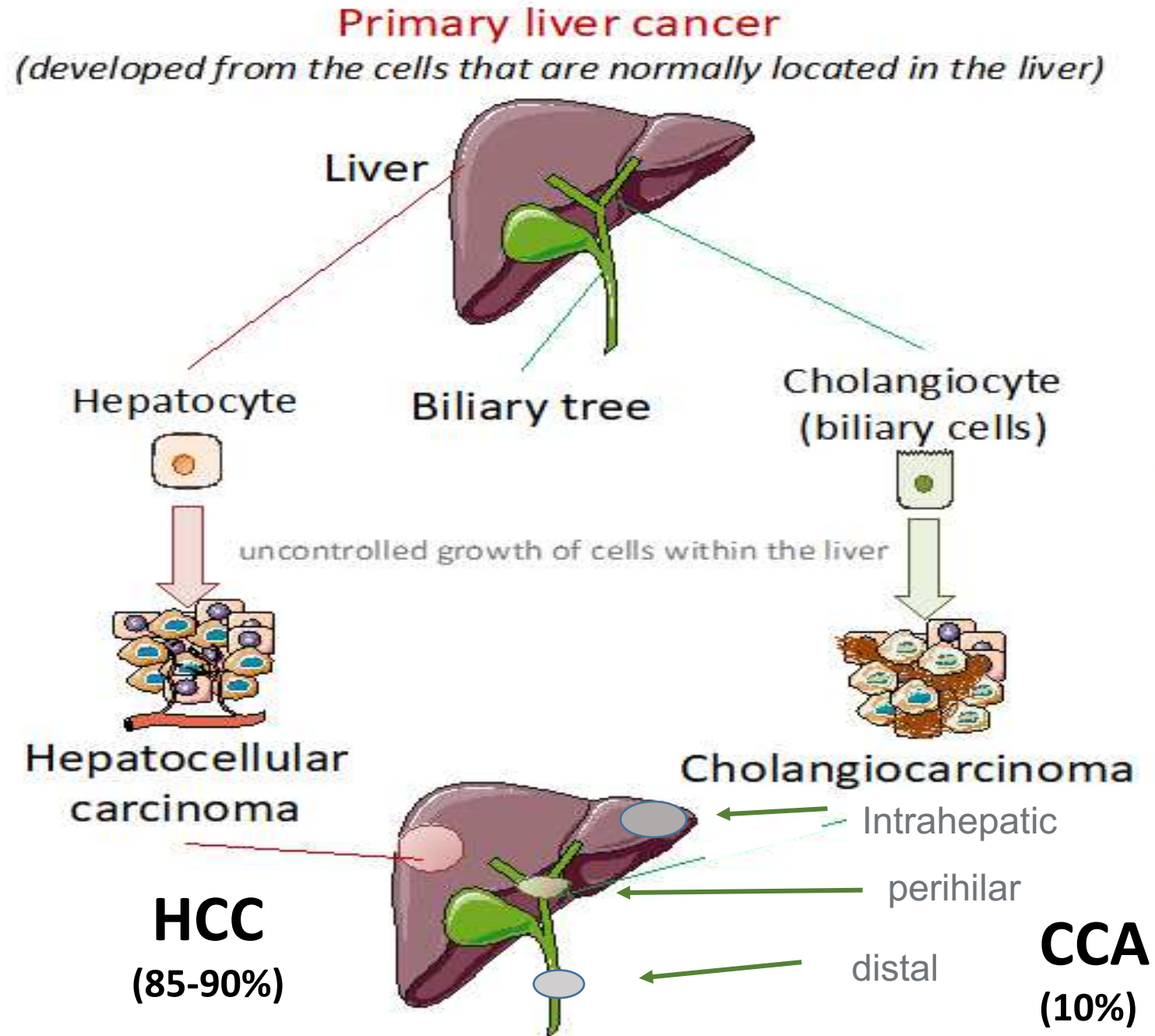


LEADING CHANGE FOR IMPROVED PATIENT OUTCOMES

Masterclass Series DiCE 21st October **2020 – VIRTUAL EXPERIENCE**

Dr Teresa Casanovas Taltavull, hepatologist
ELPA, European Liver Patients' Association, Scientific Committee

Introduction to Primary Liver Cancer



Agenda

Hepatocellular Carcinoma (HCC) (85-90% of primary liver cancer)

