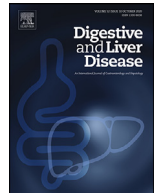




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Guidelines

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 II - Solid lesions

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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 hepatic 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 second part of the

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guideline, concerning the diagnosis and clinical management of hemangioma, focal nodular hyperplasia, and hepatocellular adenoma.

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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. 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 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), [1]. 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 of the PICO questions, the literature on the 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 [2] according to the CNEC manual [1,3]. All aspects concerning the 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 [4]. The quality of the studies was assessed applying the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklist for diagnostic accuracy questions [5], the revised tool for Risk of Bias in randomized trials (RoB 2) [6], and the Risk Of Bias in Non-randomized Studies - of interventions (ROBINS-I) tool [7] for randomized clinical trials and non-randomized studies, where applicable.

2. Hemangioma

Hemangioma is the most common benign liver tumor [8,9]. The prevalence ranges from 2% to 5% in series with imaging techniques but raises up to 20% in autopsy series [8,10–14]. Hemangiomas are more common in females (female/male ratio 3:1 to 6:1), at age between 30 and 50 years [13,15]. They may occur as solitary (with sizes ranging from a few millimeters to 20 cm) or multiple, and rarely concur with focal nodular hyperplasia nodules. Formerly, they were classified as “giant” when > 4 cm, more recently only when > 10 cm [8,16,17].

The diagnosis is usually incidental, and rarely associated with symptoms. In very large hemangiomas, symptoms are related to compression of adjacent organs with abdominal pain or vomit, or

to the occurrence of systemic inflammatory response syndrome. Kasabach-Merritt syndrome is characterized by thrombocytopenia and coagulopathy [13,18]. The etiology of hemangiomas is unclear. They are considered vascular malformations or hamartomas rather than true neoplasms. Despite a possible hormonal influence, estrogen receptors have never been demonstrated and hemangiomas grow even in subjects not taking oral contraceptive pills (OCP) [13,19,20]. During pregnancy, a volumetric increase may be observed, but complications have been rarely reported [21].

In 40–60% of cases, hemangiomas' volume may increase over time with a variable, usually slow, rate. Factors determining growth are not completely clear: size (the largest ones increase faster) and age (the growth rate is higher in subjects below 30 years and slower in those over 50) have been implicated [20,22]. The main complication of hemangiomas, especially giant and pedunculated ones, is rupture with possible hemoperitoneum [23].

PICO 1 - a. In adult patients diagnosed with hemangioma, should imaging surveillance be indicated? b. If surveillance is required, what imaging technique should be used?

Studies assessing the natural course of hemangioma are mainly retrospective [22–28] and at high-risk of bias for patients' selection and missing data. The diagnosis is almost always obtained by ultrasound (US), less frequently by computed tomography (CT) or magnetic resonance imaging (MRI), and rarely by scintigraphy or angiography. The follow-up is variable, preventing any comparison. No study compared imaging surveillance to no surveillance and only the number of complications detected during surveillance can be assessed. Most studies report size changes, especially in hemangiomas > 4–5 cm. A study, using CT or MRI, showed in 40% of hemangiomas a volume increase during a follow-up of 3.7 years, with a growth rate of 17.4%/year [22]. Complications (ruptures, hemorrhages) have been demonstrated mainly in hemangiomas larger than 5–10 cm [25]. Glinkova estimated an odds ratio for enlargement of 3.02 (95% CI 0.99–9.12) without complications [27]. Yedibela reported an increased risk of complications and recommended follow-up in patients with hemangiomas > 10 cm [25]. Further studies should assess the outcome of asymptomatic large volume hemangiomas > 10 cm, using US in view of non-invasiveness, low costs, and absence of biological risk. In case of giant hemangiomas > 15 cm, the repeatability of US may be an issue and MRI may be more accurate [22].

Recommendation

- a. In patients with asymptomatic hemangioma < 10 cm we suggest no follow-up. In symptomatic patients or with hemangiomas > 10 cm we suggest follow-up, due to possible complications. Very low quality of evidence (D); strength of recommendation 2 (conditional)
- b. When indicated, follow-up should be performed with ultrasound in view of non-invasiveness, low costs, and absence of biological risk. In hemangiomas > 15 cm, due to the difficulty of assessing dimensional variations by means of ultrasound, we suggest using magnetic resonance. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 2 - In patients with hemangioma, should ultrasound surveillance be indicated during pregnancy?

