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Syrian Private University (SPU)

Chairman of the NASH committee ASSLD

Member of SWGSVH

Member of national committee for viral hepatitis

Member of the Syrian scientific board of Gastroenterology

Co-Author of the Cochrane collaboration Hepato-biliary group

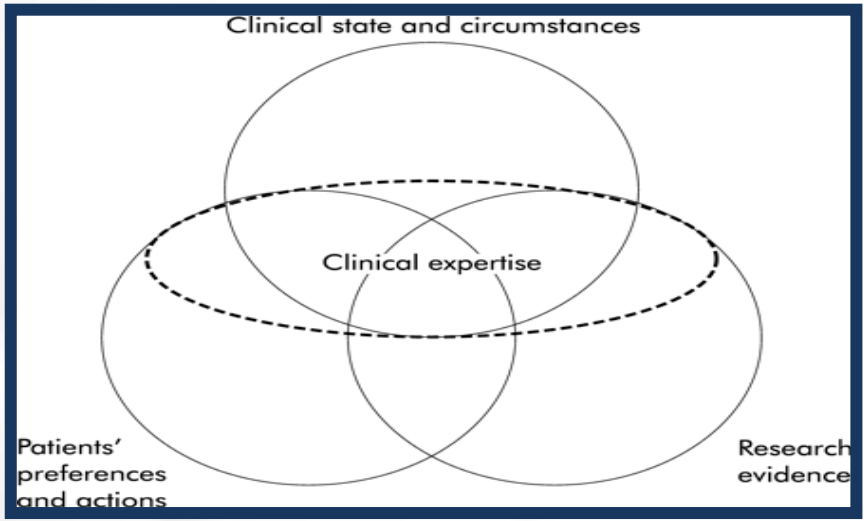
HCC

-Incidence
-Risk factors
-Surveillance ??

Ibn Alnafis 2019

Evidence-based medicine

- **“Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values”**



EBP

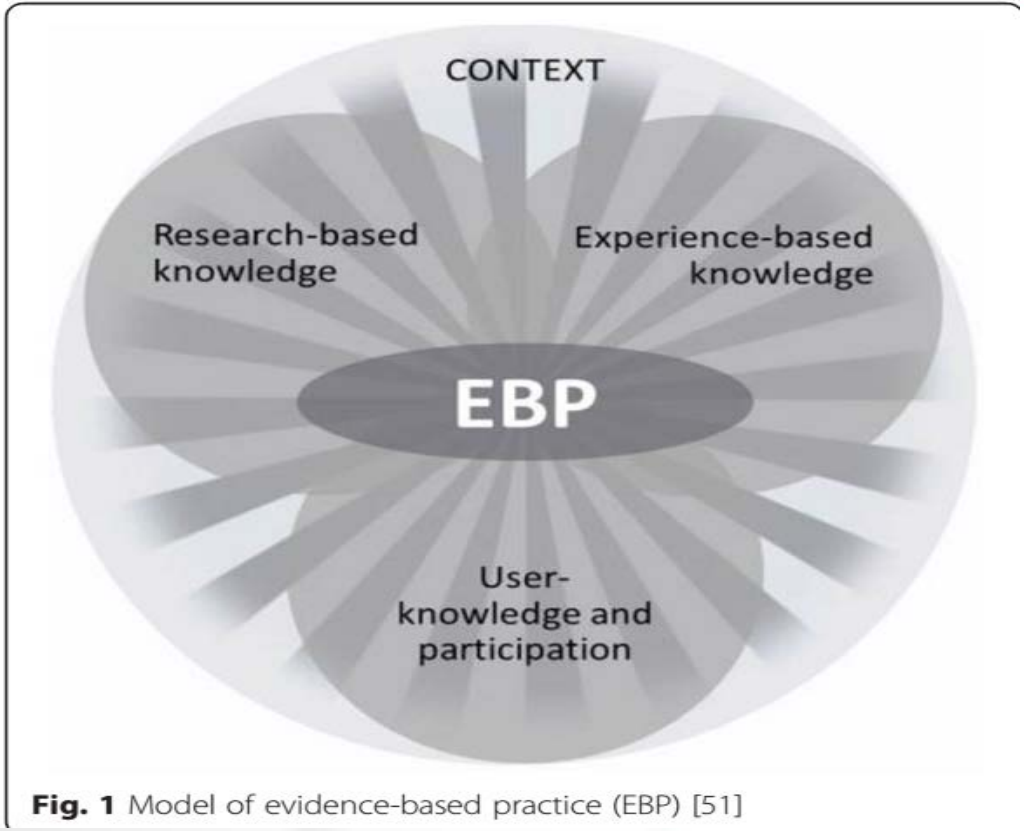


Fig. 1 Model of evidence-based practice (EBP) [51]