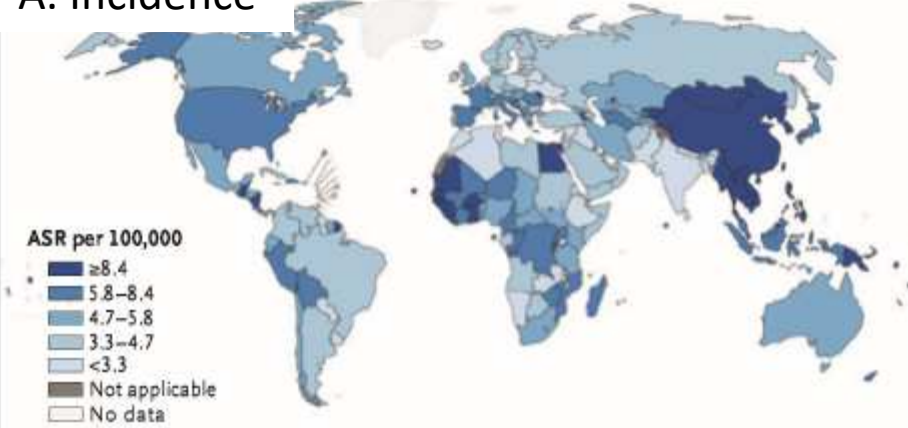
- Epidemiology
- Pathogenesis
- Surveillance and Diagnosis
- Staging and Prognosis
- Treatment: medical, surgical, combined

Epidemiology

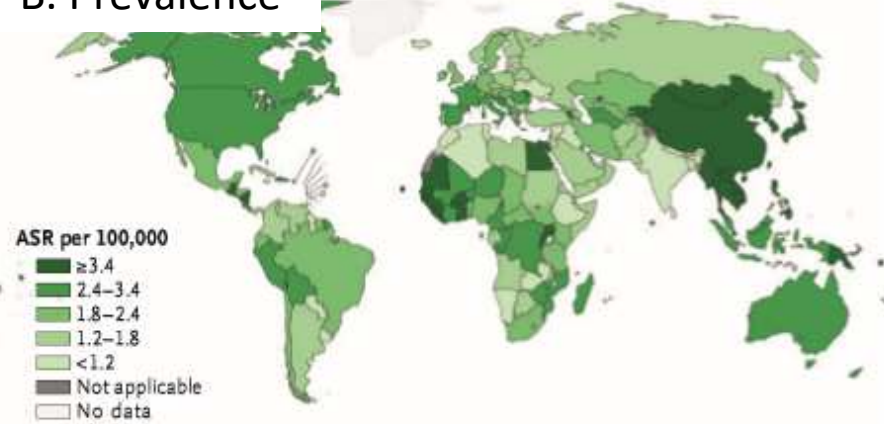
- // Most hepatocellular carcinoma cases (90%) occur in **cirrhosis**.
- // In sub-Saharan Africa and Eastern Asia, the main risk factors are **chronic hepatitis B and aflatoxin exposure**.
- // In US, Europe, and Japan the main risk factor is **hepatitis C together with an excessive alcohol intake and NASH**.
- // Non-alcoholic fatty liver disease (NAFLD/NASH) is becoming an important cause of hepatocellular carcinoma in developed regions.
- // Growing evidence supports the association between metabolic syndrome, diabetes, obesity and HCC in patients with NAFLD.