The higher prevalence of hemangiomas in women [28,15] raises the question if estrogens may be responsible for their development, and if pregnancy plays a role in growth or in complications occurrence. Complications such as bleeding or Kasabach-Merritt

syndrome are very rarely reported [29]. Cobey reports volume increase without any complication after pregnancy in four women with hemangiomas larger than 5 cm, [21]. Etemadi found that 14 out of 38 cases increased in size during pregnancy without any complication [24].

Recommendation

In patients with asymptomatic hemangiomas we suggest no ultrasound surveillance during pregnancy. Ultrasound surveillance during pregnancy might be required in women with giant hemangiomas. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 3 – Do patients with symptomatic giant hepatic hemangiomas show better outcomes if treated surgically rather than with conservative loco-regional methods?

Treatment should be considered in cases of symptomatic hemangiomas (pain, sense of heaviness), Kasabach-Merritt syndrome (bulky hemangioma associated with severe thrombocytopenia, microangiopathic-hemolytic anemia, and consumption coagulopathy), or in presence of pedunculated hemangiomas at risk of rupture. Surgical treatment is a well-established option, and a recent meta-analysis shows that resection with enucleation is preferable to anatomical resection reducing the duration of surgery, blood loss, and postoperative complications [30]. Beside surgical procedures, other therapeutic options are interventional radiology techniques such as trans-arterial embolization (TAE) and thermal ablation; the latter can also support surgery in selected cases (e.g., laparoscopic/laparotomic thermal ablation) [31]. Ablation techniques should be considered a therapeutic option especially in patients with lesions < 10 cm refusing surgical treatment or at high surgical risk [32,33]. Percutaneous radiofrequency ablation (RFA) has an effectiveness higher than 80% for complete hemangioma ablation [34–36], with a complications rate (bleeding, rupture, injury to adjacent organs) of 5.5% for lesions between 5.5 and 9.9 cm, and of 13.2% for lesions ≥ 10 cm [34]. Contraindications to RFA include lesions in subcapsular space, close to vascular structures greater than 4 mm in caliber or close to perihepatic viscera. In case of proximity to viscera or subcapsular locations, RFA can be safely performed using the laparoscopic approach. Percutaneous or laparoscopic microwave ablation (MWA) can also be used. In comparison to conventional open resection, laparoscopic MWA is associated with reduced blood loss, shorter operative time and post-operative hospital stay, with the same risk of long-term complications [37]. Finally, a systematic review including 18 studies and 1,284 patients, reported that TAE of hemangiomas was associated to volume reduction in 89.9% of cases and an improvement or disappearance of symptoms in 98.5%. Grade 3 complications were found in 2.9% of patients, and failure of the procedure with need of surgery, in 2.7% [38].

Recommendation

- a. **In patients with symptomatic hemangiomas (Kasabach-Merritt syndrome or bulk symptoms) or pedunculated hemangiomas or hemangiomas with a diameter of 10 cm or more, we suggest surgical treatment. Very low quality of evidence (D); strength of recommendation 2 (conditional)**
- b. **Symptomatic hemangiomas less than 10 cm may be initially approached with locoregional ablation techniques. In case of unfavorable clinical evolution or volume increase after treatment we suggest resection with radical intent. Very low quality of evidence (D); strength of recommendation 2 (conditional)**

PICO 4 - Do patients with severely symptomatic hemangioma or multiple hemangiomas show better outcomes with liver transplant compared to conservative therapeutic approach?

Liver transplantation is rarely an option for hepatic hemangiomas due to their benign nature. It is indicated in symptomatic

patients with bilobar multiple hemangiomas, complicated hemangiomas, or with Kasabach-Merritt syndrome, when intra-arterial embolization is ineffective and surgical resection is unfeasible. In the European Liver Transplantation Registry, 71 patients underwent liver transplant for single or multiple hemangiomas from 1988 to 2016, with a 1-year and 5-year survival rate of 80% and 77%, respectively [39]. According to the United Network for Organ Sharing (UNOS), 23 patients received liver transplant for hemangioma from 1988 to 2013, with a 1-year and 5-year survival rate of 87.8% and 74.8%, respectively [40]. A recent systematic review showed an overall transplant-related morbidity of 31%; surgical complications were recorded in 2/16 patients (one bleeding and one hyperacute rejection requiring re-transplantation) whereas medical complications (acute cellular rejections) were observed in 3/16 patients [41].