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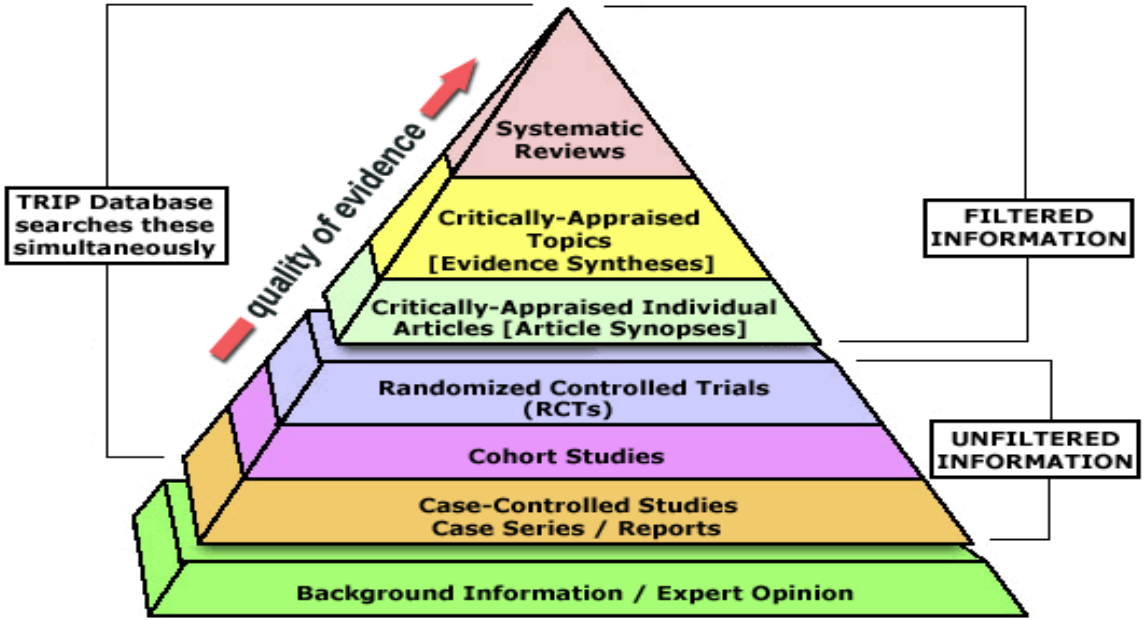
Quality of evidence
=
quality of data
+
quality of interpretation

Quality of evidence



Grading evidence and recommendations

Level of evidence*		***Confidence in the evidence***
High	Data derived from meta-analyses or systematic reviews or from (multiple) RCTs with high quality	*Further research **is unlikely to change** our confidence in the estimate of benefit and risk*
Moderate	Data derived from a single RCT or multiple non-randomized studies	*Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate*
Low	Small studies, retrospective observational studies, registries	*Any estimate of effect is uncertain*
Grade of recommendation† ***(wording associated with the grade of recommendation)***		
Strong	*"Must", "should", or "EASL recommends"*	
Weak	*"Can", "may", or "EASL suggests"*	

EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma

European Association for the Study of the Liver

European Organisation for Research and Treatment of Cancer

THE COCHRANE LIBRARY

Independent high-quality evidence for health care decision making

[redacted]

World Gastroenterology Organisation Global Guideline

WORLD GASTROENTEROLOGY ORGANISATION · WGO ·

Hepatocellular carcinoma (HCC): a global perspective

November 2009

ARTICLE IN PRESS

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma☆

European Association for the Study of the Liver*

Summary

Liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death globally. Hepatocellular carcinoma represents about 90% of primary liver cancers and constitutes a major global health problem. The following Clinical Practice Guidelines will give up-to-date advice for the clinical management of patients with hepatocellular carcinoma, as well as providing an in-depth review of all the relevant data leading to the conclusions herein.

Introduction

In 2012, the previous guidelines for the management of hepatocellular carcinoma (HCC) were published as a result of a joint effort by the European Association for the Study of the Liver (EASL) and the European Organisation for Research and Treatment of Cancer (EORTC).[1] Since then several clinical and scientific advances have been achieved. Thus, an updated version of the document is needed.

Objectives of the guideline

These EASL Clinical Practice Guidelines (CPGs) are the current update to the previous EASL-EORTC CPGs.[1] These EASL CPGs define the use of surveillance, diagnosis and therapeutic strategies recommended for patients with HCC.

The purpose of this document is to assist physicians, patients, healthcare providers and health-policy makers from Europe and worldwide in the decision making process, based on the currently available evidence. Users of these guidelines should be aware that the recommendations are intended to guide clinical practice in circumstances where all possible resources and therapies are available. Thus, they should adapt the recommendations to their local regulations and/or team capacities, infrastructure and cost-benefit strategies. Finally, this document sets out some recommendations that should be instrumental to advancing the research and knowledge of this disease, and ultimately contributing to improved patient care.

Methodology

Composition of the guidelines group

The guideline development group (GDG) of this guideline project is composed of international experts in the field of HCC, comprising the areas of hepatology (PRG, AF, JL, FP), surgery (VM), radiology (VV), oncology (JJR) and pathology (PS). Initially, the EASL governing board nominated a chair (PRG) and a governing board member (AF) to propose a panel of experts and finally nominated the above GDG. Additionally, a guideline methodologist was appointed to support the GDG (MF).

Funding and management of conflict of interests

This guideline project has kindly been supported by EASL. The financial support did not influence the development of this guideline. Key questions to be answered and outcomes were chosen in accordance with the consensus of the expert panel. Recommendations were reached by consensus of the expert panel and based on clinical expertise and existing evidence. A declaration of conflicts of interest was required to participate in the guideline development. The ethical committee of EASL assessed the individual interests and decided that there were no substantial conflicts of interest.

Generation of recommendations

In a first step the panel identified, prioritised and selected relevant topics and agreed on key questions to be answered. These questions were clustered and distributed according to the defined working groups, which are reflected in the different chapters.

According to the key questions, a literature search was performed. The studies identified and included were assessed and assigned to categories related to study design and strength of evidence according to endpoints. Based on this evidence, the drafts for recommendation and chapters were created.