Global Epidemiology of HCC

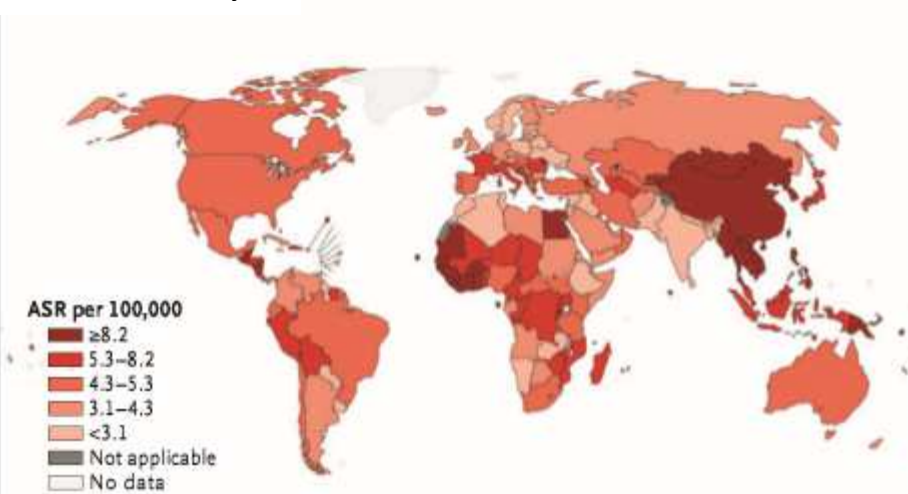
A. Incidence



B. Prevalence



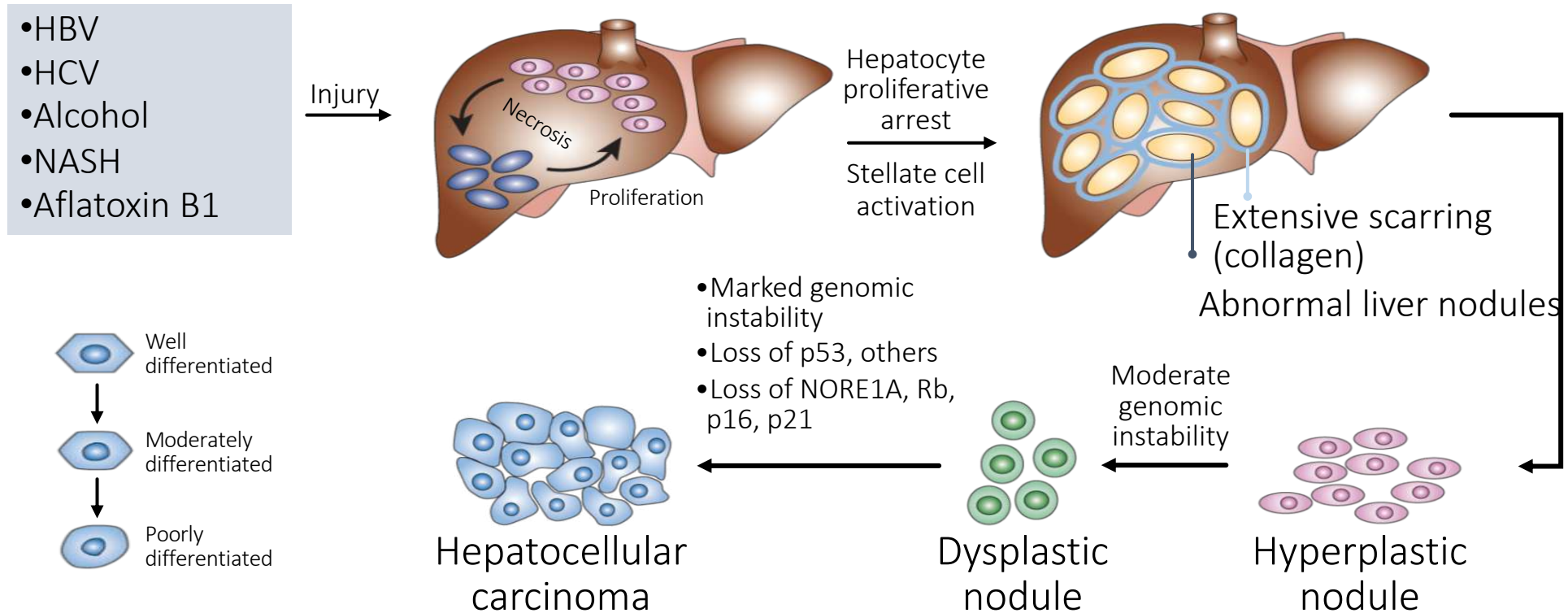
C. Mortality



- Data from the **International Agency for Research on Cancer**. The incidence and prevalence of liver cancer are shown in panels A and B, respectively, and the associated deaths are shown in panel C.
- Data is expressed as the **age standardized rate (ASR)** per 100,000 inhabitants.

A. Villanueva. Hepatocellular Carcinoma
N Engl J Med 2019; 380:1450-1462

Histopathological progression and molecular features of HCC



The Many Challenges of HCC

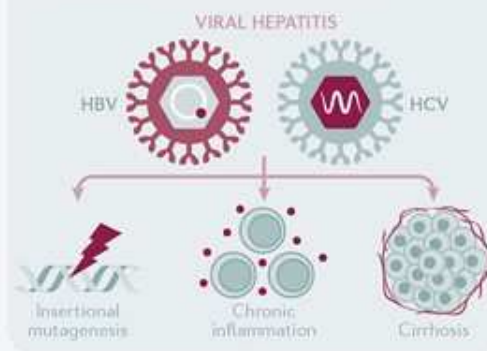
- Common malignancy
- Complex malignancy
 - Heterogeneous etiologies
 - Complex molecular carcinogenesis
 - Propensity for vascular invasion
- One patient, two diseases
 - Cirrhosis leads to multifocal hepatocarcinogenesis, high recurrence rates
 - Portal HTN, thrombocytopenia
 - Impaired hepatic function
 - Difficult clinical trial design
 - Although transplant is potentially curative, candidacy/access are limited

American Cancer Society. Cancer Facts & Figures 2019. Global Burden of Disease Liver Cancer Collaboration. JAMA Oncol. 2017;3:1683. Weledji. Ann Med Surg (Lond). 2014;3:71. Llovet. J Natl Cancer Inst. 2008;100:698. Madkhali. Saudi J Gastroenterol. 2015;21:11.

➔ **Hepatocellular carcinoma (HCC)** accounts for 85–90% of all primary liver cancers. Each year, 850,000 new cases of liver cancer are reported, making it the second leading cause of cancer-related deaths worldwide.

