Benign liver tumors: Diagnosis and management

Pr Laurence Chiche
Hepato biliary surgery and transplantation
Bordeaux, FRANCE
• Benign liver tumors are common

• Two presentations:
  – Asymptomatic tumors, solitary or multiple
    • more frequent feature (widespread and improvement of imaging)
  – Symptomatic tumors
    • Large or complicated neoplasm

• Management consists in
  – Obtaining a certain diagnosis
  – Deciding
    • to treat (surgery, interventional radiology) or not to treat
    • To follow up or not to
INTRODUCTION

The spectrum of BLT

Hepatocellular tumors

- Adenoma
- Focal Nodular hyperplasia

Non hepatocellular tumors

- Biliary adenoma
- Hepatic cysts
- Mucinous tumors

Epithelial tumors

- Focal Nodular hyperplasia

Mesenchymal tumors

- Adenoma
- Focal Nodular hyperplasia

MANAGEMENT
Diagnostic tools

- Clinical presentation and biology
  - The typical features
  - Atypical data
- Imaging
  - US: easy, informative (solid/cystic, homogeneous/heterogeneous)
  - CT scan & Contrast US: dynamic behavior
  - MRI +++: tissue characterisation, vascular behavior
- Biopsy
  - when mandatory?
# DIAGNOSIS: baseline clinical records

<table>
<thead>
<tr>
<th></th>
<th>Probably benign</th>
<th>Possibly not benign</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>&lt; 40 y old</td>
<td>&gt; 40</td>
</tr>
<tr>
<td><strong>sex</strong></td>
<td>woman</td>
<td>male</td>
</tr>
<tr>
<td><strong>Past medical history</strong></td>
<td>No</td>
<td>Cancer or drug history</td>
</tr>
<tr>
<td><strong>Underlying liver</strong></td>
<td>No</td>
<td>yes</td>
</tr>
<tr>
<td><strong>disease</strong></td>
<td>Normal or subnal</td>
<td>abnormal</td>
</tr>
<tr>
<td><strong>Liver biology</strong></td>
<td></td>
<td>Weight loss, anorexia</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Not /pain/ disabling</td>
<td>Fever ...</td>
</tr>
</tbody>
</table>

Histology required
ANGIOMA

• Angioma : the most common BLT
  – Incidence : 0,4 % to 20% (imaging, autopsy)
  – Female/male : 1,2/1 to 6/1
  – Large >5cm, giant >10 cm
  – Solitary or multiple (angiomatosi)
  – Most patients asymptomatic, even with large tumors
  – Symptoms in giant angiomas :
    • pain , discomfort
    • Kasabach Merrit sd (inflammation and coagulopathy)
ANGIOMA

• Angioma: diagnosis
  – Small angioma: US
    • ENOUGH!
  – Large and giant: CT scan and MRI
HEPATOCYTIC TUMORS

FOCAL NODULAR HYPERPLASIA

- Cholangiocellular proliferation
- Fibrosis
- Polyclonal proliferation
- Hepatocytes, arteries, no portal tract

Prevalence = 1/2000

ADENOMA

- Monoclonal proliferation

Prevalence = 1/20000

Paradis V et al 1997
FRENCH

INTRODUCTION

DIAGNOSIS

MANAGEMENT

Hepatocellular Adenoma and Focal Nodular Hyperplasia: Value of Gadoxetic Acid–enhanced MR Imaging in Differential Diagnosis

Differentiation of hepatocellular adenoma and focal nodular hyperplasia using 18-F-fluorocholine PET/CT

Jacqueline W. van den Esschert - Matthias Bierze - Ulrich H. Bowers - Thomas M. van Galik - Roelof J. Bennink

FOCAL NODULAR HYPERPLASIA

DIAGNOSIS

- MRI is the most specific
  - HB contrast agents
- Differential dg
  - Adenoma
  - HCC (fibrolamellar variant)
ADENOMA

• A quite rare liver tumor
  – Female predominance 9/10, usually in relation with estrogen intake,
  – Possibly associated to metabolic disease (GSD) or vascular liver abnormalities

• Potentially dangerous
  – With two well known potential risks: hemorrhage and malignant transformation
ADENOMA

• Risk of hemorrhage (intratumoral or rupture)
  - 40% initial presentation
  - Risk related to the size (5cm +++)
  - Danger: subcapsular tumor +++

• Risk of malignant transformation: 6%
  - Risk related to size (5 cm), sex (male)...