Consent was provided for all recommendations during the consensus conference, moderated by Markus Follmann, MD MPH MSc, a certified moderator for the German Association of Scientific Medical Societies (AWMF). Formal consensus

* Clinical practice guideline panel: Peter R. Galle (chair), Alejandro Forner (EASL governing board representative), Josep M. Llovet, Vincenzo Mazzaferro, Fabio Piscaglia, Jean-Luc Raoul, Peter Schirmacher, Valérie Vilgrain.

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2018

Liver cancer - HCC

- Liver cancer
  - Fifth / common cancer
  - Second /death globally
    - 854,000 new cases
      810,000 deaths per year
  - 7% of all cancers
- HCC
  - Accounts for approximately 90% of primary liver cancers

Global prevalence and incidence

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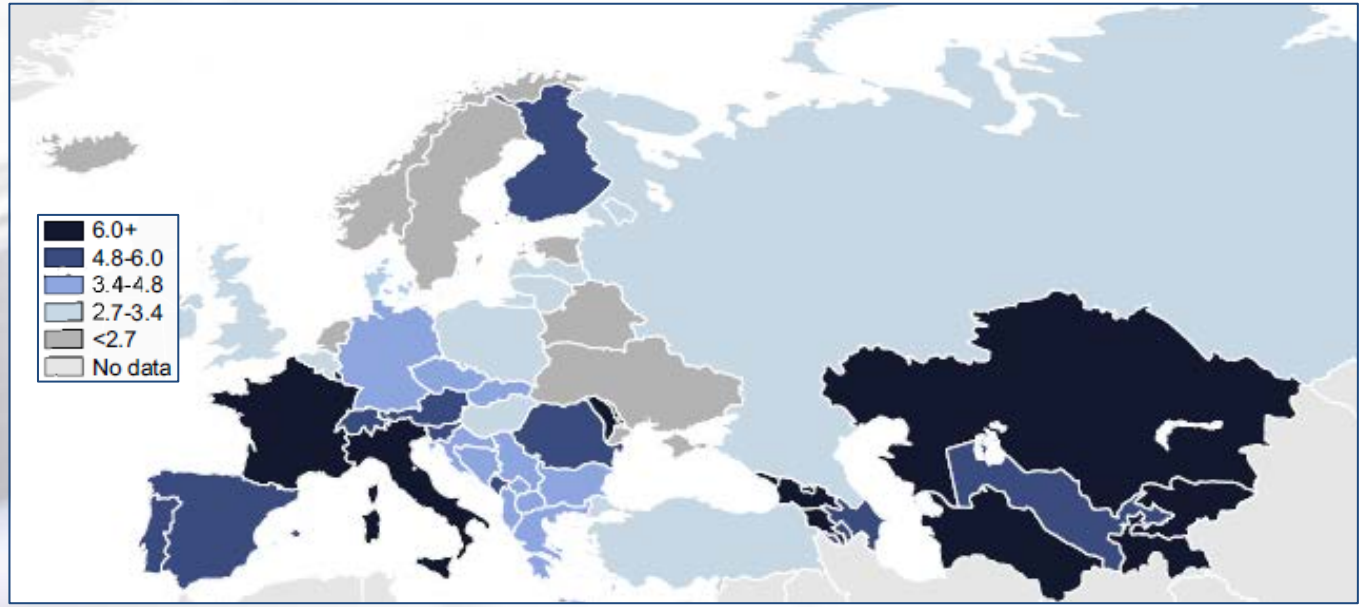
Incidence of primary liver cancer in Europe

Incidence rates per 100,000



Main risk factors for primary liver cancer worldwide

	Alcohol (%)	HBV (%)	HCV (%)	Others (%)
Europe				
Western	32	13	44	10
Central	46	15	29	10
Eastern	53	15	24	8
North America	37	9	31	23
Andean Latin America	23	45	12	20
Asia				
East Asia	32	41	9	18
Asia-Pacific	18	22	55	6
South-East Asia	31	26	22	21
Africa				
North Africa, Middle East	13	27	44	16
Southern (sub-Saharan)	40	29	20	11
Western (sub-Saharan)	29	45	11	15