MECHANISMS

HCC can arise in mature hepatocytes or their progenitor cells. The molecular pathogenesis of HCC has been well-studied, and tumours typically contain ~40 genetic alterations, of which only a few are considered driver mutations. Processes that commonly contribute to HCC initiation and development include re-expression of fetal genes, changes in cell cycle control, dysregulation of protein folding, constitutive activation of the oxidative stress pathway and the activation of the WNT- β -catenin, RAS-RAF-MAPK and PI3K-AKT-mTOR signalling pathways. In addition, enhanced telomere maintenance through telomerase activation contributes to uncontrolled hepatocyte proliferation by inhibiting cellular senescence. An altered microenvironment is fundamental to liver carcinogenesis, and HCC usually develops on a background of liver damage (most commonly cirrhosis). Indeed, HCC can be considered a classic inflammation-associated cancer, with most cases linked to prolonged hepatitis due to viral infection or excessive alcohol intake.



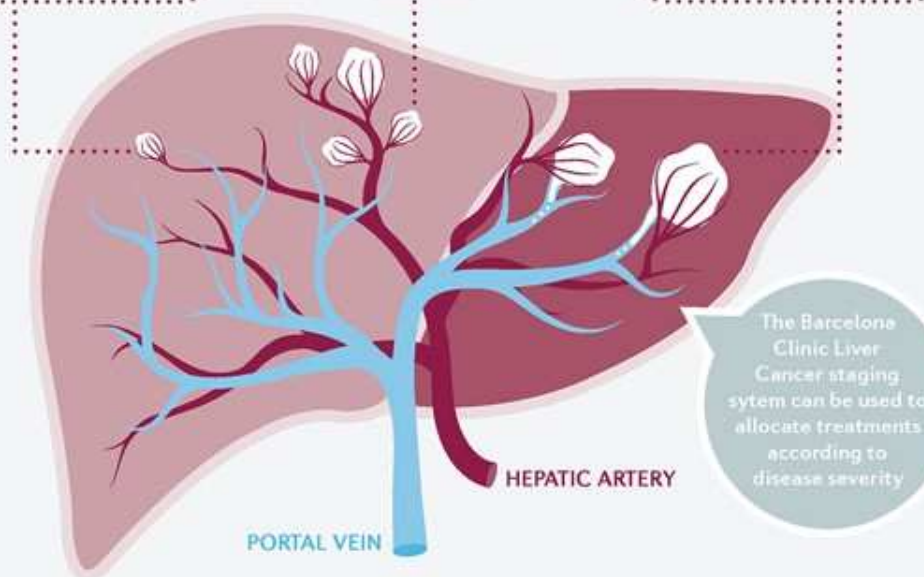
Designed by Laura Marshall

MANAGEMENT

Early-stage HCC is characterized by one or a few small nodules without portal vein invasion and by preserved liver function. Treatment involves liver resection, transplantation or local ablation.

Intermediate-stage HCC involves multiple nodules, preserved liver function and no portal vein invasion or symptoms. Treatment is commonly transcatheter arterial chemoembolization, which delivers chemotherapy directly to the tumour using drug-eluting beads.

Hallmarks of advanced disease are portal vein invasion, metastases and/or symptoms. Treatment with the multikinase inhibitor sorafenib increases survival by approximately 3 months.



PREVENTION

The risk factors for developing HCC include cirrhosis, alcohol abuse, infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), and ingestion of the fungal metabolite aflatoxin B1, which

is associated with mutations in the tumour suppressor gene *TP53*. In addition, metabolic syndrome has been linked to HCC that develops on a non-cirrhotic background. Prevention or treatment of hepatitis B using

vaccines or antivirals has reduced the incidence of HCC. With the advent of improved drugs against HCV, it is hoped that similar improvements will be made in populations with high rates of hepatitis C.

DIAGNOSIS

HCC can be diagnosed using either invasive (biopsy) or non-invasive (radiological) methods. Patients with cirrhosis can be diagnosed radiologically (usually with CT and/or MRI) alone, whereas those who do not have cirrhosis or whose imaging results are inconclusive require a biopsy. HCC symptoms usually do not occur until the disease is advanced, by which time potentially curative treatments are no longer an option. As such, screening of at-risk populations using ultrasonography is important for early diagnosis.