Recommendation

In symptomatic patients with unresectable giant hepatic hemangioma or multiple hemangiomas, we suggest liver transplantation as a feasible treatment. Very low quality of evidence (D); strength of recommendation 2 (conditional)

3. Focal nodular hyperplasia

Focal nodular hyperplasia (FNH) is the second most common benign tumor of the liver and is generally detected incidentally during US. In non-selected autopsy series, the prevalence was 0.4–3% [42,43]. FNH is mainly diagnosed in reproductive-aged women (up to 90%, age 35–50 years), is usually solitary and less than 5 cm in diameter, multiple in 20–30% of cases, and associated with hepatic hemangiomas in about 20% of cases [44,45]. FNH is considered a hyperplastic-proliferative cell response to vascular malformations [46]. This hypothesis is supported by absence of somatic mutations, deregulation of genes involved in vascular remodeling [47], and association with other intrahepatic arterial injuries such as hereditary hemorrhagic telangiectasia [48], or exposure to oxaliplatin in adults [49]. Pregnancy and OCP showed no role in the development or progression of FNH [50,51].

FNH is generally stable, only occasionally a mild volume increase has been reported, with rare complications [51,52]. Macroscopically, a star-shaped scar, centrally located with radiating fibrous septa containing large-sized artery and veins, is the typical form. Histologically, it is composed of benign hepatocytes arranged in nodules partially surrounded by fibrous septa, with ductular proliferation and inflammatory cells. Several atypical forms are recognized, including FNH without a central scar (the most common atypical form, particularly in <3 cm lesions) and FNH with steatosis [53]. Molecular analysis identified up-regulation of extracellular matrix genes, associated with activation of the transforming-growth factor beta-pathway, and overexpression of Wnt/b-catenin target genes, including glutamate ligase, coding for glutamine synthase (GS) [54,55].

PICO 5 - a. In asymptomatic adults with focal nodular hyperplasia should imaging surveillance be indicated? b. If surveillance is required, what imaging technique should be used?

In patients with FNH no algorithm supporting surveillance is currently available. Although large FNHs can be associated with symptoms due to compression, almost all FNHs remain stable without complications, such as hemorrhage and rupture [56,57]. In a retrospective study including 96 patients with FNH, symptoms worsened in 13% and FNH increased only in 4%, during imaging surveillance (with US or MRI) [58]; no major complications and no increased disease-related mortality were reported in patients refusing resection despite symptoms. However, albeit rare, some cases of rupture, often with hemoperitoneum, are reported [59–65]. In particular, large lesions, localized in the subcapsular region,

appear at higher risk of rupture. Accordingly, imaging surveillance might be proposed for selected patients refusing treatment despite large and/or located in the subcapsular or pericaval region FNHs. MRI, with hepato-specific contrast agents, is more accurate than US and CT, in differentiating adenoma from FNH, with 91%–100% sensitivity and 93%–100 specificity [66–70]. However, most studies overestimated the MRI accuracy failing to classify hepatocellular adenoma (HCA) subtypes with possible misclassification of inflammatory adenomas as telangiectatic FNH [67]. When surveillance is required, US could be used for single small lesion, and MRI with hepato-specific contrast agent for multiple, atypical, or very large lesions.

Recommendation

- a. In asymptomatic adults with focal nodular hyperplasia not localized in the subcapsular or pericaval region, we suggest not performing imaging surveillance. Very low quality of evidence (D); strength of recommendation 2 (conditional)
- b. In symptomatic patients with pain or compression symptoms, refusing treatment, and in patients with lesions located in the subcapsular or pericaval region, we suggest ultrasound or magnetic resonance surveillance. Very low quality of evidence (D); strength of recommendation 2 (conditional). We suggest referring patients with lesions undefined by imaging techniques as focal nodular hyperplasia to a tertiary reference center. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 6 - In patients, with focal nodular hyperplasia and on treatment with oral contraceptives, should discontinuation of therapy be indicated?