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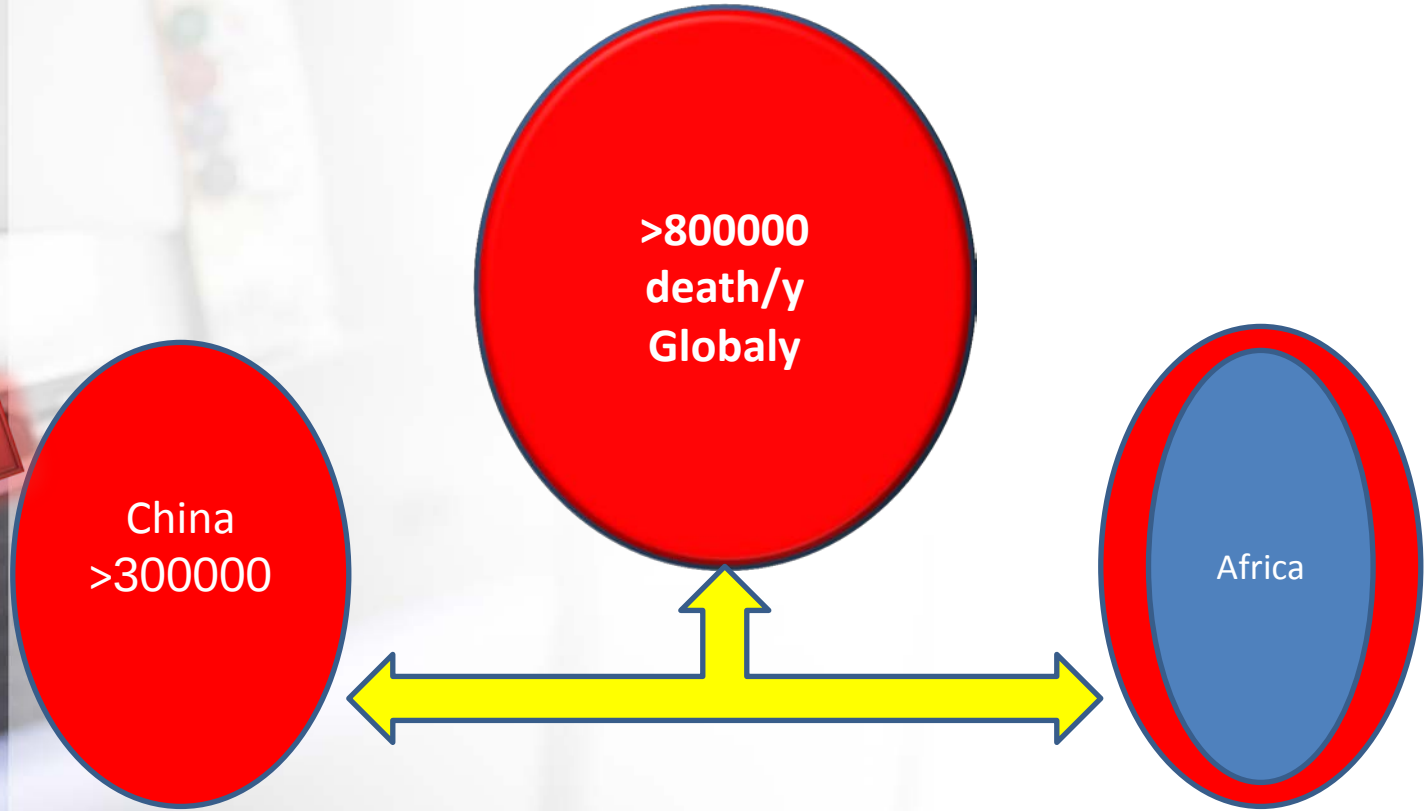
HCC related death per year



HCC related death per year

>**800.000**
death/y
Globaly

- Up to 90% of HCC arises on a background of cirrhosis in the Western world[1]