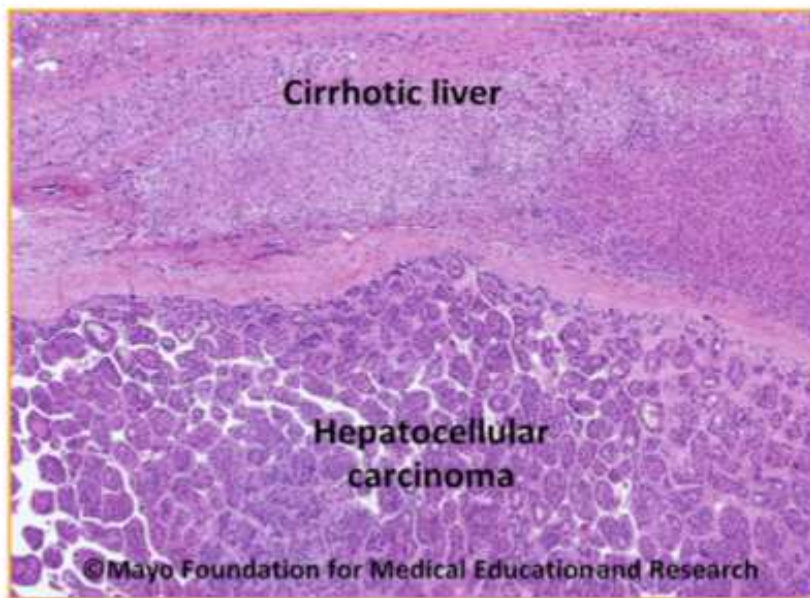
OUTLOOK

Despite detailed knowledge of driver genes in HCC, few of these have proven to be druggable targets. Consequently, only one systemic treatment (sorafenib) is currently available for treating this cancer, which improves survival by a few months. Moreover, first-line treatment for early-stage disease remains surgical removal of the affected liver, and no adjuvant therapy has been shown to be effective in this setting. Future progress in these areas will probably involve improved clinical trial design and greater understanding of tumour heterogeneity, which together will enable targeting of treatments to specific subsets of patients.

HCC

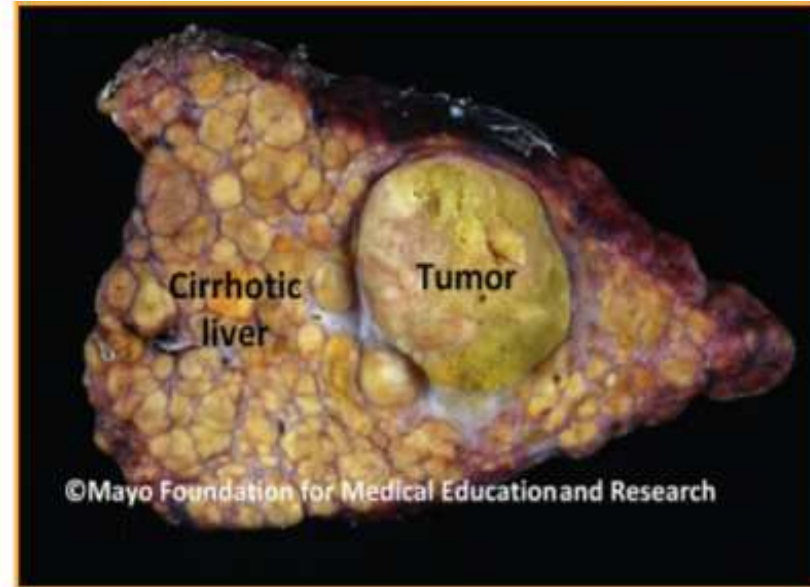
Surveillance and Diagnosis

MICRO



- **Hepatocellular carcinoma (HCC)** is the most common primary liver cancer, 85-90%.
- **In the United States/Europe, most HCC arise in the setting of cirrhosis.**
- **Risk factors for HCC** include cirrhosis from any cause, hepatitis B or C virus, alcohol, NASH, hemochromatosis, etc.
- **Serum alfa-fetoprotein (AFP)** levels are often elevated, particularly in patients with large tumors. However, they can be elevated due to other causes.