The largest study reports data from 216 women diagnosed with FNH, enrolled between 1989 and 1998, and grouped according to the use of OCP: 28 non-users, 46 on high-dose OCP therapy, 98 on low-dose therapy, 33 on high-dose and then on low-dose therapy, and 11 on therapy with progestin only. No difference was found between the five groups in number and size of FNH. In addition, 136 of these patients were kept under surveillance: a change in size was detected only in 2.9%, without difference according to the use of OCP [71]. In another study, FNHs grew in 4 of 44 cases regardless of the use of OCP [51]. On the contrary, a case-control study suggested that the prolonged use of OCP in 23 women could be a risk factor for developing FNH [72].

Recommendation

In patients with focal nodular hyperplasia, we suggest not discontinuing oral contraceptives, that show no role in the development and evolution. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 7 - In symptomatic adults with focal nodular hyperplasia, is surgical treatment associated with better outcomes compared to follow-up?

Several studies showed that surgery is effective for symptoms relief and low recurrences in symptomatic adults with FNH [73–75]. Moreover, TAE proved to be safe and effective as an alternative to surgery, with long-term control of symptoms and significant lesions downsize [76,77]. However, in absence of randomized clinical trials, the therapeutic algorithm remains controversial [52,56,58,73,78–80]. Perrakis retrospectively analyzed two groups of patients with FNH, 93 underwent surgery and 96 remained in follow-up. Indications for surgery were abdominal discomfort (68), tumor growing (16) and uncertain diagnosis (15). Symptoms' relief occurred in 92% of surgically treated patients. In the untreated group, 13% reported additional symptoms and 4% showed increased volume [52]. It is currently accepted that surgery is indicated in symptomatic patients with FNH in case of uncertain diagnosis or in case of marked increase in size of the lesion [52,75,78–81].

Recommendation

In symptomatic adults with focal nodular hyperplasia, we suggest surgical treatment of the lesion, as it might improve the quality of life. However, follow-up does not appear associated with the occurrence of major complications. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 8 - In patients with focal nodular hyperplasia, should ultrasound surveillance be indicated during pregnancy?

The largest published study reports data from 216 women with FNH enrolled between 1989 and 1998: 136 were maintained in surveillance and 12 had at least one pregnancy during the study. The lesions size did not change, and no complications occurred during pregnancy and after delivery [71]. Two other studies confirmed these findings [50,51].

Recommendation

In patients with focal nodular hyperplasia, we suggest not performing surveillance during pregnancy that does not play a role in the development and evolution of the lesion. Very low quality of evidence (D); strength of recommendation 2 (conditional)

4. Hepatocellular adenoma

HCA is a rare epithelial benign tumor that usually develops in a healthy liver, mainly in young women. In 70–80% of cases HCAs are solitary and vary widely in size (from 1 to 30 cm). Symptoms are more frequent in larger lesions [82]. Complications, such as hemorrhage and malignant transformation, may occur. The major risk factors for developing HCA include OCP and anabolic steroids, obesity, metabolic syndrome, and alcohol abuse. Other associated conditions are glycogen-storage diseases (types 1 and 3), galactosemia, tyrosinemia, familial polyposis coli, polycystic-ovary syndrome, and β -thalassemia. The recent increase in HCA prevalence seems related to the increased prevalence of obesity and metabolic syndrome [83–87].

HCAs were rarely diagnosed before the advent of the OCPs [86,88] and their development correlates with the dose and duration of hormonal therapy [87,89–92]. The annual incidence is 1/1,000,000 in women never using OCPs, and 30–40/1,000,000 in women on OCPs [89,93]. The risk is greater in women > 30 years assuming high-estrogen OCP for > 25 months [89,94]. The introduction of low-estrogen OCP may have reduced the HCA incidence [94,95]. OCP use affects the HCA natural course with more numerous and larger and more likely to bleed lesions [85,92,96,97]. Volume reduction or complete regression were observed discontinuing OCP, with relapses in patients resuming therapy or during pregnancy [89,98–103]. HCA development is also associated with the administration of anabolic steroids, mainly 17- α -alkylated steroids, in patients with aplastic anemia or Fanconi's syndrome, in body-builders, and in transgender people [104–107,101]. Androgens induce the development of multiple HCA, and regression is frequently observed after discontinuation [105,108]. HCAs are described in type I (51%) and III (25%) glycogen storage disease; they are often multiple, more frequently found in males and usually seen before the age of 20. Regression has been occasionally described after protracted nocturnal gastric drip feeding and correction of insulin, glucose, and glucagon levels [96,109–113].

