If Western Blot cannot be used in the first instance, the use of two first-level tests (e.g., ELISA and indirect hemagglutination), with the Western Blot confirmatory method in the event of a discordant or negative concordant result, proved to be an equally valid strategy [148].

Recommendation

In patients with uncertain imaging diagnosis of parasitic cyst, we suggest serological tests for diagnostic confirmation. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 18 - In patients diagnosed with single or multiple parasitic cysts, should a therapeutic intervention be indicated?

Complications of active cysts are frequent and include rupture, infection, and biliary fistula. Rupture occurs up to 35% of untreated active cysts, mostly in the biliary tree causing cholangitis and/or obstruction [149,150]. More rarely, rupture may occur in the peritoneum, causing anaphylactic shock or acute abdomen [151]. Bacterial super-infection was found in 7.3% of cases with possible further complications to septic shock and death [152]. Biliary fistula is common and its frequency increases with size as cysts > 7.5 cm have 80% probability of being associated with this complication [129,130]. Based on these data, an expert consensus recommends the treatment of active cysts [134].

Recommendation

In patients diagnosed with single or multiple parasitic cysts, staged CE1, CE2, CE3a and CE3b, we suggest a therapeutic intervention to avoid cyst growth and complications. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 19 - In patients with stage CE1 and CE3a parasitic cysts, does surgical treatment give better results than percutaneous treatment?

A study randomized 50 patients with EC with predominant liquid component to PAIR or surgery (cystectomy). The two techniques were equally effective; however, patients treated with PAIR experienced fewer complications and required shorter hospital stay [153]. PAIR is less invasive than surgical treatment, and a success rate of 97% was reported in patients with stage CE1 and CE3a cysts. Mortality ranges from 0% to 1% and morbidity from 8.5% to 32% [154–157]. A prospective study demonstrated that perioperative adjuvant administration of ABZ reduces cyst recurrence [158]. A recent systematic review showed that the results of PAIR are comparable to those of laparoscopic surgery in terms of efficacy and safety [159]. WHO-IWGE experts suggest treating CE1 and CE3a cysts larger than 5 cm with PAIR while smaller cysts may be treated with medical therapy alone [134].

Recommendation

a. **In patients with stage CE1 and CE3a cysts larger than 5 cm, PAIR is preferred over surgical treatment. Very low quality of evidence (D); strength of recommendation 2 (conditional)**
b. **In patients with stage CE1 and CE3a cysts smaller than 5 cm, we suggest medical treatment. Very low quality of evidence (D); strength of recommendation 2 (conditional)**

PICO 20 – In patients with stage CE2 and CE3b cysts, does surgical treatment give better results than percutaneous treatment?

Radical or conservative surgical treatments of hepatic cysts are associated with perioperative mortality between 0% and 6.5%, morbidity between 12% and 84%, and recurrence between 0% and 30% [160–164]. Among percutaneous treatments, the "modified catheterization technique" (MoCat) was first described in 2007 to treat CE2 and CE3b cysts [165]. This technique can kill parasites, evacuate the endocyst and the matrix, and obliterate the residual cavity. Encouraging results have been reported in small series [166–168]. However, the MoCat technique is performed only in few centers and there are no studies comparing it to surgery that remains the standard treatment for stage CE2 and CE3b cysts.

Recommendation

In patients with stage CE2 and CE3b parasitic cysts, surgical treatment is preferred over percutaneous or medical therapy. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 21 - In patients with stage CE4 and CE5 asymptomatic/inactive parasitic cysts, does surgical or percutaneous treatment give better results than follow-up?

There are no randomized studies comparing treatment with "watch-and-wait" in CE4 and CE5 cysts. Retrospective studies show a negligible risk of reactivation and complications in patients undergoing US follow-up. In one study, 38 patients with 47 CE4 and CE5 liver cysts were followed with US at 6–12 months intervals (median follow-up 51.9 months); in 97.4% of patients the cysts remained inactive [169]. An update of the same study included 53 patients with 66 cysts; 41.5% of patients completed a 5-year follow-up and only one case of reactivation was observed [170]. Overlapping results were shown in a prospective cohort of 30 patients with 46 inactive cysts. No reactivation was reported in a median follow-up of 5.4 years [171].

Recommendation

In patients with asymptomatic/inactive parasitic cysts in stages CE4 and CE5, follow-up is preferred over treatment. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 22 - In patients with single or multiple complicated parasitic cysts, is surgical treatment indicated?

The most frequent complication is rupture in the biliary tree causing abdominal pain, jaundice, cholangitis, or septic shock. Surgery is the choice treatment and a systematic review showed that the best treatment is common bile duct exploration with intraoperative cholangiography and choledochoscopy. When the biliary tract is cleared of cystic content, Kehr-tube positioning is sufficient [172]. A retrospective study showed that the morbidity following this technique was significantly lower than that after choledocho-duodenostomy (18% vs. 40%) [173]. When possible, surgical removal of cysts should also be considered. In a study of 35 complicated cysts, treated with removal of cystic and pericystic

tissue and simultaneous treatment of the fistulous tract, postoperative morbidity was 23% without mortality and recurrence (follow-up > 8 years) [174].

Recommendation

In patients with single or multiple complicated parasitic cysts, we suggest surgical treatment. Low quality of evidence (C); strength of recommendation 2 (conditional)

Declaration of Competing Interest

None declared.

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