Linee guida epatocarcinoma: applicabilità nella pratica clinica

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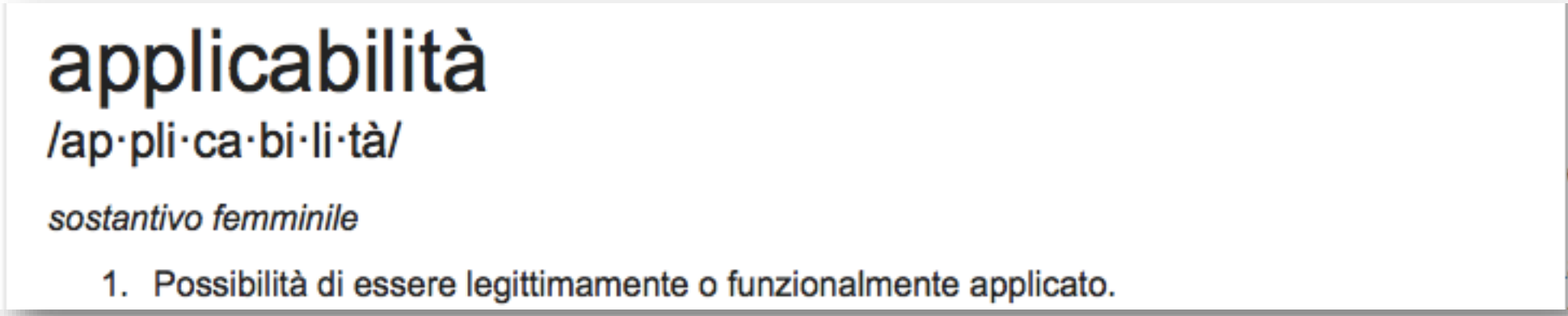
Applicability (or better applicabilità): what does it actually mean?

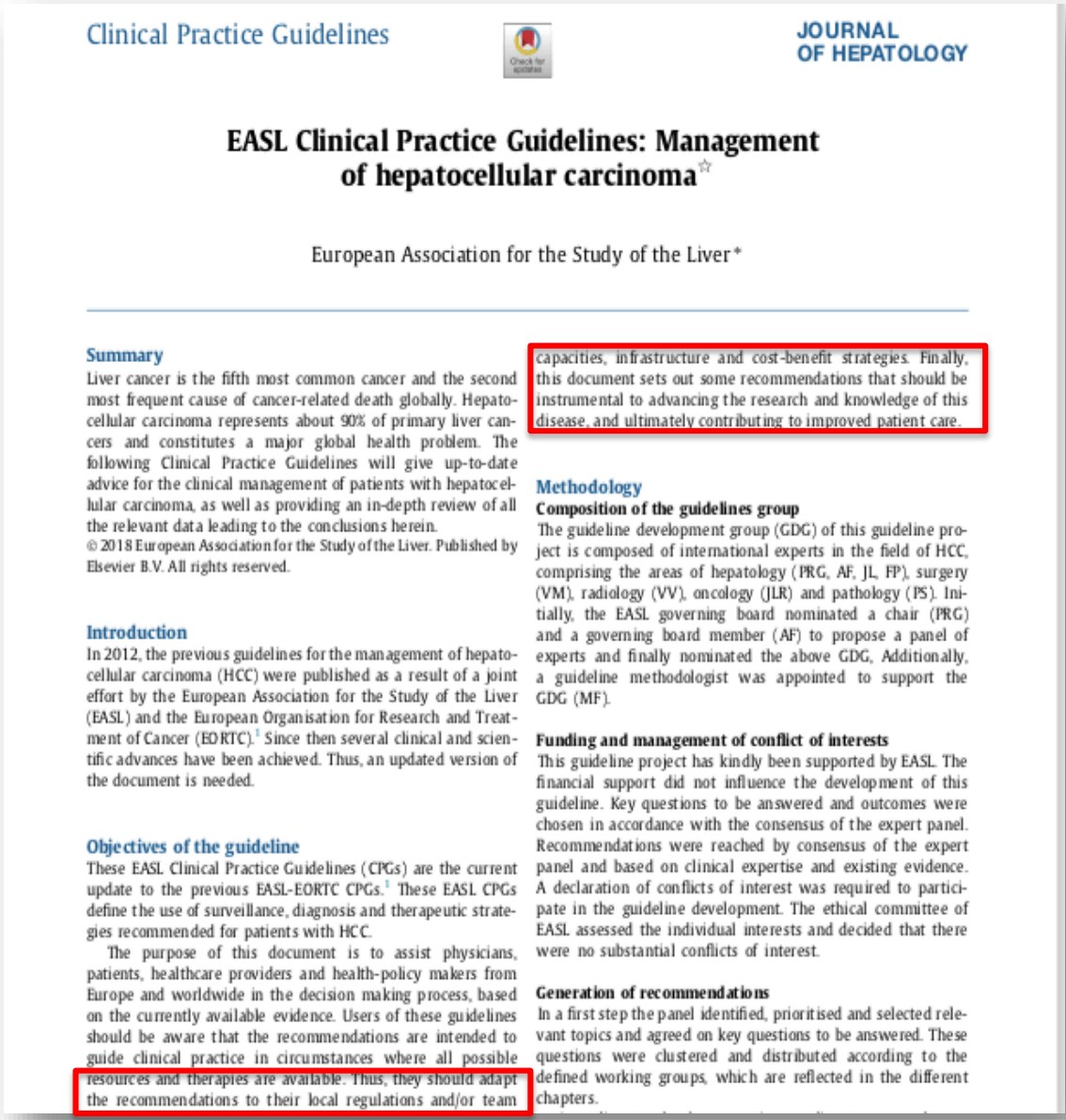


applicabilità

/ap·pli·ca·bi·li·tà/

sostantivo femminile

1. Possibilità di essere legittimamente o funzionalmente applicato.



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 (JLR) 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.

Physicians should adapt the recommendations to their local regulations and/or team capacities, infrastructure and cost-benefit strategies….

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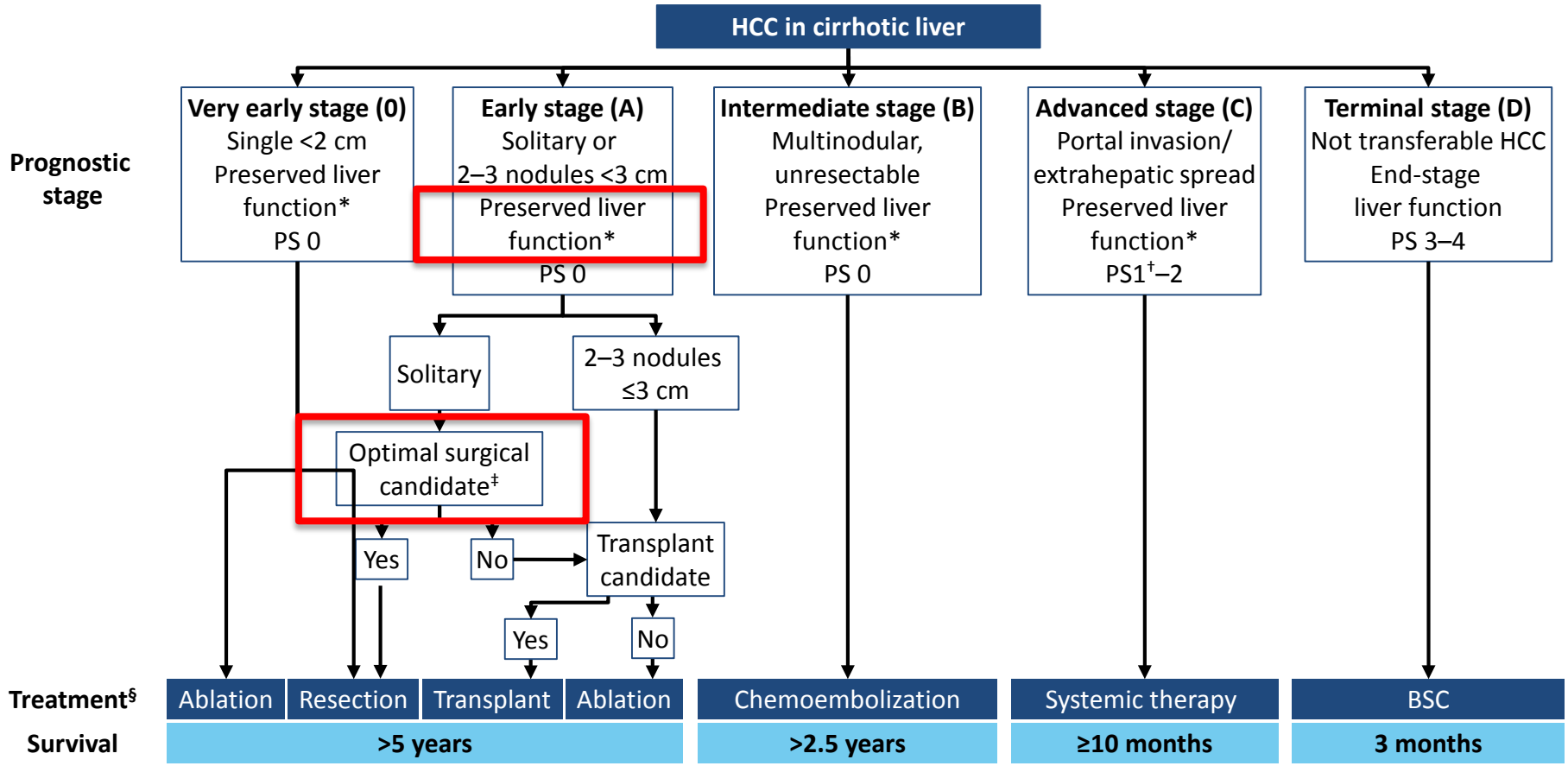
Applicability: surgery