MACRO



Segment of HCC resection in the setting of cirrhosis and regenerative nodules

- The preferred test for surveillance is **ultrasonography**

- Screening of patients **every 6 months** recommended





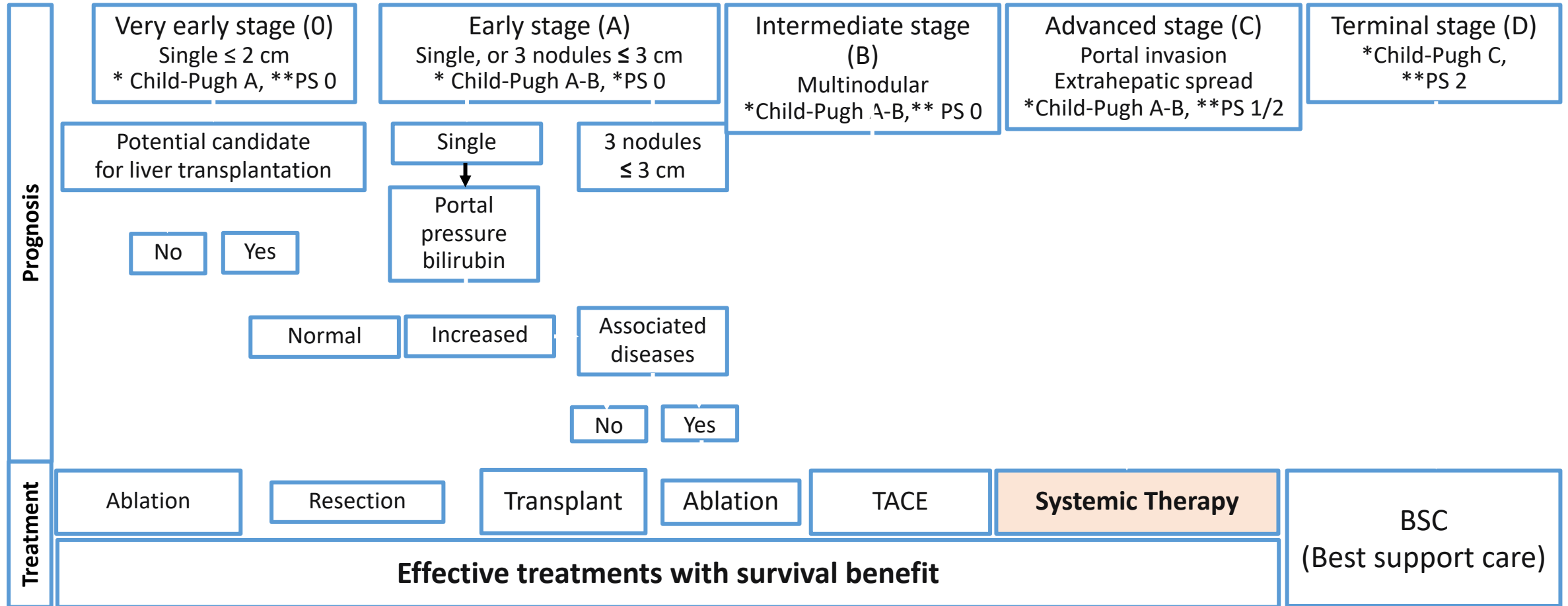
(a) Dynamic computed tomography shows a hypervascular lesion at the arterial phase, located at the right lobe of the liver. Lesion has isoattenuation in the portal-phase image (b) and shows washout in the late-phase (c) image.

Typical Small Hepatocellular Carcinoma in the Cirrhotic Liver

By using extracellular agents, the hallmark diagnostic features of HCC on multiphasic CT or MRI are arterial-phase hyperenhancement followed by portal venous or delayed-phase washout appearance

Management of HCC/ Diagnosis and stage assessment

BCLC (Barcelona Clinic Liver Cancer) Staging and Treatment Strategy for HCC



* Child-Pugh prognosis classification on cirrhotic liver, **PS : performance Status

Management of HCC/Treatment (s)

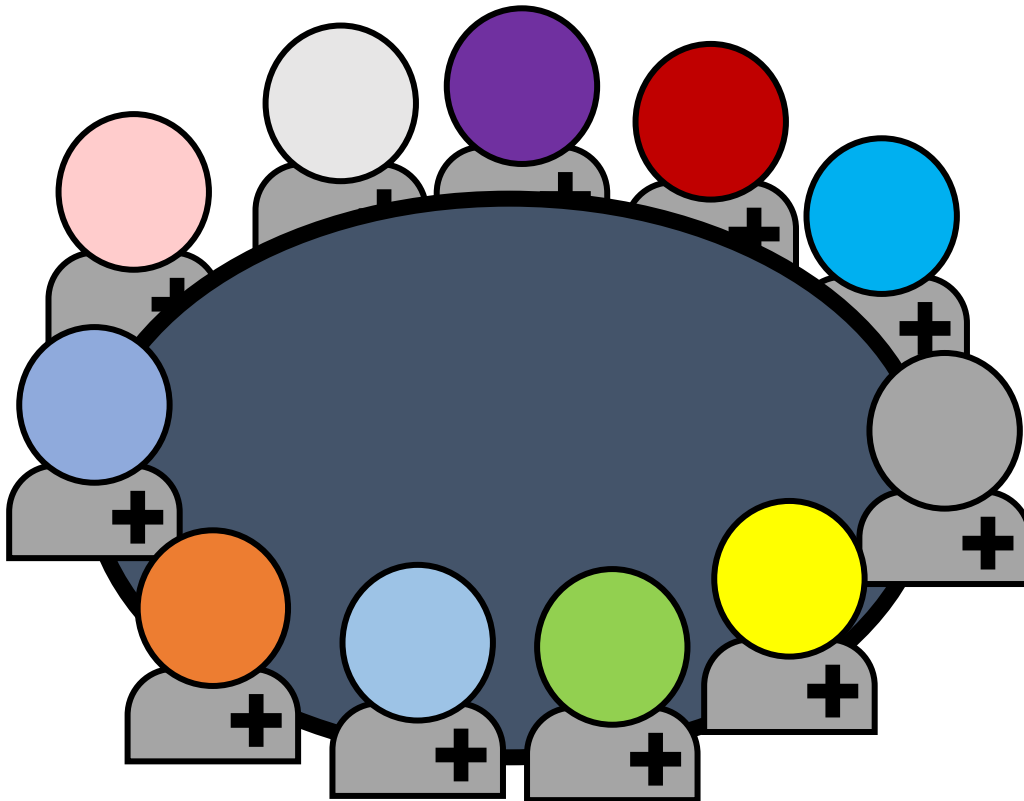
- Determining the best treatment options must take into account not only the burden and extent of HCC, but also the patient's performance status, underlying liver function, extra-hepatic disease and co-morbidities.
- Radiofrequency or microwave ablation, liver resection, or liver transplantation, all potential curative therapies for HCC, should be the first-line treatments when possible.
- For patients who are not candidates for curative treatments, locoregional therapies such as transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and stereotactic body radiation (SBRT) can improve survival and quality of life.
- Patients at advanced HCC stage, may receive new systemic agents recently approved or drugs in the setting of RTC (Randomized Clinical Trials).
- Patients with end-stage disease will receive symptomatic treatment.