Hepatocellular adenomatosis was described in 1985 and defined as the presence of 10 or more adenomas. Initially considered as a pathological entity distinct from HCA, it is now considered part of the spectrum of HCA. Indeed, it has been observed that HCA could be solitary, multiple < 10 or multiple > 10 in all hepatocellular subtypes and in particular etiologies such as glycogenosis and male hormone administration [114–117].

HCA histotype and size seem to correlate with outcomes. Hemorrhage is particularly common in HCA > 4 cm located in the subcapsular region. Bleeding is more frequent in patients with ade-

nomatosis than with single HCA (62% vs 26%) (114). Malignant transformation was reported in a small case-series of adenomatosis (2/15 patients) [118] and in case reports relating to patients with single HCA or with adenomatosis [119–122]. A study including 40 patients with adenomatosis showed a 3% risk of malignant transformation and a 15% risk of bleeding at a 11-years follow-up [123].

The Bordeaux Classification identifies six major subgroups of HCAs: HNF1- α mutated, inflammatory, beta-catenin-activated mutated in exon 3 and in exon 7–8, sonic hedgehog (SH), and unclassified HCA [124–129]. HNF1- α mutated HCAs (30–40%) are characterized by marked steatosis with clear cells. Cyto-architectural atypia is rare and inflammation usually absent. The main risk factors are estrogens, familial liver adenomatosis, and maturity onset diabetes of the young (MODY) [127]. Inflammatory HCAs (40–55%) are characterized by marked sinusoidal dilation, inflammatory infiltrate, dystrophic arteries with thickened walls and pseudo portal tracts, and increased cytoplasmic expression of C-reactive protein and serum amyloid A protein. They are mainly related to obesity, alcohol abuse, and glycogen storage disease [128]. The risk for HCC transformation is generally low but increased by concurrent beta-catenin activation. Beta-catenin mutated HCAs represent 10–20% of HCAs; those mutated in exon 7–8 have no specific risk factor, whereas those mutated in exon 3 are more frequent in males, sensitive to androgenic stimulation, and characterized by cyto-architectural atypia, with pseudo-gland formation. Beta catenin exon 3 (Bex3) mutated HCAs show high risk of malignant transformation. They are also observed in combination with vascular liver diseases and type 1 glycogen-storage disease [129]. In about 4% of cases, HCAs are characterized by activation of the sonic-hedgehog (SH) pathway due to small somatic deletions of INHBE, leading to the fusion of INHBE and GLI1. shHCAs, involving overweight women with fatty liver and using OCP show risk of spontaneous bleeding even in HCAs < 5 cm [124–126]. The risk of symptomatic bleeding is also higher than in other HCA subtypes (71% vs. 14%) [124] and the rate of emergency hospitalization for acute bleeding is particularly high [125].

To note, HCA transformation into HCC can be observed almost exclusively in the Bex3 mutated subtype, rarely in the HNF1- α mutated, and never in the inflammatory subtype in the absence of beta-catenin mutation. In glycogen storage disease type I, HCAs show 10% risk of malignant transformation [128].

PICO 9 - In adults with hepatocellular adenoma and with histological subtype not classifiable with imaging, is biopsy of the lesion useful for histopathological and biomolecular typing and for assessing the risk of malignant transformation?