Surgery in the early stage



EASL HCC Committee, J Hepatology 2018

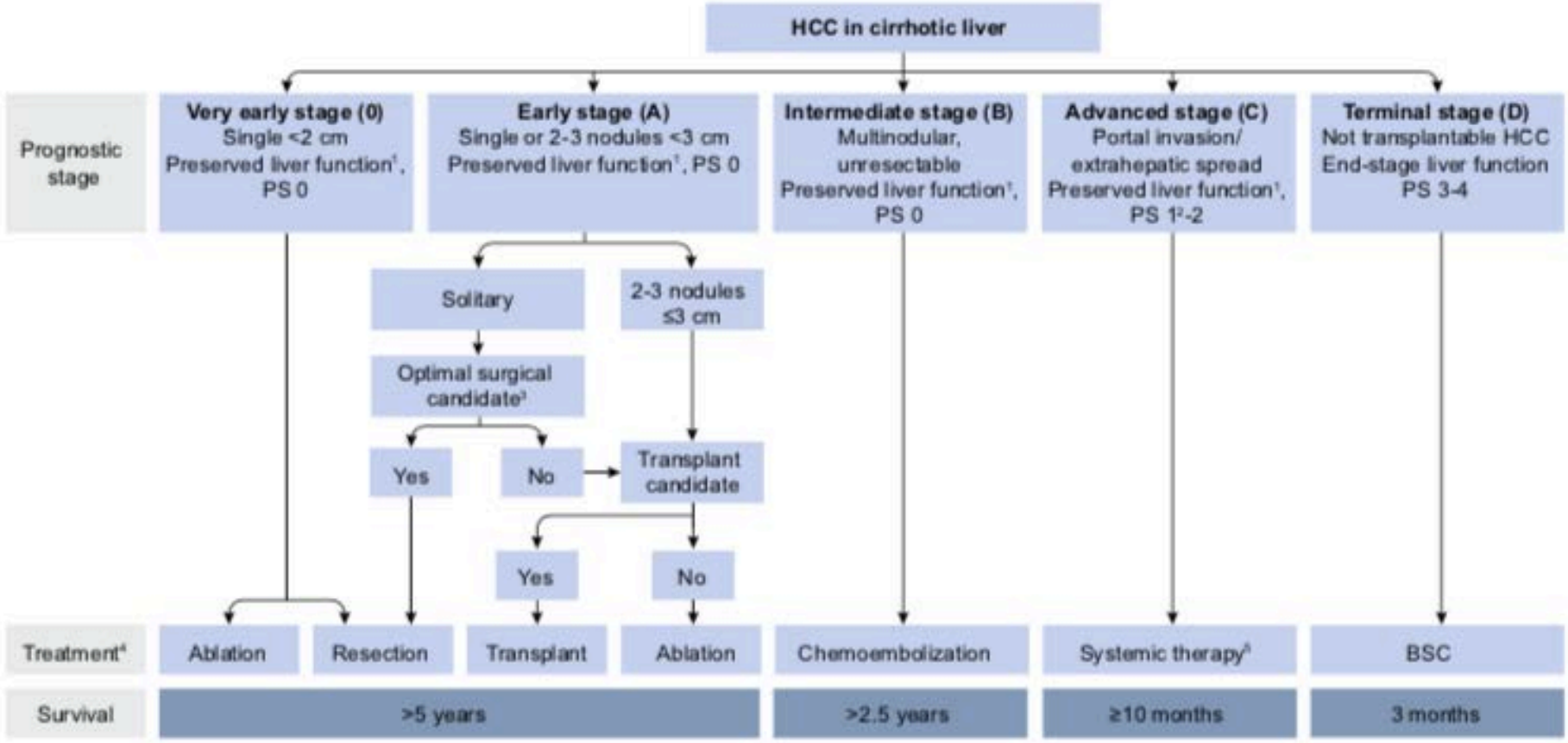


Fig. 3. Modified BCLC staging system and treatment strategy. [1]"**Preserved liver function**" refers to Child-Pugh A without any ascites, considered conditions to obtain optimal outcomes. This prerequisite applies to all treatment options apart from transplantation, that is instead addressed primarily to patients with decompensated or end-stage liver function. [2]**PS 1** refers to tumour induced (as per physician opinion) modification of performance capacity. [3]**Optimal surgical candidacy** is based on a multiparametric evaluation including compensated Child-Pugh class A liver function with MELD score <10, to be matched with grade of portal hypertension, acceptable amount of remaining parenchyma and possibility to adopt a laparoscopic/minimally invasive approach. The combination of the previous factors should lead to an expected perioperative mortality <3% and morbidity <20% including a postsurgical severe liver failure incidence <5%. [4]The **stage migration strategy** is a therapeutic choice by which a treatment theoretically recommended for a different stage is selected as best 1st line treatment option. Usually it is applied with a left to right direction in the scheme (*i.e.* offering the effective treatment option recommended for the subsequent more advanced tumour stage rather than that forecasted for that specific stage). This occurs when patients are not suitable for their first line therapy. However, in highly selected patients, with parameters close to the thresholds defining the previous stage, a right to left migration strategy (*i.e.* a therapy recommended for earlier stages) could be anyhow the best opportunity, pending multidisciplinary decision. [5]As of 2017 sorafenib has been shown to be effective in first line, while regorafenib is effective in second line in case of radiological progression under sorafenib. Lenvatinib has been shown to be non-inferior to sorafenib in first line, but no effective second line option after lenvatinib has been explored. Cabozantinib has been demonstrated to be superior to placebo in 2nd or 3rd line with an improvement of OS from eight months (placebo) to 10.2 months (ASCO GI 2018). Nivolumab has been approved in second line by FDA but not EMA based on uncontrolled phase II data. ASCO, American Society of Clinical Oncology; BCLC, Barcelona Clinic Liver Cancer; EMA, European Medicines Agency; FDA, Food and Drug Administration; MELD, model for end-stage liver disease; PS, performace status; OS, overall survival. Modified with permission from[87].

Preserved liver function

refers to Child-Pugh A without any ascites

Optimal surgical candidate

Optimal surgical candidacy is based on a multiparametric evaluation including:

- compensated Child-Pugh class A liver function with MELD score <10

To be matched with:

- grade of portal hypertension
- acceptable amount of remaining parenchyma
- possibility to adopt a laparoscopic/minimally invasive approach

Liver resection in cirrhotic liver

Several refinements in techniques, perioperative management and case selection have improved surgical interventions for liver cancer in patients with chronic liver disease and cirrhosis. Since no single surgical modality fits all HCC presentations, a multidisciplinary approach to surgical intervention is mandatory. This should be focussed on the key conditions affecting decision making in the area of surgical HCC, resulting in a multi-parametric approach to cancer and non-cancer components in the single patient. Criteria presented in the previous European Association for the Study of the Liver (EASL)/European Organisation for Research and Treatment of Cancer (EORTC) Clinical Practice Guidelines in 2012[1] (*i.e.* solitary tumours and very well-preserved liver function, hepatic vein to portal system gradient ≤10 mmHg or platelet count ≥100,000/ml) describe the "ideal" candidates for LR in cirrhosis. Such prescription remains confirmed, especially in a non-experienced context.

However, in the last few years patients exceeding one or more of the described criteria have been approached with LR in experienced centres, providing accurate balance of the relative weight of each determinant of prognosis. This has been enabled by general optimisation of surgical technique, pre-resection imaging planning, ultrasonic and bipolar dissector devices, intermittent hilar clamping (Pringle manoeuvre), low central venous pressure maintenance, mini-invasive approaches and intensive post-operative management. Indirect confirmation of improved perioperative management of the surgical patient emerges from the reported decrease in blood transfusion during LR in cirrhosis, from 80% to 90% to less than 10% in two decades.[332] Overall, outcome results achieved in patients undergoing LR in experienced centres (*i.e.* post-operative mortality and severe post-surgical morbidity of <3% and <30%, respectively) seem to favour the use of extended criteria for LR, namely of HCCs in which one or more conventional selection criteria for LR summarised in the 2012 EASL/EORTC Guidelines are not satisfied.