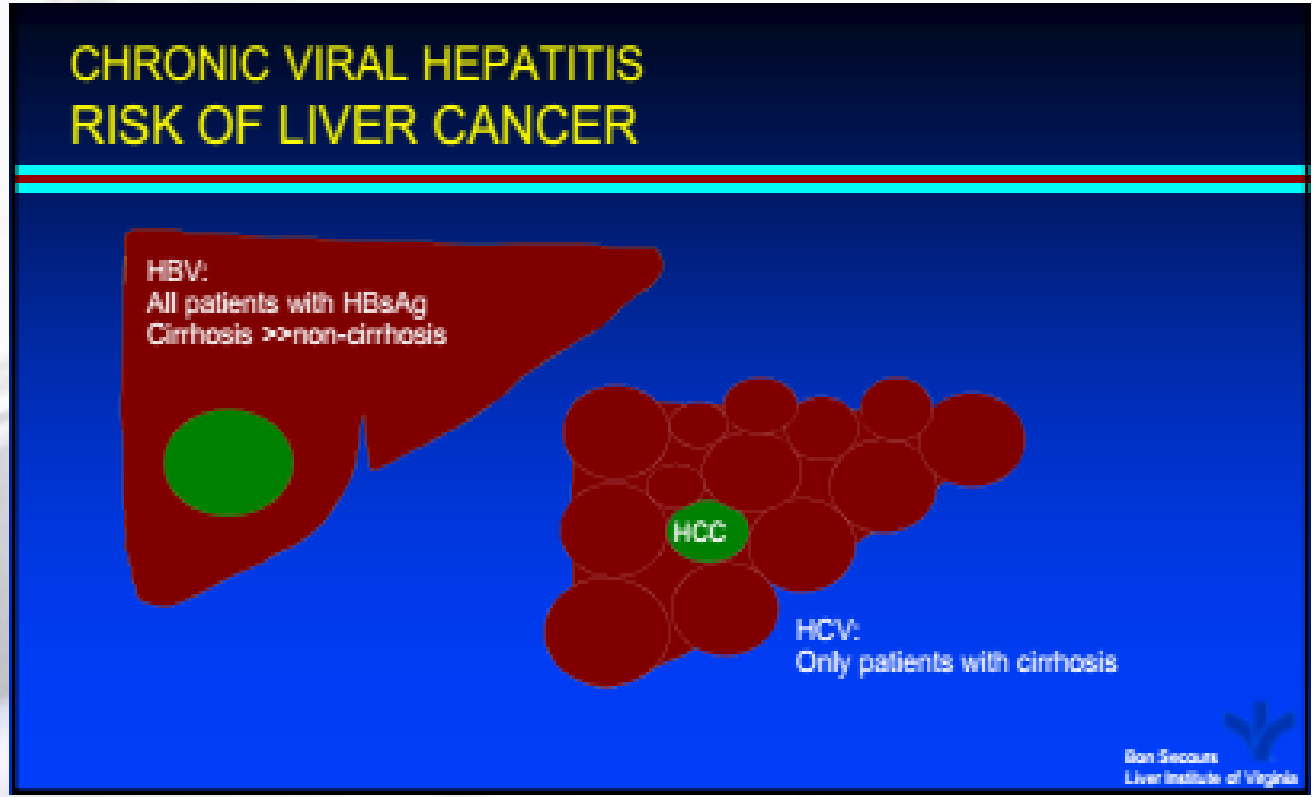
HBV

oncogenic

HCV

+

HBV - HCV



- incidence rate

- Incidence rate mirror the prevalence of HBV &HCV

- Mortality rate

- Mirror the incidence rate

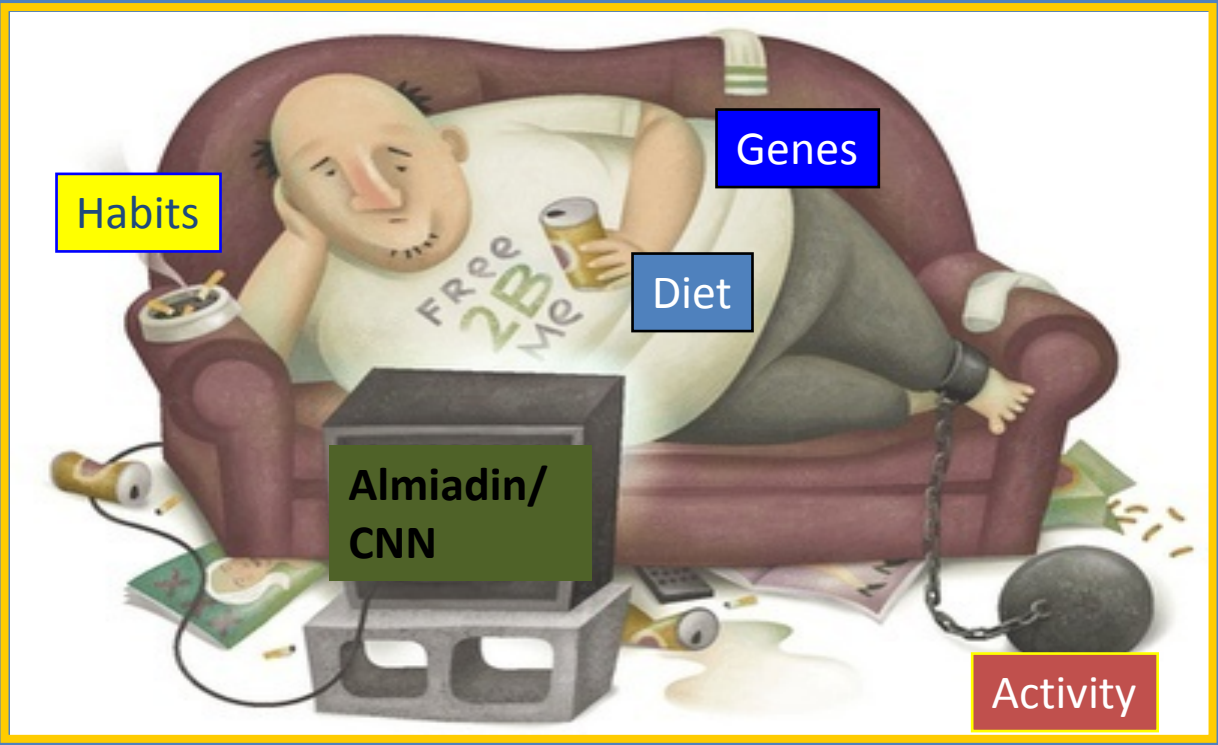
HCV infection	HBV infection
increases the risk of developing HCC by • **17-fold**	increases the risk of developing HCC by • **100 fold**,

Epidemiology and risk factors

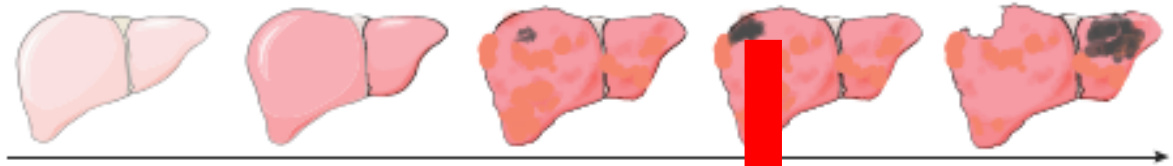
- **Cirrhosis is an important risk factor for HCC**
  - Multiple causes, including viral hepatitis, chronic alcohol use, **NAFLD**

The Liver Disease of the Modern Times!

A Complex Disease: Genes and Environment



HCC preventive interventions



HCC progression	Normal hepatocyte	Subclinical molecular/ histological IEN		1° agnosed imary HCC	2nd primary HCC
Liver disease progression	Chronic hepatitis	Advanced fibrosis	Cirrhosis		
	Exposure/presence of risk factors				
Type of prevention	Primary	Secondary			Tertiary (adjuvant)
		HCC screening			Post-treatment monitoring
Potential chemoprevention strategies	Antiviral therapies				
	Anti-inflammation therapies				
	Anti-fibrotic therapies				
	Metabolic disease treatment				
	Molecular targeted therapies				

Epidemiology and risk factors

- **Incidence of HCC has been rising**
  - **Driven by increases in chronic viral infections and lifestyle-related risk factors**

Recommendations

The incidence of HCC is increasing both in Europe and worldwide; it is amongst the leading causes of cancer death globally	High	
Chronic liver disease should be treated to avoid progression	High	Strong