The European Association for the Study of the Liver (EASL) [10], the American College of Gastroenterology (ACG) [43], and the Brazilian Society of Gastroenterology (BSG) [130] guidelines, and a recent review [131], suggest using MRI for the identification of HNF1- α mutated HCA (sensitivity 87–90%; specificity 89–100%) and of inflammatory HCA (sensitivity 85–88%; specificity 88–100%), while underlining that the identification of the beta-catenin mutation subtype is impossible. Moreover, about 10% of the inflammatory HCA have a mixed, inflammatory beta-catenin mutated phenotype, which cannot be identified by imaging techniques [132–135]. Broker et al reported that the findings of CEUS and MRI with hepatospecific contrast showed fair agreement for the differential diagnosis between HCA and FNH, but MRI is more accurate in cases with discordant findings [136]. A recent study reported that hepato-specific MRI contrast agent might be used as a marker of beta-catenin mutated forms [137]. A systematic review of image-guided liver biopsy reported a percentage of major complications between 0.1% and 4.6%. The risk factors for bleeding were related to patient characteristics (>50 years or <2 years, inpatient status, comorbidities), coagulation status (INR >1.5), and

biopsy technique [138]. The risk of complications related to percutaneous biopsy of HCA is currently considered acceptable (no mortality, 2% of major and 10% of minor complications) [139].

Recommendation

In adults with hepatocellular adenoma and histological subtype not classifiable with imaging techniques, we suggest biopsying the lesion to identify the beta-catenin mutated adenoma (exon 3), the subtype with highest risk of malignant transformation, and the sonic hedgehog adenoma subtype associated with a high risk of spontaneous bleeding. The risk of complications of percutaneous biopsy of adenomas is considered low. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 10 - In female patients with hepatocellular adenoma in surveillance, what imaging technique should be used and how long the follow-up intervals should be?

Observational studies document that discontinuation of OCP reduces the HCA volume [140,141], that the risk of neoplastic transformation is 4.2% and is very rare in HCA < 5 cm [142], and that MRI is the most used imaging technique during follow-up [143,144]. The ACG [43], BSG [130], and EASL [10] guidelines, and a recent review [131], suggest using MRI as for the follow-up after discontinuation of OCPs.

Recommendation

In women with adenoma in follow-up who discontinued oral contraceptives, we suggest a magnetic resonance re-evaluation at six months. Very low quality of evidence (D); strength of recommendation 2 (conditional)

If the adenoma is unchanged or is reduced to less than 5 cm, we suggest a re-evaluation at one year. Very low quality of evidence (D); strength of recommendation 2 (conditional)

After the first 18 months of follow-up, if the adenoma is unchanged, we suggest continuing the follow-up with annual ultrasound examination which is accurate to evaluate the lesion size, safe and cheap. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 11 - In female patients with hepatocellular adenoma > 5 cm does surgical resection offer better results than follow-up?

Malignant transformation is reported in 4.2% of HCAs and is the main factor supporting surgical resection. The highest risk of malignancy is observed in males with Bex3 mutated HCA, in patients on androgen treatment, and, more controversially, in lesions $\geq$ 5 cm [142]. In women with Bex3 mutated HCA, available data do not allow stratification based on lesions' size. Currently, surgery is indicated for Bex 3 mutated HCA, regardless the tumor size, and when malignant degeneration cannot be ruled out [145,146].

Recommendation

In female patients with hepatocellular adenomas that, 6 months after discontinuation of oral contraceptives, remain equal to or greater than 5 cm, or with malignant features on imaging or with histologically proven beta catenin mutation we suggest surgical resection. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 12 - In male patients with diagnosis of hepatocellular adenoma does surgical resection offer better results than follow-up?

Male sex is one of the main risk factors for malignant transformation [147]. In a series of 218 HCAs, it was observed in 23 patients. The risk of malignancy was 4% in women and 47% in men. Two-thirds of HCAs transformed were beta-catenin activated and one-third displayed cell atypia. The median diameter of the transformed HCAs was 10 cm and only three were $\leq$ 5 cm [148]. In a study including patients with biopsy-confirmed HCA, men had a 10-year cumulative HCC risk > 60.0% (95%CI 15.3%–87.0%) [149]. In a cross-sectional study, male and tumor size > 10 cm were the main risk factors (RR 11.6) [150]. In a review [151], malignant

transformation was reported in 4.2%: the most important risk factors were male sex (8–10 times higher than in females), lesion size (>5 cm), and the beta-catenin-activated subtype. Another review [142] reported malignant transformation in 4.2% and only three cases (4.4%) with tumors < 5 cm. A retrospective study involving 66 male patients with HCA, showed that, after expert revision of histological material and new generation genetic tests, the diagnosis was changed in 50% of cases (33/66), and four beta-catenin-mutated HCA were further identified. Accordingly, the systematic application of next generation genetic tests is suggested in males with HCA for a more precise definition of beta-catenin-mutated forms [152].