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Outcome results achieved in patients undergoing resection in experienced centres seem to favour the use of extended criteria for liver resection

EASL HCC Committee, J Hepatology 2018

Identifying extended criteria for sugery

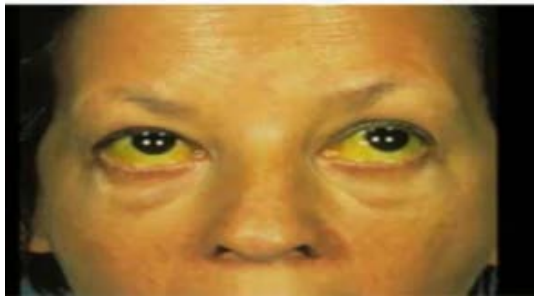
Liver function assesment

Extension of surgery

MINIMAL INVASIVE SURGERY

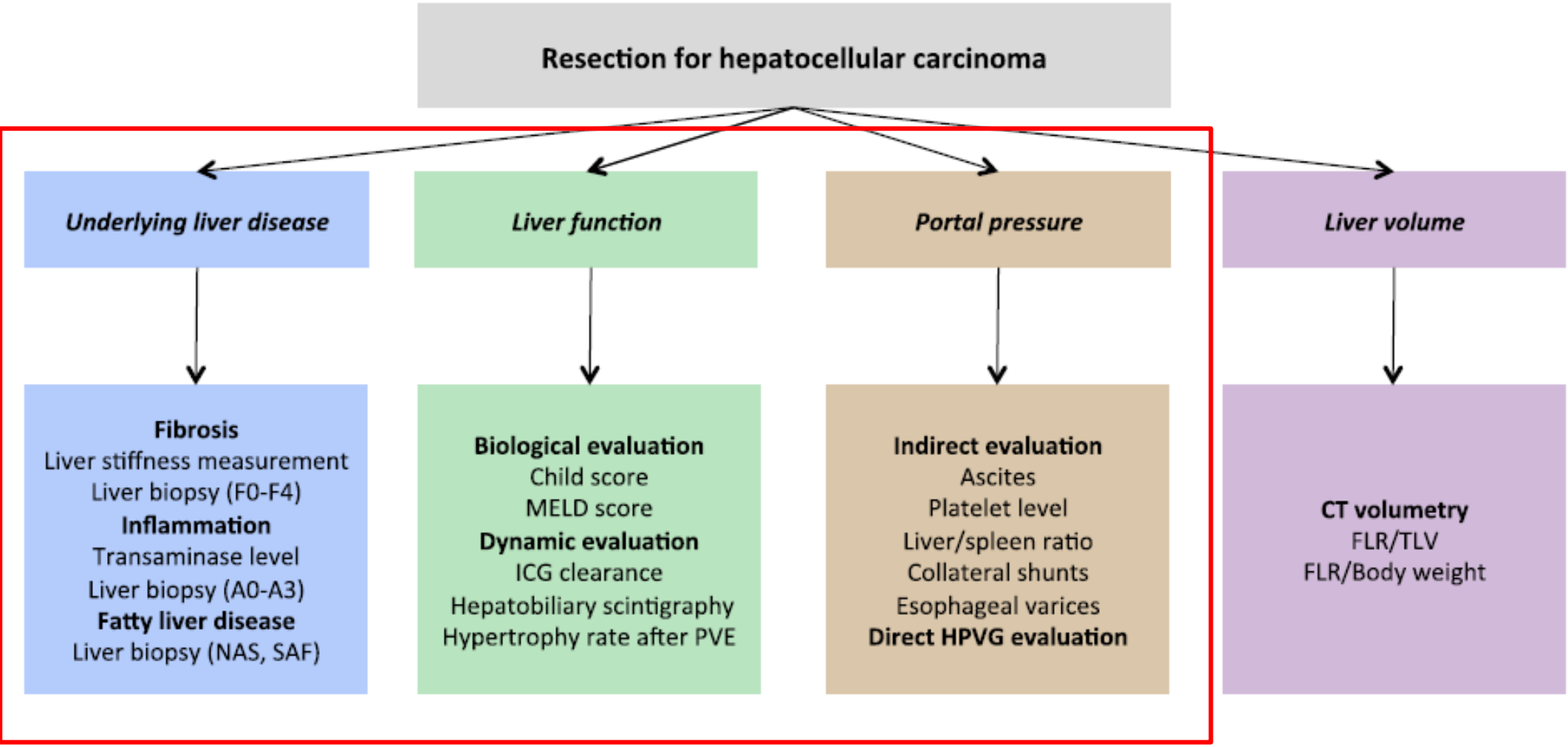
< 3% mortality, < 30% morbidity, < 5% PHLF

Risk of PHLF



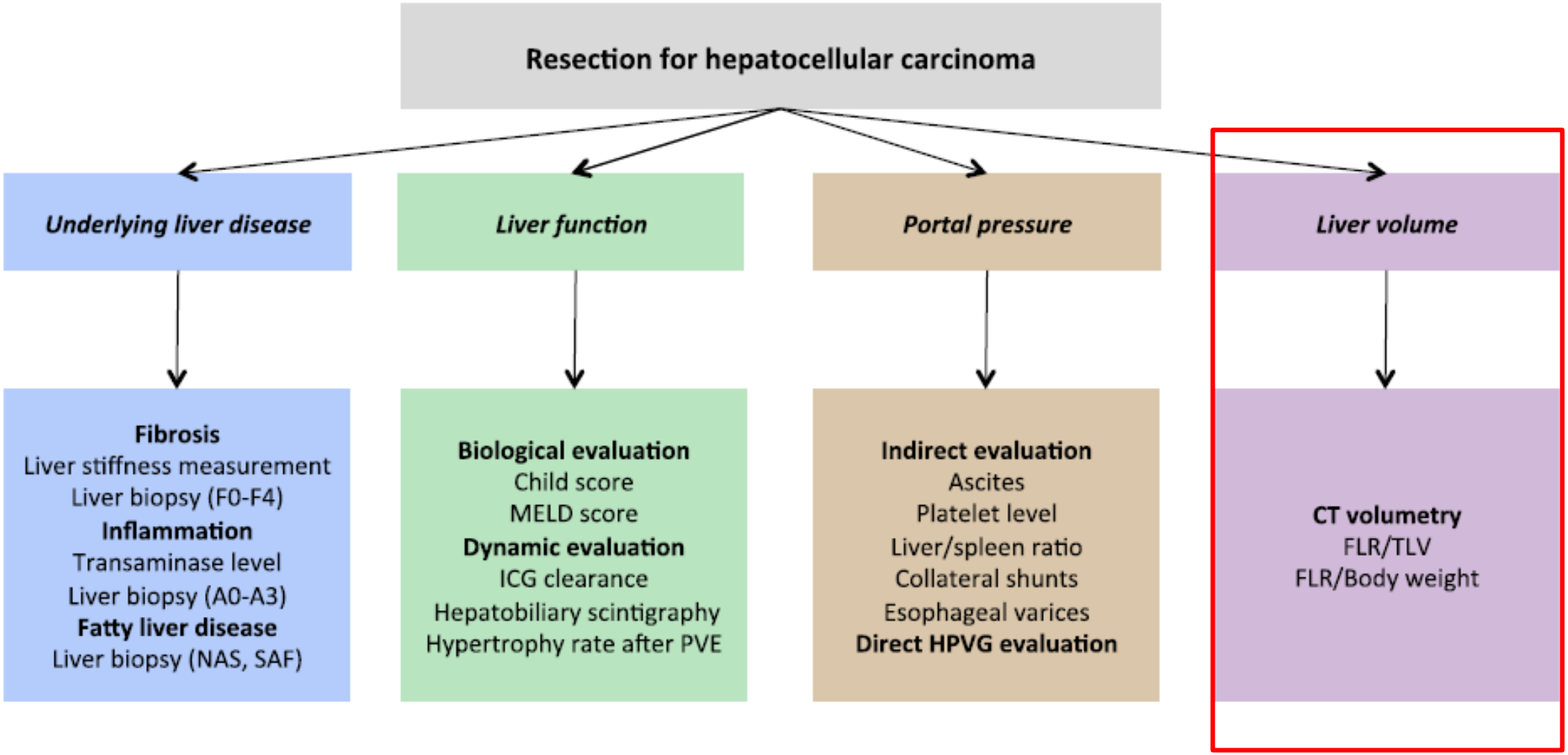
- Insufficient secretory capacity
  - Hyperbilirubinemia
- Decrease synthetic function
  - Coagulopathy
- Decreased detoxifying function
  - Encephalopathy