Prevention

- **Primary prevention** of HCC can be achieved with universal **vaccination** against HBV
- **Progression to cirrhosis** and HCC can be prevented by:
  - Antiviral treatment in patients with chronic hepatitis B and C*
  - **Adoption of healthy lifestyle measures**

Prevention

Recommendations		
Vaccination against hepatitis B reduces the risk of HCC and is **recommended for all newborns and high-risk groups**	High	Strong
Governmental health agencies should **implement policies** that: • Prevent **HBV/HCV** transmission • Counteract **chronic alcohol abuse** • Promote lifestyles that prevent **obesity** and **metabolic syndrome**	Moderate	Strong
In patients with chronic hepatitis, use antiviral therapies to: • Maintain HBV suppression in chronic hepatitis B • Maintain SVR in chronic hepatitis C	High	Strong

Role of DAAs for HCV in HCC

- Effect of DAAs on HCC in patients with cirrhosis is debated
  - Robust conclusion impeded by retrospective assessment, absence of HCC screening, short follow-up and loss to follow-up

Recommendations		
Once cirrhosis is established: • **Antiviral therapy*** is beneficial in **preventing cirrhosis progression** and decompensation • Successful **antiviral therapy reduces but does not eliminate** the risk of **HCC** development	Moderate	
For patients with HCV-associated cirrhosis and treated HCC: • **HCC recurrence rate is high** even after SVR with DAA therapy† • **Close surveillance is advised** in these patients • The benefit of viral cure must be weighed against a potentially higher recurrence risk	Low	Strong

Role of NAs for HBV in HCC

- HCC may still develop and remains the major concern for CHB patients treated with NAs

Recommendations

Once cirrhosis is established: • **Surveillance is mandatory for all** • Successful **antiviral therapy reduces but does not eliminate** the risk of **HCC** development	Grade 1 evidence 2-2	
Patients on NAs should remain under surveillance Those with moderate or **high HCC risk scores** at the onset of NA therapy **PAGE-B**, (GAC-HCC,CU-HCC,REACH-B.)	Grade 1	evidence 2-2

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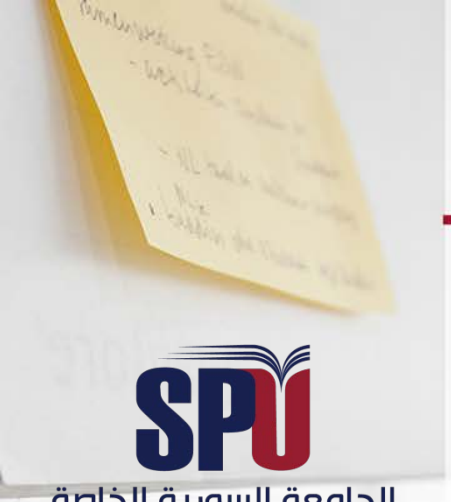
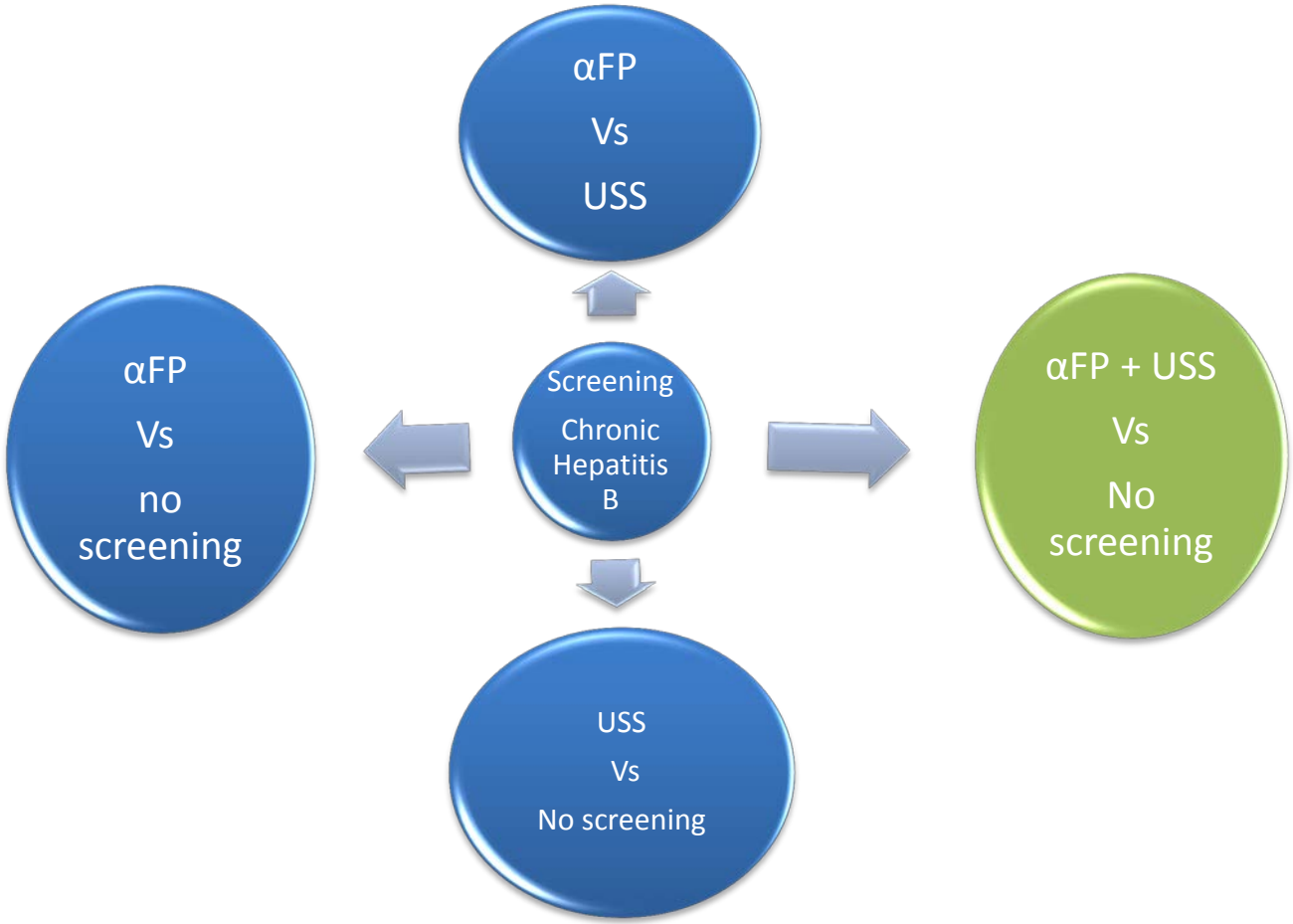
Treatment approaches depends to large extent on the stage of disease at time of diagnosis