Recommendation

In male patients with hepatocellular adenoma, we suggest surgical resection regardless of the size of the lesion. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 13 - In patients with hepatocellular adenoma does laparoscopic resection offer better results than laparotomy?

Available studies show an advantage of laparoscopy over laparotomy in terms of quality of life and operative outcomes [153]. The minimally invasive approach was associated with lower intra-operative blood loss (93 vs 196 ml), reduced need for transfusion (8 vs. 24 red blood cells units), and shorter hospital stay (5 vs. 7 days) [154]. A Dutch nationwide retrospective study examined 415 patients undergoing laparoscopic (230 pts) or laparotomic (185 pts) resection for benign liver tumors (HCA in 59%). Comparison of the two surgical techniques, adjusted with propensity score matching, showed a shorter hospital stay and reduced overall post-operative morbidity with laparoscopy [155].

Recommendation

In patients with hepatocellular adenoma, we suggest laparoscopic surgical resection as it may provide better outcomes than laparotomy in terms of postoperative complications, quality of life, and length of hospital stay. Low quality of evidence (C); strength of recommendation 2 (conditional)

PICO 14 - In female patients with hepatic adenoma in follow-up, should discontinuation of oral contraceptives be indicated?

There are no randomized clinical trials evaluating the outcome of HCA in women on treatment with OCPs versus women discontinuing OCPs. Only data from small case-series, case-control studies, and case reports are available. Epidemiological studies suggest a higher (40-fold) incidence in women on long-time OCP treatment. The risk is higher in women > 30 years on OCP for > 25 months, (particularly with high estrogen content) [91,94]. Discontinuation of OCP may result in an HCA reduction/regression [100] and a recent cross-sectional study, including 48 post-menopausal women, suggests that for lesions < 5 cm, no further follow-up would be necessary; in fact, after a median time of 60.5 months, 43.5% of the lesions were undetectable, 32.6% were stable, and 19.6% became smaller [156]. In another retrospective study including 78 HCA patients, 37.2% of HCA showed $\geq 30\%$ regression, 5.1% complete regression, 56.4% stability of the lesion, and 1.3% progression, after discontinuation [141]. A recent publication of the American Association for the Study of Liver Disease (AASLD), strongly recommends discontinuing OCPs in women with adenoma [157].

Recommendation

In female patients with hepatocellular adenoma on follow-up, we recommend discontinuing oral contraceptives. Low quality of evidence (C); strength of recommendation 1 (strong)

PICO 15- Should periodical ultrasound surveillance be indicated in patients with hepatocellular adenoma during pregnancy?

The EASL [10], ACG [43], and BSG [130] guidelines, and a recent review [131], recommend monitoring during pregnancy and

post-partum all women with HCA, indicating US as the imaging technique of choice. Several HCAs growths and ruptures during pregnancy are reported, with high risk of maternal/fetal mortality (59% and 62%, respectively) [158,159]. The most recent literature, suggests “watching-and-waiting”, particularly in women with HCA < 5 cm. In a study, 17 pregnancies in 12 women with HCA were followed; in 4 cases, HCAs grew during pregnancy, requiring a caesarean section in one patient (two pregnancies) at 36 and 34 weeks because of a presumed high risk of rupture. In one case radiofrequency ablation therapy was applied in the first trimester for treating a hormone sensitive HCA with high risk of growth later in pregnancy. No intervention was performed in the other 14 pregnancies which had an uneventful course [160]. In another prospective study of 48 women with HCA < 5 cm, followed during 51 pregnancies, only in one case the growth of the lesion was significant (> 7 cm) requiring embolization. Median increase of 14 mm was seen in 25.5% of cases and pregnancies proceeded without any risk for mother and child. Accordingly, authors suggest a conservative approach and surveillance with US performed at 14-20-26-32-38 weeks of pregnancy and at 6-12 weeks postpartum, combining MRI in case of increased lesion size [161]. In a single-center retrospective study of 11 patients (4 with HCA > 5 cm), only two patients showed lesion growth and there were no hemorrhages during 34 months of follow-up. A systematic review of the literature including 33 studies was also performed; 39 lesions remained stable (53.4%), 11 regressed (15.1%), and 23 (31.5%) progressed. Overall, 15 HCA-related hemorrhages occurred in lesions measuring 6.5–17 cm in diameter (8 during pregnancy, 2 during labor, and 5 postpartum). The Authors conclude that HCA hemorrhage, although rare and only reported in HCA ≥ 6.5 cm, can be fatal, and suggest close surveillance in pregnancy and postpartum [162]. The guidelines of the ACG on liver disease and pregnancy [163] and the recent AASLD position-paper (157) reaffirm the need to monitor HCA with US during pregnancy.