Factors contributing to PHLF



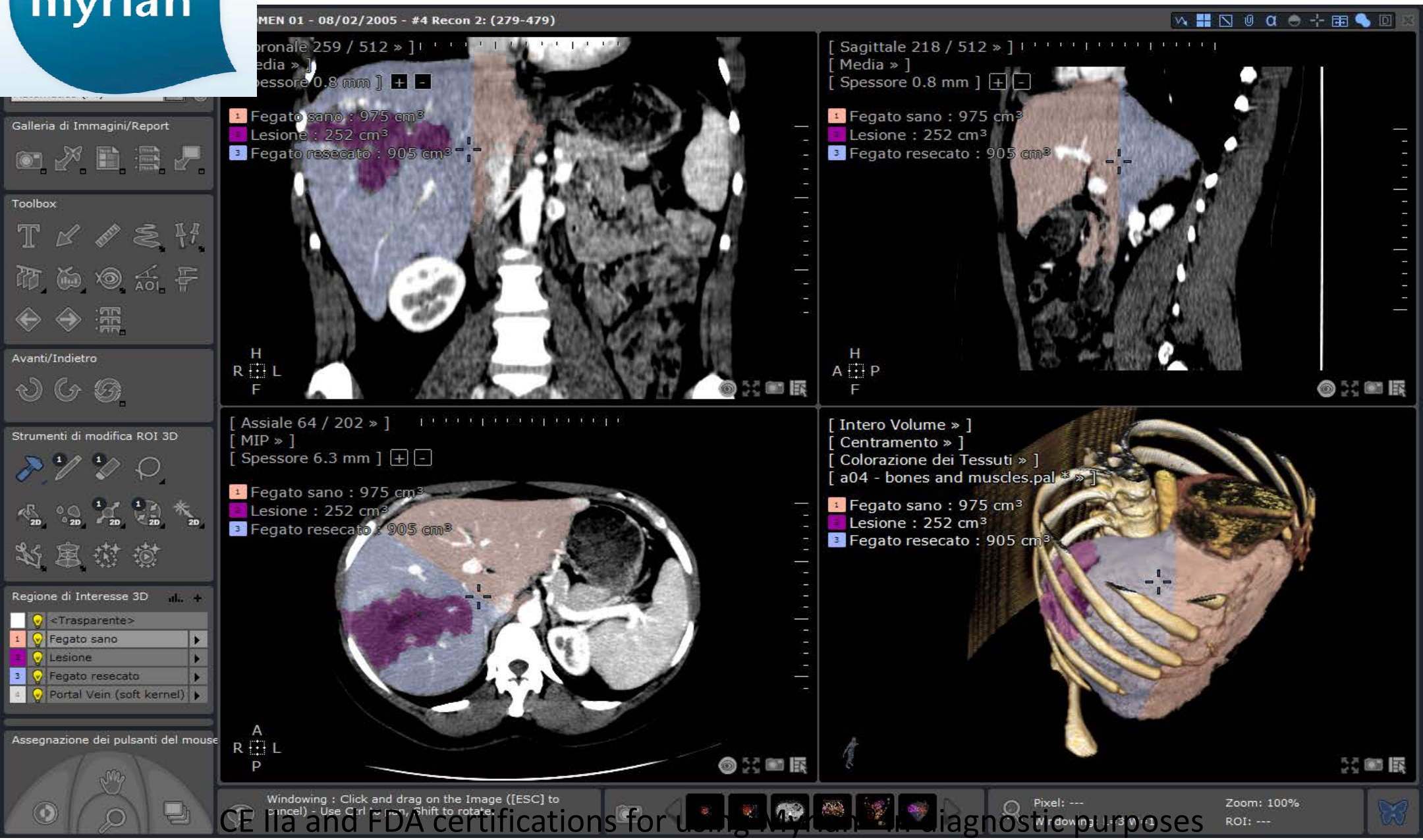
Cauchy et Al. Best Pract. & Research Clin. Gastroenterology 2014

Factors contributing to PHLF



Cauchy et Al. Best Pract. & Research Clin. Gastroenterology 2014

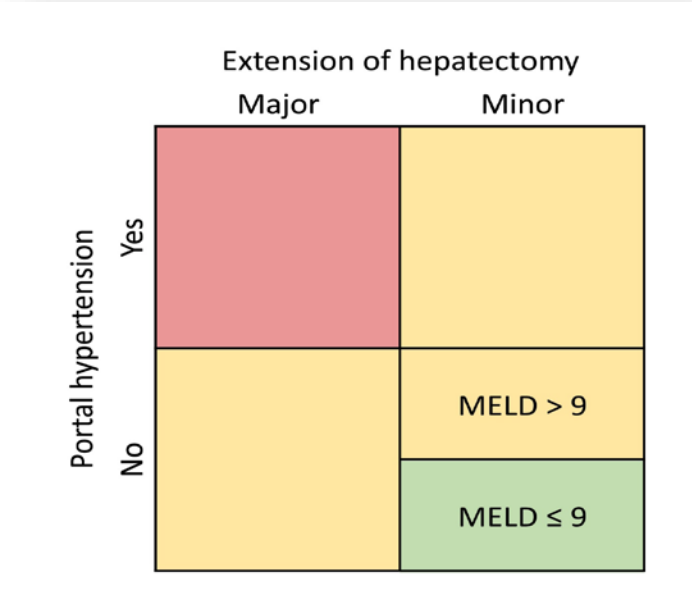
Liver volumes

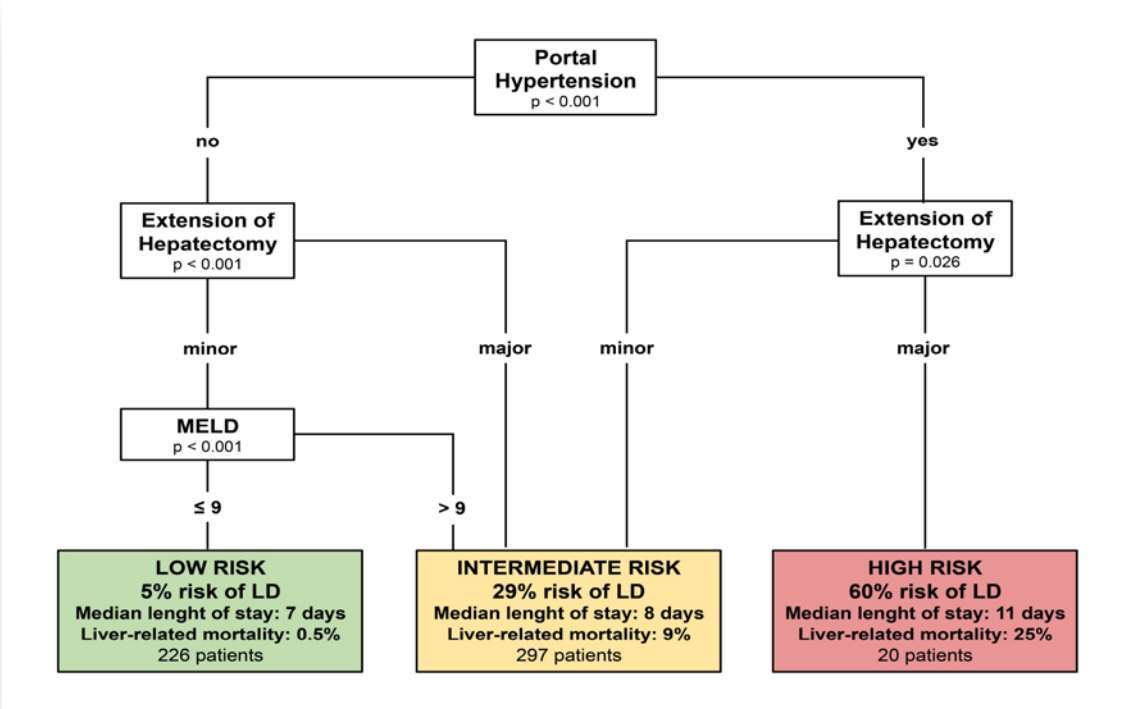


CE IIa and FDA certifications for using Myrian® in diagnostic purposes

Liver resection and risk of decompensation
A recursive partioning analysis of prognostic factors

Recursive Partitioning Analysis classifications identified three risk classes:
low (5%), intermediate (30%) and high (60%) risk of liver decompensation (LD)