Woman, 3.5 cm adenoma pre op biopsy ::adenoma
ADENOMAS: recent advances

- Mutation of TCF1 gene (inactivation of HNF1α)
  - Somatic mutation (90%)
  - Germline mutation (in MODY 3 patients)
  - Associated with repression of glycogenosis and fatty acid synthesis (silencing of LFABP)

- Activation of the JAK/STAT pathway with Somatic mutations activating different actors such as gp130, STAT3, JAK 1 and abnormal expression of members of the acute phase inflammatory response

- Mutation of CTNNB1 exon 3, resulting in activation of βcatenin (using the WNT/β cat pathway (like in HCC)
  - Exclusive /HNF1α
  - Frequent in glycogenosis, man
ADENOMA

Not one tumor but several types of tumors

Changes in the management of benign liver tumors
Paulette Bioulac-Sage, Laurence Chiche, Charles Balabaud

4 groups of adenomas
<table>
<thead>
<tr>
<th>Geno/phenotype</th>
<th>Molecular pathways</th>
<th>histology</th>
<th>presentation</th>
<th>risks</th>
<th>Diff diag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I 35%</td>
<td>HNF1α inactivation</td>
<td>Steatotic adenomas LFABP neg</td>
<td>Woman MODY 3 adenomatosis</td>
<td>LOW</td>
<td>Focal steatosis</td>
</tr>
<tr>
<td>Group II 50%</td>
<td>Acute phase of protein inflammation</td>
<td>Inflam infiltrate Sinusoidal dilat SAA or CRP + B cat (10%)</td>
<td>Obesity alcohol</td>
<td>BLEEDING</td>
<td>HCC, angioma other</td>
</tr>
<tr>
<td>Group III 10%</td>
<td>B-catenin activation</td>
<td>Cyto abnorm GS expression B cat nuclear expression</td>
<td>Male Hormones Glycogenosis</td>
<td>HCC ++</td>
<td>HCC</td>
</tr>
<tr>
<td>Group IV &lt;10%</td>
<td>unidentified</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
ADENOMA : how to diagnose ?

• BEFORE : no possible radiological diagnosis !

• TODAY : some adenomas can be diagnosed by imaging
Group I: HNF alpha mutated

T2 weighted

SAT FAT

Contrast enhanced T1 weighted

LFBPA neg
INTRODUCTION

MANAGEMENT

DIAGNOSIS

GROUP II

Inflammatory adenomas

T1W

T2W fat s

Atoll sign

Strong arterial enh

Persistent portal phase
Radiologists can diagnose uncomplicated HNF 1 adenoma, may be infl adenomas. Radiologists cannot be affirmative in necrotic/hemorrhagic adenomas and cannot diagnose beta mutated or unclassified adenomas. BIOPSY or SURGERY is most often required for IMMUNOHISTOLOGICAL STUDY.
• Ideally, liver tumors should be discussed in front of a panel:
  – A good and specialized radiologist
  – A pathologist expert in liver disease
  – A hepatologist
  – An HPB surgeon

Clinical Practice Guidelines

The benign liver tumour multidisciplinary team

The team should be one with expertise in the management of benign liver lesions and should include a hepatologist, a hepatobiliary surgeon, diagnostic and interventional radiologists and a pathologist. Each member of the team must hold specific and relevant training, expertise and experience relevant to the management of benign liver lesions. The team
Solitary tumors

• Three situations
  – Symptomatic tumor (acute or chronic)

  – Asymptomatic tumor with still a diagnostic doubt

  – Asymptomatic tumor with definitive diagnosis
Solitary tumors

- Three possibilities
  - Refer to surgeons or to int radiologists
  - Follow up the patient
  - Forget the tumor
Management

Indications of surgery or when to refer to surgeons

• FOUR TYPES OF SURGERY
  – Salvage surgery (bleeding)
  – Symptomatic surgery (large and complicated tumor)
  – Preventive surgery (avoid evolutive risk = adenomas)
  – Diagnostic surgery (if doubt)
Management

the rules and modalities of surgery

• Surgery for benign tumors
  – Justified
  – Safe (no mortality, minimal morbidity, no transfusion, minimal long term effects)