Recommendation

In pregnant women with hepatocellular adenoma, we suggest ultrasound surveillance to identify adenoma growth. Very low quality of evidence (D); strength of recommendation 2 (conditional)

The suggested surveillance timing is at 14-20-26-32-38 weeks of pregnancy and at 6-12 weeks post-partum. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 16 - In patients with hepatocellular adenoma on follow-up, planning medically assisted procreation procedures, should ultrasound surveillance be indicated?

No randomized clinical trial nor observational studies evaluated HCA patients on hormonal therapy for medically assisted procreation. Data may be extrapolated from studies evaluating patients with adenoma during pregnancy (a physiologically similar condition) [160–162]. In addition, a study reported three cases of HCA after treatment with norethindrone acetate for endometriosis [164], another one reported a case of malignant transformation of HCA during ovulation induction [165], and another documented one case of HCA in 60 patients on long-term methyltestosterone therapy [166].

Recommendation

In patients with hepatocellular adenoma on hormonal therapy for medically assisted procreation, we suggest ultrasound surveillance. Very low quality of evidence (D); strength of recommendation 2 (conditional).

Similarly to pregnancy, ultrasound may be suggested every 6 weeks during therapy, and at 6 and 12 weeks after discontinuation. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 17 - In adults with multiple hepatocellular adenomas (≥ 10) does surgical resection offer better results than follow-up?

EASL guidelines recommend management based on the size of the largest tumor, because the clinical presentation and risk of bleeding and malignant transformation in patient with multiple HCAs do not differ from those with a single HCA [10]. However, the natural course of liver adenomatosis is poorly described. A study demonstrated that, during a follow-up of 26 years, 23% of patients with adenomatosis presented a new lesion or increased size of preexisting lesions. Surgery was performed in 4 patients (10%) due to a change in size or in number of tumors [123].

Recommendation

In adults with multiple hepatocellular adenomas, we suggest surgical resection in case of malignant degeneration or bleeding of one or more lesions. Very low quality of evidence (D); strength of recommendation 2 (conditional)

PICO 18 - In adults with multiple hepatocellular adenomas (≥ 10) does liver transplantation offer better results than surgical resection?

A list of major and minor criteria indicating liver transplantation was proposed [167]. Proof of malignant transformation in one or more HCAs is sufficient to justify liver transplantation and represents a major criterion. Other clinical or pathological parameters (minor criteria) include: more than two serious hemorrhages, more than two previous liver resections, presence of beta-catenin mutated or inflammatory adenomas, underlying liver disease (severe steatosis or vascular abnormalities), age > 30 years. Using these criteria to support the decision-making process, liver transplant is indicated in patients with the major criterion or at least 3 minor criteria [167]. In a retrospective study including five patients with type I glycogen storage disease who underwent liver transplantation for prevention of HCC, multiple HCAs with focal hemorrhage and necrosis without evidence of malignancy were identified in all explanted specimens. The authors suggest that transplant could provide a definitive prevention against HCC in this clinical context by removing all HCAs and correcting the metabolic derangements [168].

Recommendation

In adults with multiple hepatocellular adenomas (≥ 10), liver transplantation is suggested in case of malignant degeneration, and might be considered in patients at high risk of liver functional decompensation after resection and in symptomatic massive forms. Very low quality of evidence (D); strength of recommendation 2 (conditional)

Declaration of Competing Interest

The Authors declare no conflict of interest.

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