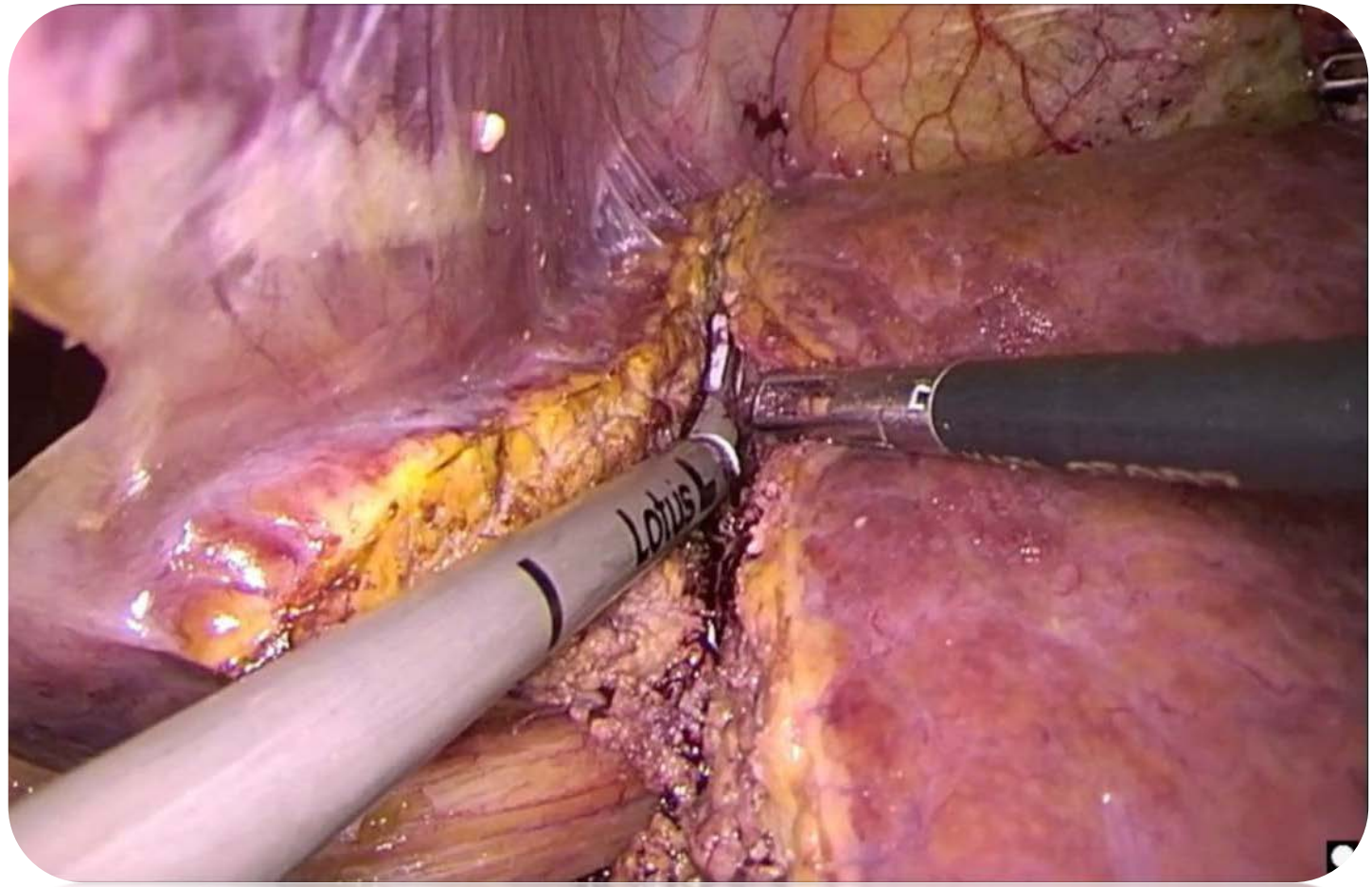




The risk of LD after resection can be accurately stratified preoperatively according to an algorithm built on presence of portal hypertension, planned extension of the hepatectomy and MELD score.

Citterio D, JAMA Surgery 2016

Liver resection



Laparoscopic vs. open limited resection for HCC

269 limited resections for HCC

226 open resections

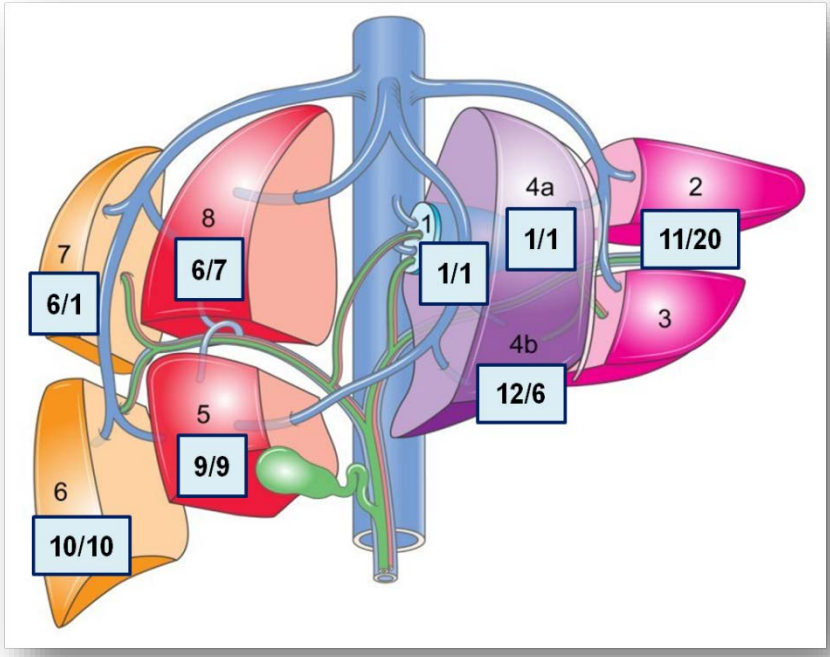
43 laparoscopic resections

PS matching

43 open resections

Vs.

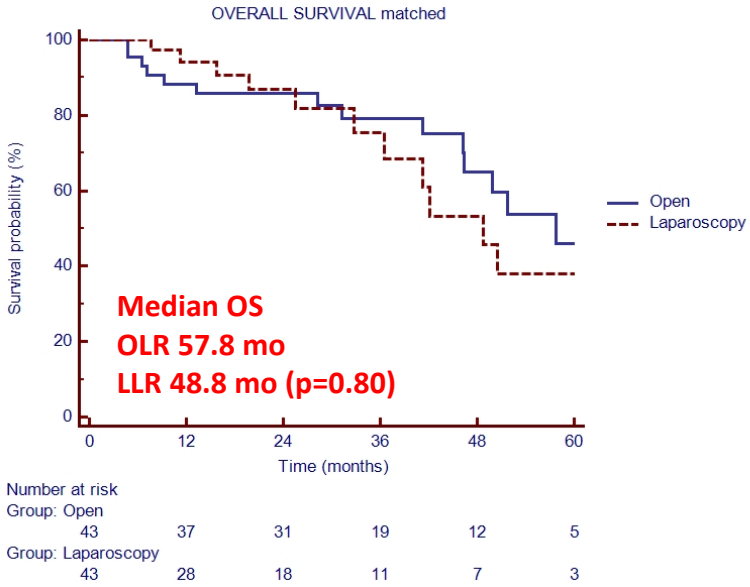
43 laparoscopic resections

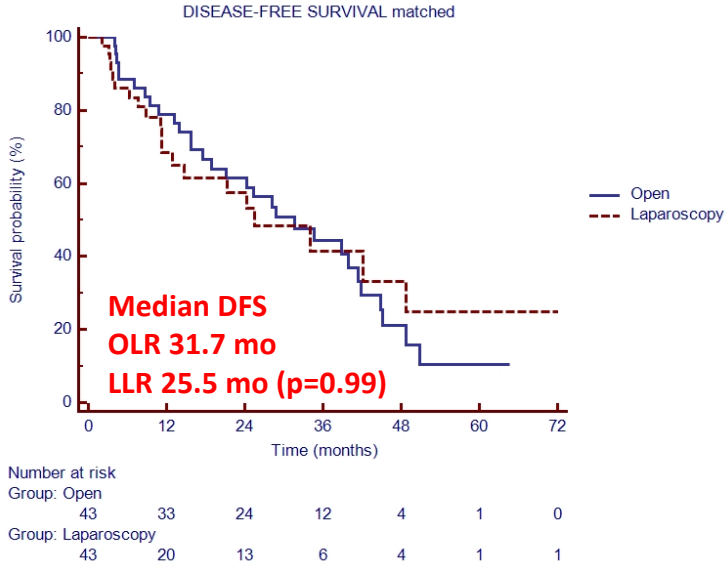


	Open 43 pts	Laparoscopy 43 pts	p
Intraoperative bleeding			0.50
- < 100 mL	31 (72.1%)	29 (67.5%)	
- 100-500 mL	8 (18.7%)	12 (27.9%)	
- > 500 mL	4 (9.2%)	2 (4.6%)	
Hospital stay (days)	8 (5-42)	5 (1-31)	**<0.001**
Complications (DCC)			**0.004**
- none	22 (51.2%)	35 (81.4%)	
- 1-2	20 (46.5%)	7 (16.3%)	
- 3-4	1 (2.3%)	1 (2.3%)	
30-days mortality (days)	0 (0%)	0 (0%)	1.0
Radical R0	42 (97.7%)	42 (97.7%)	0.61
Margins (mm)	5 (1-30)	6 (1-20)	0.96