Treatment - General Aspects

- // Patients diagnosed with HCC should be managed by a **multidisciplinary team** involving hepatologists, surgeons, radiologists (including interventional radiologists), pathologists, oncologists, etc.
- // Treatment indication should be evaluated individually, taking into account that they have two diseases: cirrhosis and cancer.
- // **Treatment will be sequential/and possibly stage migration, advancing or downstaging.**

Multidisciplinary Approach to the Patient With HCC

Joining: Hepatologists, surgeons, radiologists (including interventional radiologists), pathologists, oncologists, nurses, social workers..



- Multidisciplinary expert care can improve outcomes for patients with HCC
- Group Discussion:
 - Do you have a multidisciplinary team, experienced with diagnosis and treatment of HCC?
 - Do you have an expert, an academic center that you could consult with for specific patients?

Treatment – (Very) Early Stage

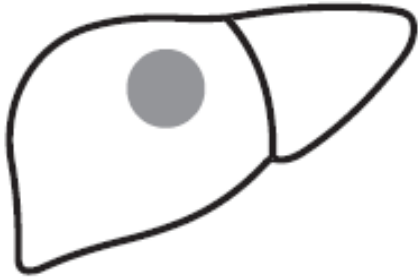
Resection

- // Hepatic resection is the treatment of choice for HCC in patients without cirrhosis, in whom major resections could be done without life-threatening complications.
- // In patients with decompensated cirrhosis, hepatic resection is contraindicated and liver transplantation should be considered.

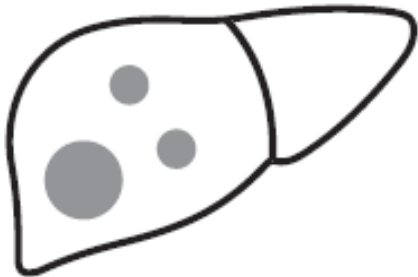
Liver transplantation (LT)

- // Theoretically, LT is the best treatment option since it might simultaneously cure the tumour and the underlying cirrhosis.
- // It has to meet **Milan criteria** (a single nodule ≤ 5 cm or up to three nodules ≤ 3 cm) are the benchmark to offer the best post-liver transplantation survival in HCC. (>70% 5-year survival with a recurrence rate of <10–15%).