Early detection
Best treatment as tumor as small as possible

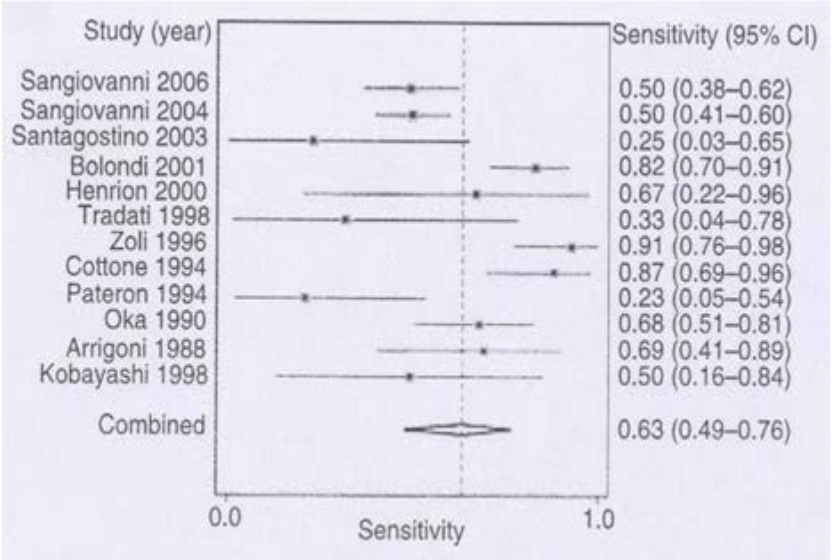


- **What screening tests to apply and how frequently?**

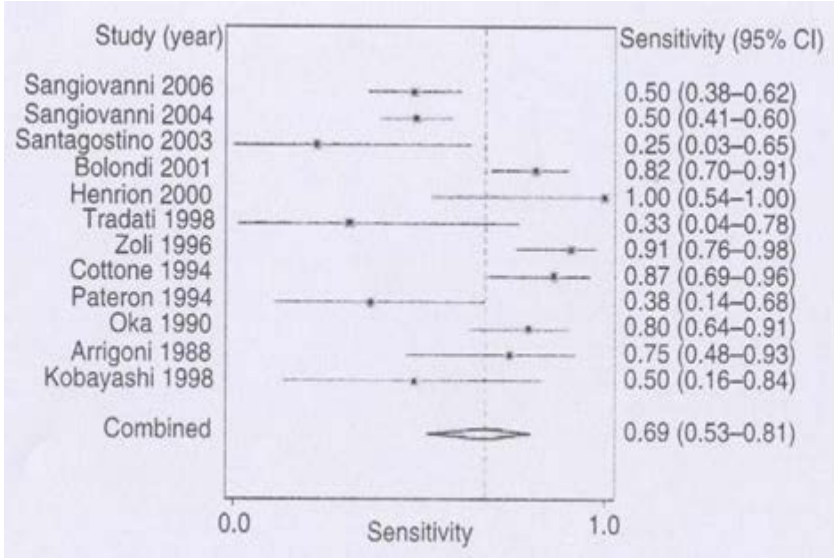

αFP
Vs
USS
αFP
Vs
no
screening
Screening
Chronic
Hepatitis
B
αFP + USS
Vs
No
screening
USS
Vs
No screening

Ultrasound Diagnosis of Early-stage HCC in Patients with Cirrhosis. Meta-analysis

Ultrasound alone



Ultrasound + AFP



PLAIN LANGUAGE SUMMARY

Inadequate evidence on screening with alpha-fetoprotein and/or ultrasound of the liver for patients with chronic hepatitis B