Sposito C et al. BJS 2016

Laparoscopic vs. open limited resection for HCC





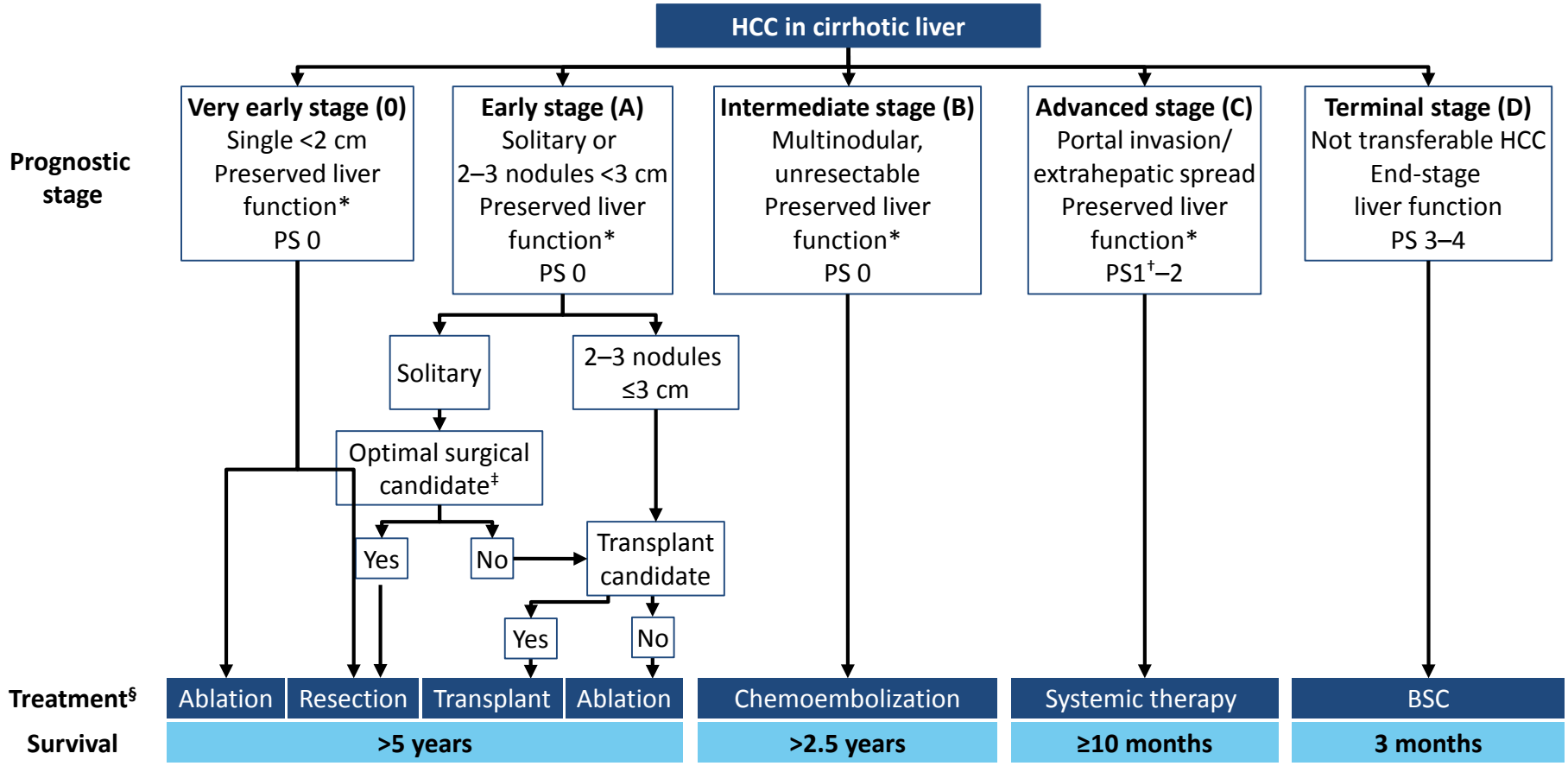
	Multivariate	P
Age (ref. ≤ 65)	1.04 (0.34-1.66)	0.44
Gender (ref. female)	0.46 (0.14-1.28)	0.13
Performance Status (ref. 0)	0.59 (0.34-6.27)	0.22
Child-Pugh (ref. A)	1.41 (0.19-8.72)	0.71
MELD (ref. ≤ 9)	1.47 (0.67-3.16)	0.30
Portal Hypertension (ref. absent)	1.42 (0.59-3.32)	0.41
R15 (ref ≤ 14)	1.84 (0.83-4.16)	0.13
Number of nodules (ref. single)	1.24 (0.04-1.69)	0.18
Max Diameter (ref. ≤ 3.5 cm)	0.79 (0.39-2.16)	0.85
AFP (ref. ≤ 20 UI/mL)	0.77 (0.34-1.70)	0.56
BCLC stage (ref. 0)	0.85 (0.27-2.88) 1.22 (0.10-13.98)	0.67
Operative time (ref. ≤ 180 min)	1.20 (0.56-2.56)	0.63
Laparoscopy (ref. open)	0.28 (0.11-0.64)	**0.03**

Multivariate logistic regression on factors associated with DCC ≥ 2

In comparison to the open approach, laparoscopic liver resections improve short-term outcomes while maintaining similar survival results

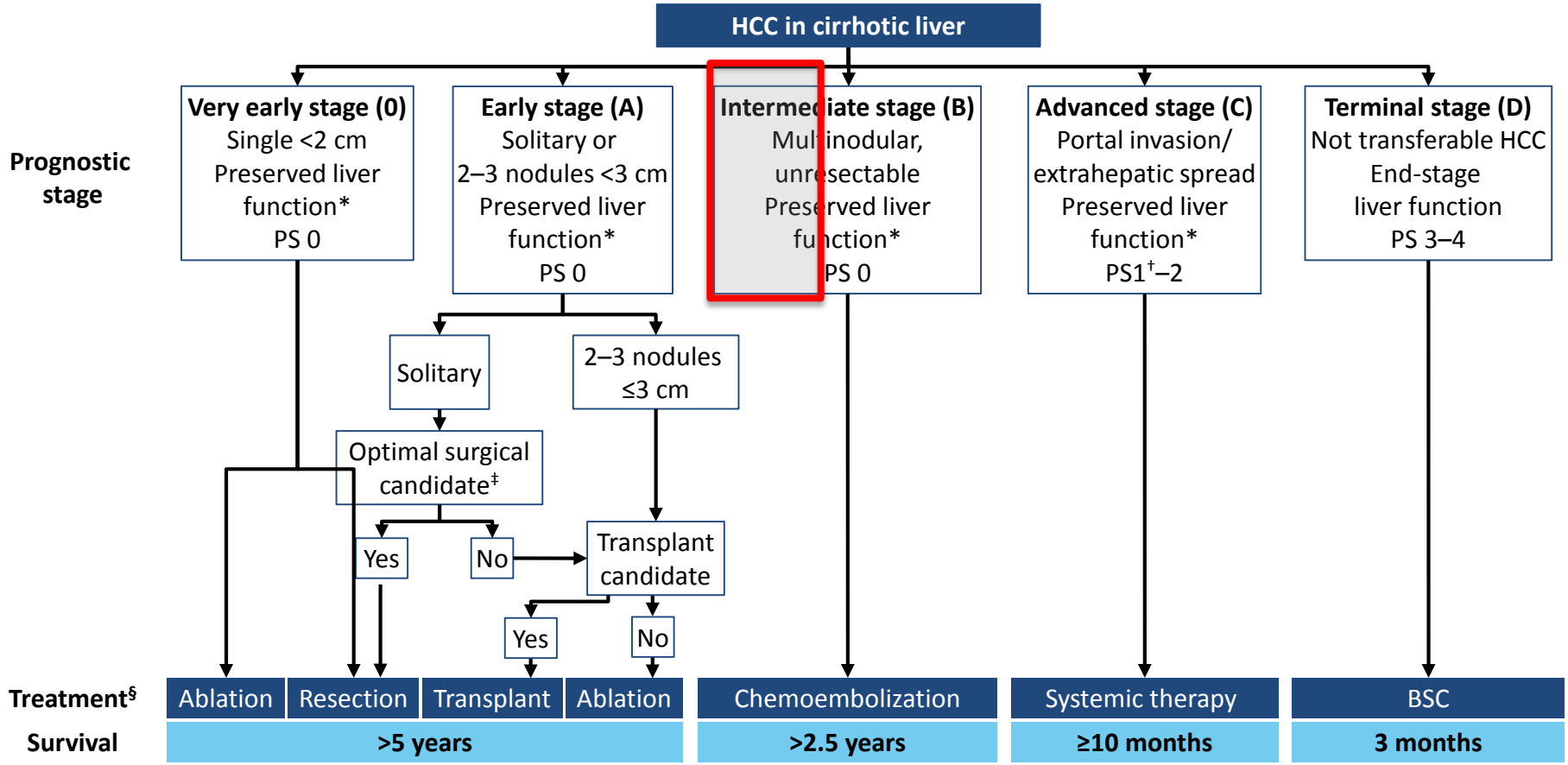
Sposito C et al. BJS 2016

Surgery in the extended criteria



EASL HCC Committee, J Hepatology 2018

Surgery in the extended criteria = intermediate



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post-operative liver decompensation.[298,355,356] That widens the curative perspective offered by modern LR approaches, particularly in hepatitis C virus (HCV)-related cirrhotic patients in which pre/post-resection treatment with direct-acting antivirals (DAAs) may optimise liver function control.