• Modalities: according to the tumor/surgeon
  – Laparoscopy
  – Laparotomy
Laparoscopy: a real advance but a careful use

Summary

Indications for surgery for benign hepatic lesions should not be widened. Unroofing of simple hepatic cysts should not be considered a liver resection and should not be included in the analyses of laparoscopic liver resection.
National trends in the use of surgery for benign hepatic tumors in the United States

Yuhree Kim, MD, MPH, Neda Amini, MD, Jin He, MD, Georgios A. Margonis, MD, Matthew Weiss, MD, Christopher L. Wolfgang, MD, PhD, Martin Makary, MD, Kenzo Hirose, MD, Gaya Spolverato, MD, and Timothy M. Pawlik, MD, MPH, PhD, FACS, Baltimore, MD

Table II. Volume and proportion of inpatient hepatic procedures for benign liver tumors, 2000–2011

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<tr>
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<tbody>
<tr>
<td>Total (n)</td>
<td>2,633</td>
<td>705</td>
<td>858</td>
<td>1,070</td>
</tr>
<tr>
<td>Hepatic wedge resection</td>
<td>207 (7.9)</td>
<td>79 (11.2)</td>
<td>69 (8.0)</td>
<td>59 (5.5)</td>
</tr>
<tr>
<td>Partial hepatectomy</td>
<td>1,153 (43.8)</td>
<td>280 (39.7)</td>
<td>339 (39.5)</td>
<td>534 (49.9)</td>
</tr>
<tr>
<td>Hepatic lobectomy</td>
<td>660 (25.1)</td>
<td>183 (26.0)</td>
<td>235 (27.4)</td>
<td>242 (22.6)</td>
</tr>
<tr>
<td>Other procedure*</td>
<td>613 (23.3)</td>
<td>163 (23.1)</td>
<td>215 (25.0)</td>
<td>235 (21.9)</td>
</tr>
<tr>
<td>Open, n (%)</td>
<td>2,489 (94.5)</td>
<td>674 (95.6)</td>
<td>817 (95.2)</td>
<td>998 (93.9)</td>
</tr>
<tr>
<td>MIS, n (%)</td>
<td>144 (5.5)</td>
<td>31 (4.3)</td>
<td>41 (4.8)</td>
<td>72 (6.8)</td>
</tr>
</tbody>
</table>

*Other procedure includes liver ablation, cauterization of hepatic lesion and enucleation of hepatic lesion.

MIS, Minimally invasive surgery.
INTRODUCTION

Diagnosis

Management

Laparoscopy

Laparotomy

The size is less determinant than the location.
ANGIOMA

• Asymptomatic angioma, whatever the size, should be neither operated nor followed up.

• Very rare complicated angiomas (supergiant, KM) are indications of surgery, sometimes LT.)
FOCAL NODULAR HYPERPLASIA

– If asymptomatic: no surgery, no follow up, no discontinuation of OP

– If symptomatic (pedunculated, extrahepatic +++)
  • Surgery: laparoscopic +++
  • Embolisation: an interesting alternative

» Vogl TJ et al Eur Radiol 2006, 16(3) 670
» Birl J et al J vasc intern radiol 2013 24 : 1647
» Yan jy et al zhonghua yi xue za zhi 2012
One month after embo

6 months after embo
ADENOMA

A generally surgical tumor

• Symptomatic adenomas (generally large tumors)
  – Hemorrhage
  – Necrosis
  – Pain
ADENOMA

The particular case of hemorrhage

GRADE I Intra tumoral 60% PAIN
GRADE II intrahepatic  30%  PAIN and bleeding symptoms
GRADE III extrahepatic 10%  PAIN AND SHOCK

• Surgery in emergency (uncontrolled bleeding) is exceptional (no resection, damage control)
• Surgery is generally delayed
GRADE I-II

Just wait 2 – 3 months
Then resect

GRADE III

Life-saving therapy for haemorrhaging liver adenomas using selective arterial embolization

J. H. M. B. Stoot¹, E. van der Linden², O. T. Terpstra¹ and A. F. M. Schaapherder¹

Ressucitation
Arterial embolisation
Wait ++++
Resect

INTRODUCTION

DIAGNOSIS

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ASYMPTOMATIC ADENOMA

SHOULD IT BE RESECTED?