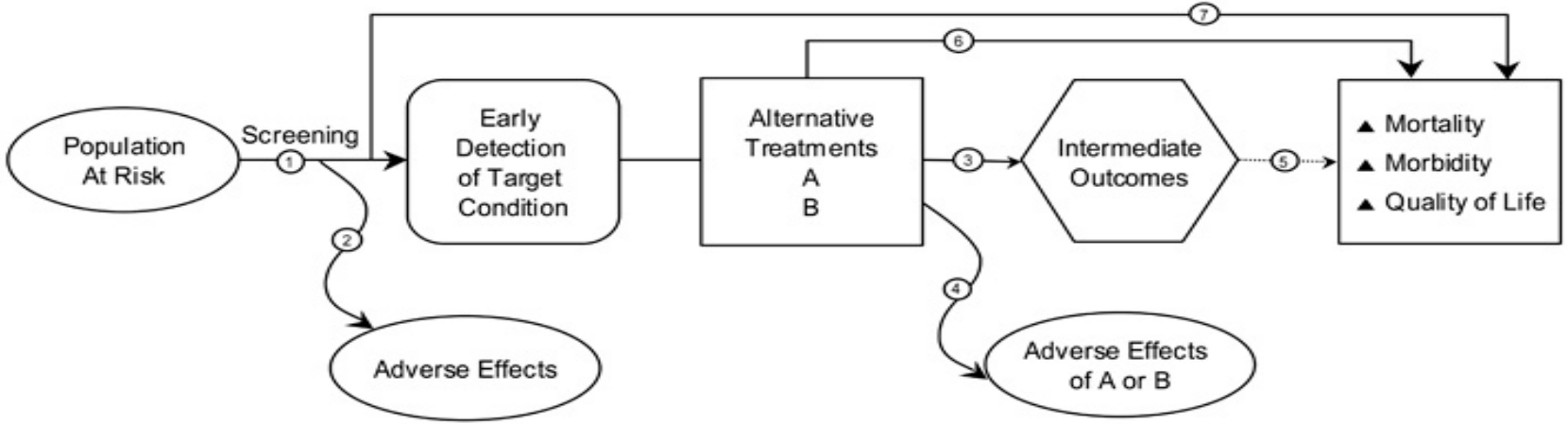
Plain language summary

Alpha-foetoprotein and/or liver ultrasonography for screening of HCC in patients with chronic hepatitis B

Cochrane Systematic Review - Intervention Version published: September 2012

- Thus, to date, there is insufficient evidence regarding screening for liver cancer among patients with chronic hepatitis B infection.

A General Causal Pathway: Screening Procedure and Alternative Treatments



1. Is screening test accurate for target condition?
2. Does screening result in adverse effects?
3. Do treatments change intermediate outcomes?
4. Do treatments result in adverse effects?
5. Are changes in intermediate outcomes associated with changes in health outcomes?
6. Does treatment improve health outcomes?
7. Is there direct evidence that screening improves health outcomes?

Source: Adapted from Harris 2001.

Surveillance

- **Utility of and applicability of surveillance is influenced by a number of factors**
  - Incidence of HCC in **target populations**
  - Availability of efficient diagnostic tests at acceptable costs
  - Availability and effectiveness of treatments

- **Definition of target populations must consider**
  - Incidence of HCC in subsets of patients
  - Probability that effective therapies, particularly radical ones, are suitable

HCC incidence is **higher** in patients with **more advanced** cirrhosis
Probability of receiving **effective therapy** is **lower***
Different incidence thresholds may apply to different target populations

Surveillance

- High rate of HCC in certain risk groups makes surveillance a cost-effective route to reducing mortality

- Conventional threshold is US $50,000 per year of life saved*

Recommendations		
• **Implementation** of screening programmes to identify at-risk candidate populations **should be improved** • Such programmes are a public health goal, aiming to decrease HCC-related and overall liver-related deaths	Low	Strong
Patients at **high risk** of developing HCC should be entered into **surveillance** programmes. Government health policy and research agencies should address these needs	Moderate	Strong

Surveillance in patients at high risk of HCC

- **Surveillance is recommended in specific target populations**

Recommendations		
• Cirrhotic patients, **Child–Pugh stage A and B**	Low	Strong
• Cirrhotic patients, **Child–Pugh stage C awaiting LT**	Low	Strong
• Non-cirrhotic HBV patients at intermediate or high risk of HCC* (according to PAGE-B† classes for Caucasian subjects, respectively 10–17 and ≥18 score points)	Low	Weak
• Non-cirrhotic F3 patients, based on an individual risk assessment	Low	Weak

- **Int … d tumour inc…**

6-month interval is reasonable and cost-effective

- **3 months**: no clinical benefit
- **12 months**: fewer early stage diagnoses and shorter survival

Uncertainties in surveillance strategy

- **Benefit of surveillance has not been established in all risk groups**
- **US remains the method of choice**
  - Serological tests are not currently cost-effective

Recommendations		
Role of **surveillance for patients with NAFLD** without cirrhosis is **unclear**	Low	
Surveillance should be performed by **experienced personnel** in all **high-risk populations** using **abdominal US every 6 months**	Moderate	Strong
Tumour **biomarkers** for accurate early detection are **still lacking***	Low	-
Patients on the **waiting list for LT** should **undergo surveillance for HCC** • To detect and manage tumour occurrence or tumour response		

Unmet needs to achieve EASL future goals

- Major health policy interventions to secure:
  - Universal vaccination against HBV
  - Universal treatment of HCV if indicated
  - Prevention of heavy alcohol intake and obesity
- Universal implementation of surveillance programs

Impact of coffee on HCC development

- Numerous epidemiological studies have addressed the prevention of HCC in patients with chronic liver disease
  - Trials analyzing the effect of coffee consumption have shown a consistently positive effect with regard to lowering HCC incidence

Recommendations		
Coffee consumption has been shown to decrease the risk of HCC in patients with **chronic liver disease** In these patients, **coffee consumption** should be **encouraged**	Moderate	Strong