Surgical Therapy for HCC early stage

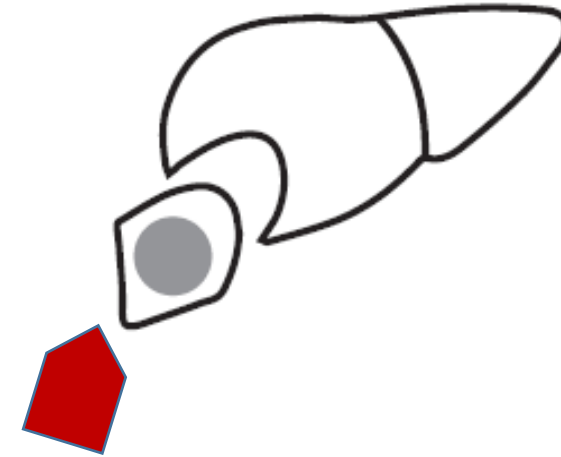


Tumor diameter
<5 cm



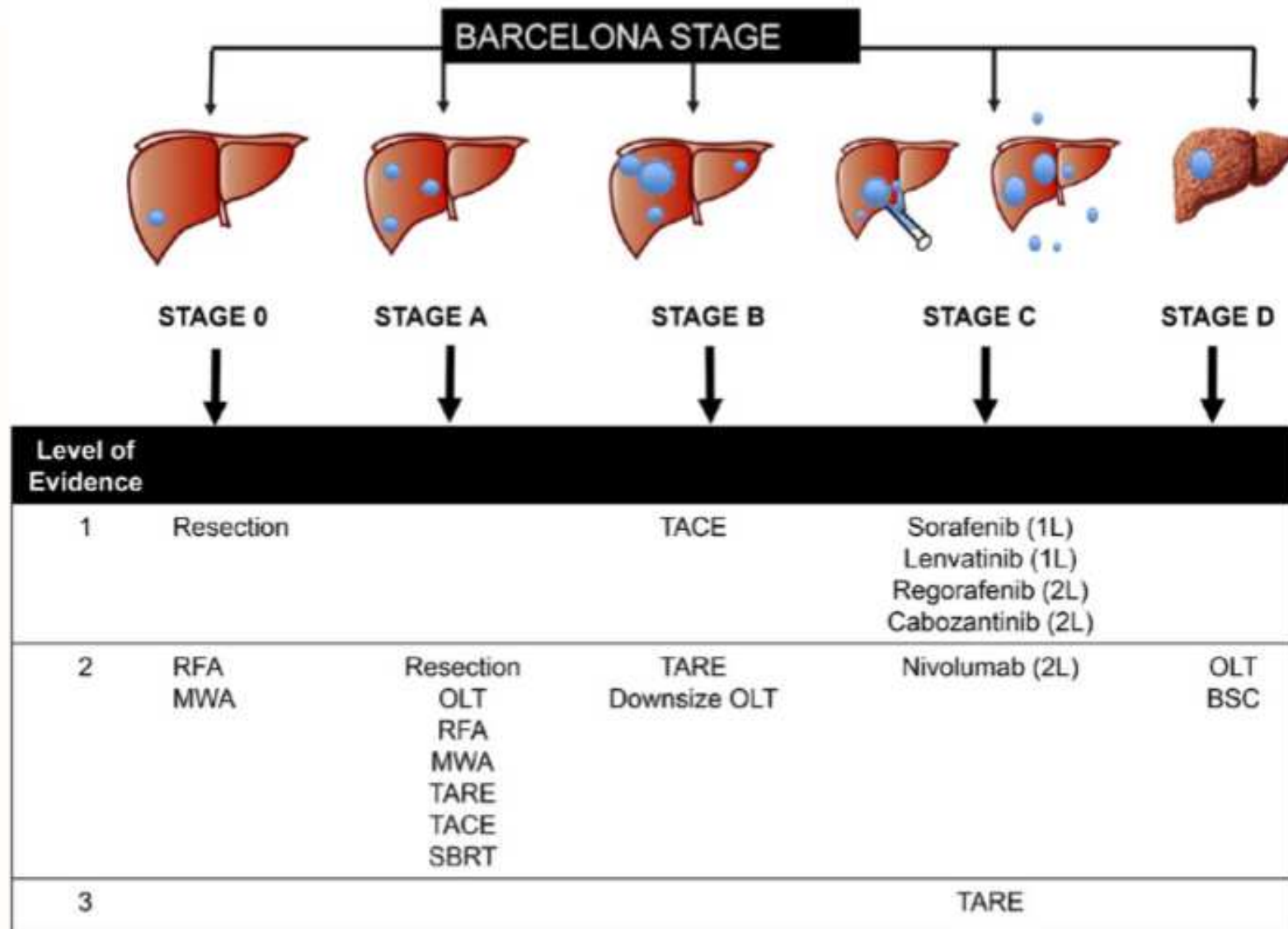
3 nodules
maximum, the
bigger < 3 cm

LIVER TRANSPLANT



SURGICAL RESECTION

Adapted from *Squaring the Circle of Selection and Allocation in Liver Transplantation for HCC: An Adaptive Approach*,
Vincenzo Mazzaferro HEPATOLOGY, VOL. 63, NO. 5, 2016



Treatment recommendations according to BCLC Stage. Abbreviations: RFA, radio frequency ablation; MWA, microwave ablation; TARE, transarterial radio embolization; SBRT, stereotactic body radiation therapy; BSC, best supportive care; 1L, first-line therapy; 2L, second-line therapy.

Unmet needs to achieve future goals in HCC

- Major health policy interventions with the aim of prevention:
 - Universal vaccination against HBV
 - Universal treatment for HCV
 - Prevention of heavy alcohol intake and obesity after elimination of viral hepatitis
- Universal implementation of surveillance programs for patients at risk of HCC
- New tools for early detection are in study, including **liquid biopsy**
- Transition to biopsy for HCC in all instances only once a **tissue biomarker predicting response will be available**
- Development of **new therapies** for improving outcome
- Development of **third-line therapies** POSSIBLY COMBINED treatment for advanced stage
- Define **optimal sequencing of systemic** therapy