On top of the previous considerations, LR for HCC – as with any surgical procedure –patients' general condition, performance status and co-morbidities must be considered ahead of any intervention. Age should not be a contraindication *per se*, if adequate performance status and no major co-morbidities are confirmed in patients undergoing LR for HCC. In particular, post-surgical survivals compared to age-sex-matched reference populations suggest that LR can be offered in patients >70 years old, who are in fact exposed to a smaller loss of their individual lifespan in comparison with their younger counterparts.[357]

When liver-preservation principles are met, and patient's general conditions have been scrutinised as permissive for surgical intervention, LR should be tailored on HCC characteristics and presentation. In this respect, at least four major considerations should contribute to decide the best approach to LR in case of single HCC in cirrhosis:

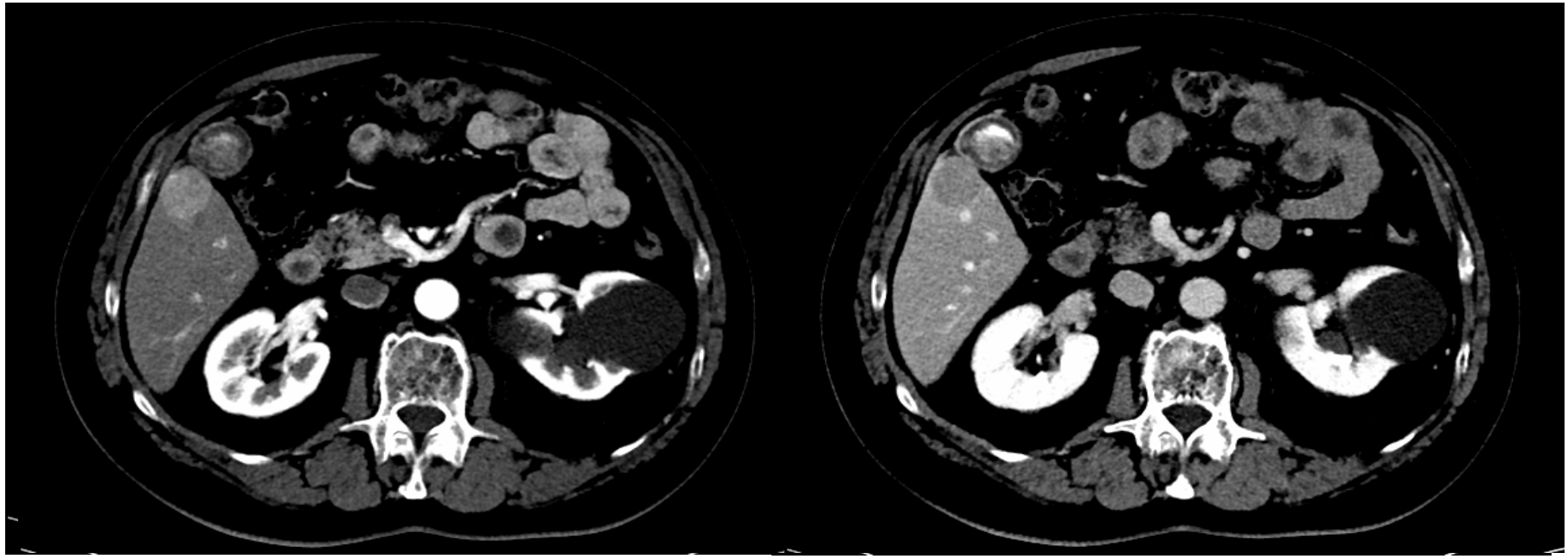
a. Tumour size and intrahepatic tumour location influence decision on surgical approach. For single HCCs ≤2 cm deeply/centrally located, radiofrequency ablation (RFA) offers competitive results with respect to LR (see paragraph on local ablation). Conversely, laparoscopic-robotic LR for HCC located in superficial-peripheral positions of the liver provides optimal survival outcomes while minimising complications and hospital stay (Fig. 6);

Clinical Practice Guidelines

On top of the previous considerations, LR for HCC must be considered ahead of any intervention…

A “surgical” BCLC B patient

Male, 71 y.o., HCV+, CPT A5, no PH, ECOG PS=0
4 nodules, bilobar, max diam 5 cm



Surgery: left lobectomy, atypical resections S8 and S6
Discharged on 6th p.o. day
Pathology: 5 nodules, max diam 6 cm, G2, mVI+
DFS: 25 months

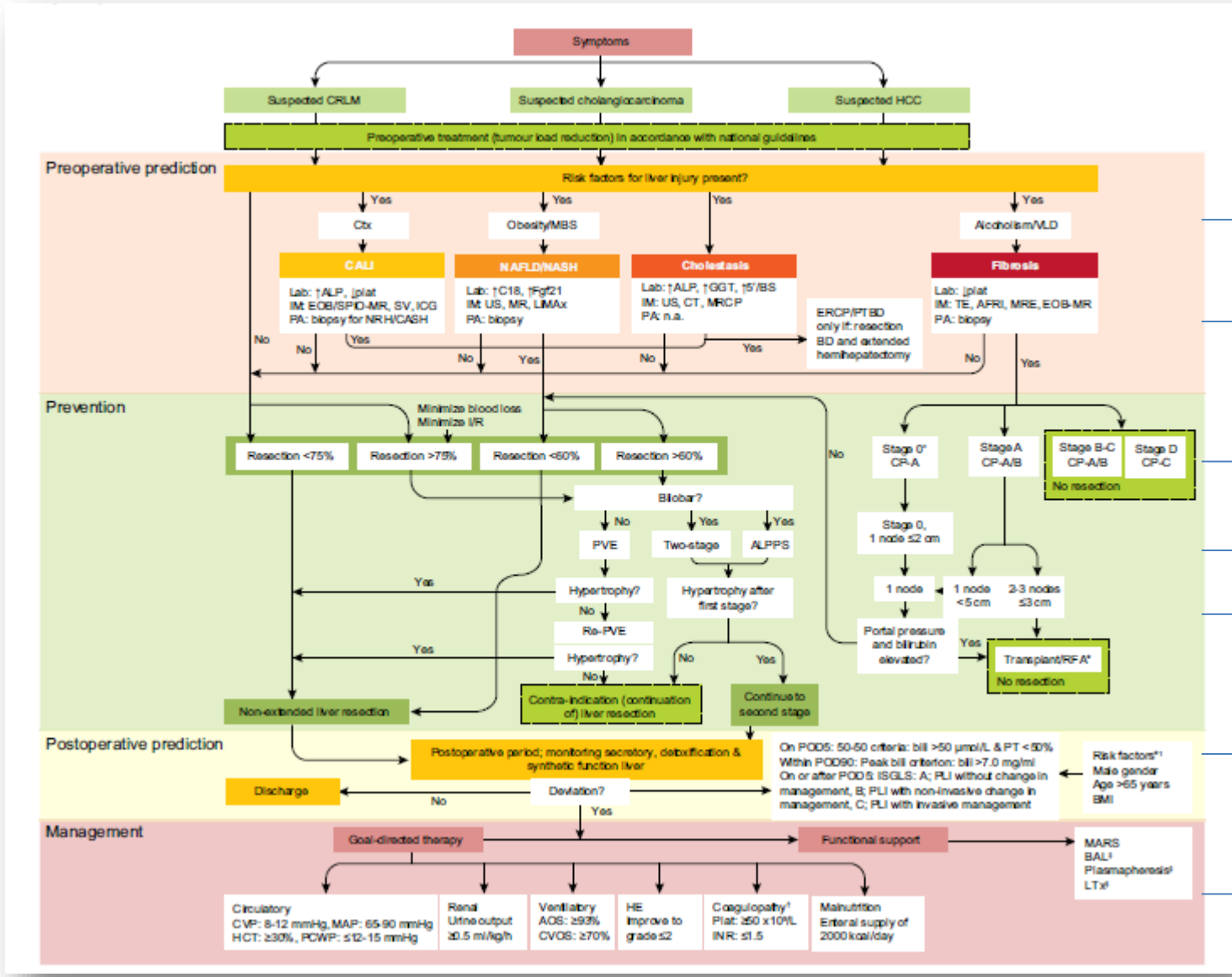
LR for multiple HCCs: literature review

Author (Journal Year)	N° patients	5-Yr OS	5-Yr DFS
Fong Y (Ann Surg1999)	42	48%	ND
Vauthey JN (J Clin Oncol 2002)	180	**24%**	ND
Ercolani G (Ann Surg 2003)	24	ND	**0%**
Ikai I (Hepatol Res 2007)	3174	30%	ND
Wu CC (Br J Surg 2005)	82	26%	26%
Portolani N (Ann Surg 2006)	38	29%	20%
Ishizawa T (Gastroenterology 2008)	126	**58%**	25%
Zhao WC (World J Surg. 2012)	162	35%	**31%**
Nojiri K (Anticanc. Res. 2014)	107	38.1%	-

Only cohort studies including patients with mixed features

- **Mean 5-yr survival: 39%** (24-58%)
- **Mean 5-yr disease-free survival: 14%** (0-31%)