• Asymptomatic adenomas to resect
  – Solitary Adenoma > 5 cm
  – Adenoma < 5cm if male, beta cat mutated on biopsy, if progressive, if subcapsular and in woman willing to be pregnant
  – Any size If diagnostic doubt after accurate diagnostic
Stop OP
Loose weight

Clinical Practice Guidelines

- Suspected HCA
  - Contrast enhanced MRI document size (+/- subtype)
    - Female (irrespective of size)
      - Advise lifestyle change
    - Male (irrespective of size)
      - Repeat MRI after 6 months
  - Biopsy if not HNF 1a To detect beta cat mut

- <5 cm stable or reduced in size
  - 1 year MRI
    - Stable or reduced size
      - Annual imaging
      - Resection
  - >5 cm or significant* increase in size
Management
MULTIPLE FORMS

- Angiomatosis and polyFNH are asymptomatic and do not require any treatment

- Adenomatosi is more problematic
  - Initial Definition: more than 4 to 10 adenomas in a normal liver
  - Modern classification:
- LA should be well characterized
  - Multiple adenomas on imaging or histology with small nodules
  - Two macroscopic forms: massive or multifocal
  - In normal livers or on vascular or metabolic disease
  - HNF 1a or inflammatory or beta mut or uncl or mixed
ADENOMATOSIS : Management

- In case of asymptomatic form :
  - The risk of complication should be evaluated
    - Agressive surgical approach : if massive, subcapsular adenomas >5 cm, underlying liver disease, inflammatory or ß cat adenomas
    - Conservative approach : multifocal, HNF1 adenomas
    - ROLE ++++ of MRI for surveillance

- In case of symptomatic or complicated forms
  - Resection « a la demande » or exceptional transplantation should be evaluated
Major indication: the suspected or proven malignant transformation.
Liver adenomatosis: serial investigation on MRI

Saowanee Srirattanapong,¹,² Wirana Angthong,¹ Bong Soo Kim,¹ Paul Hideyo Hayashi,³ David A. Gerber,⁴ John T. Woosley,⁵ Jared Peacock,⁶ Anuruddika Ranatunga,¹ Richard C. Semelka¹

**Conclusion:** During an over 2-year follow-up period, the majority of lesions of LA appeared to remain stable or showed tumor regression. Spontaneous tumor regression can be observed in approximately 37% of individuals in the age range of 28–53 years.
Indication of LT: a case by case discussion with all the 5 items (age, history, underlying disease, macroscopic form, subtypes).

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Number of Criteria Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major criteria</td>
<td>1</td>
</tr>
<tr>
<td>Minor criteria</td>
<td>3 or more</td>
</tr>
</tbody>
</table>

- Histological proof of MT in 1 (or more) adenoma
- More than 2 life threatening hemorrhage
- More than 2 previous hepatectomies
- Beta mutated or inflammatory adenomas
- Underlying liver disease
- Age > 30 years

One major criterium
Or
Three or more minor criteria
Benign liver tumors: Conclusion
TOP 10 Take home message

1. Male sex and liver benign tumor: an « a priori » suspicious combination
2. The major risk of a « benign liver tumor » is ... not to be benign
3. Don’t forget « benign » does not always mean riskless.
4. To reassure a patient, you have to be sure (or your dg)
5. Concerning the management of benign liver nodules, your best partner is the radiologist: choose him or her with caution
6. After surgery, remember that an asymptomatic patient is likely to become symptomatic.

7. It’s not because it is easy to remove that it has to be removed.

8. Sometimes it is easier to take an hepatic benign tumor off the liver than off the mind.

9. Liver surgery should always be justified and safe, but in case of benign liver tumors, be yet more stringent.

10. The 5 characteristics of ideal liver surgery for BLT whatever the approach: useful, liver parenchyma preserving, 0 mortality, 0 transfusion, 0 after effect.
Thanks you!

EASL Clinical Practice Guidelines on the management of benign liver tumours

European Association for the Study of the Liver (EASL)