Flow chart for decision-making in liver surgery



obesity/NAFLD/ETOH

fibrosis

liver function

extension of resection

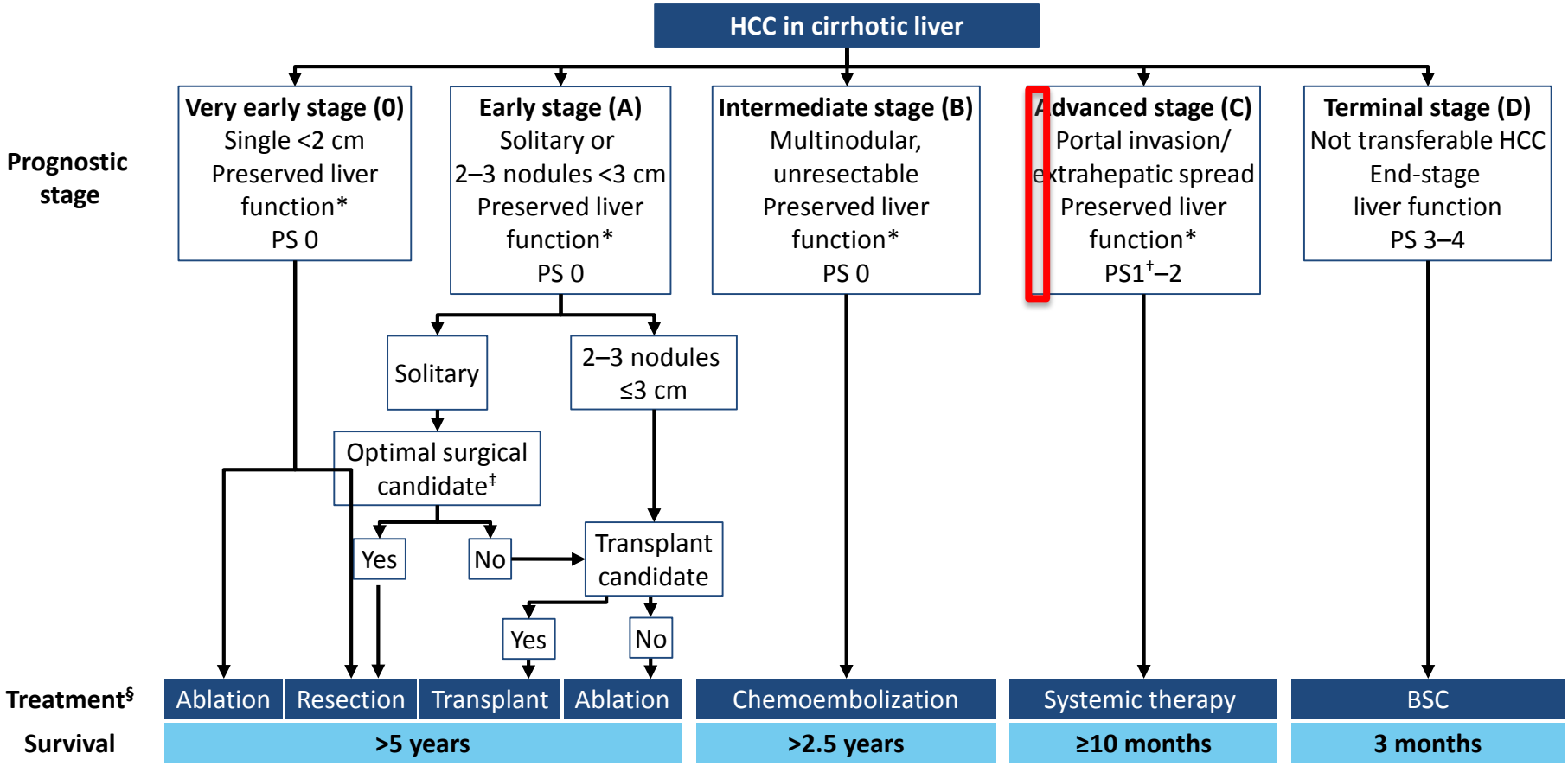
liver regeneration techniques

PHLF

medical support

van Mierlo KMC, J Hepatol 2016

Surgery for PVTT patients = advanced

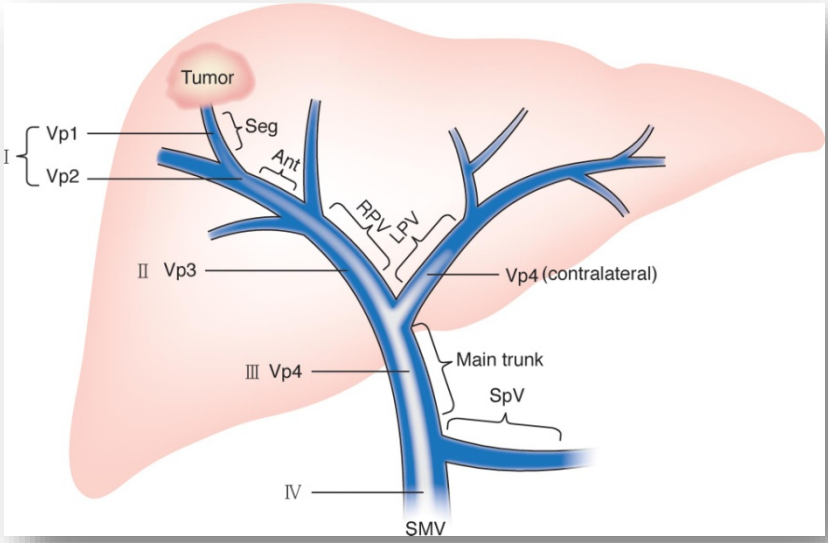


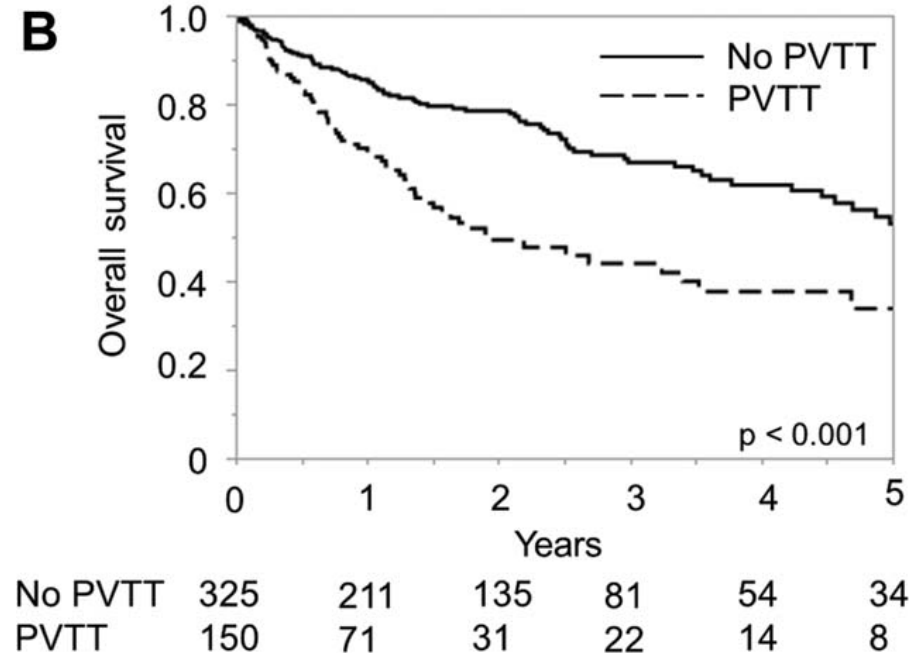
EASL HCC Committee, J Hepatology 2018

Survival advantage of LR for PVTT: East

HEPATOLOGY
HEPATOLOGY, VOL. 66, NO. 2, 2017
HEPATOBILIARY MALIGNANCIES

Liver Resection for Hepatocellular Carcinoma Associated With Hepatic Vein Invasion: A Japanese Nationwide Survey



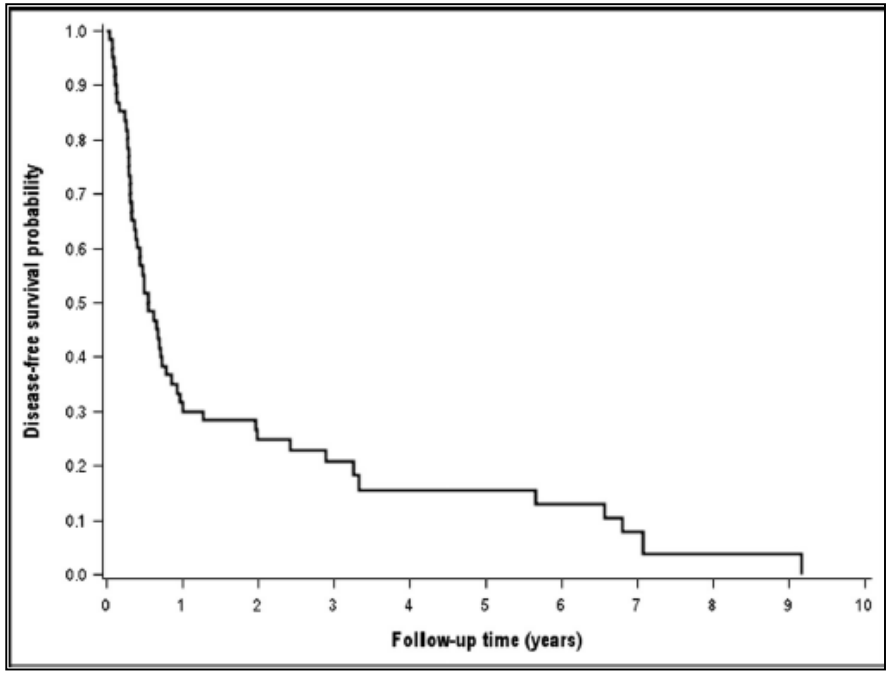


Kokudo T, Hepatol 2017

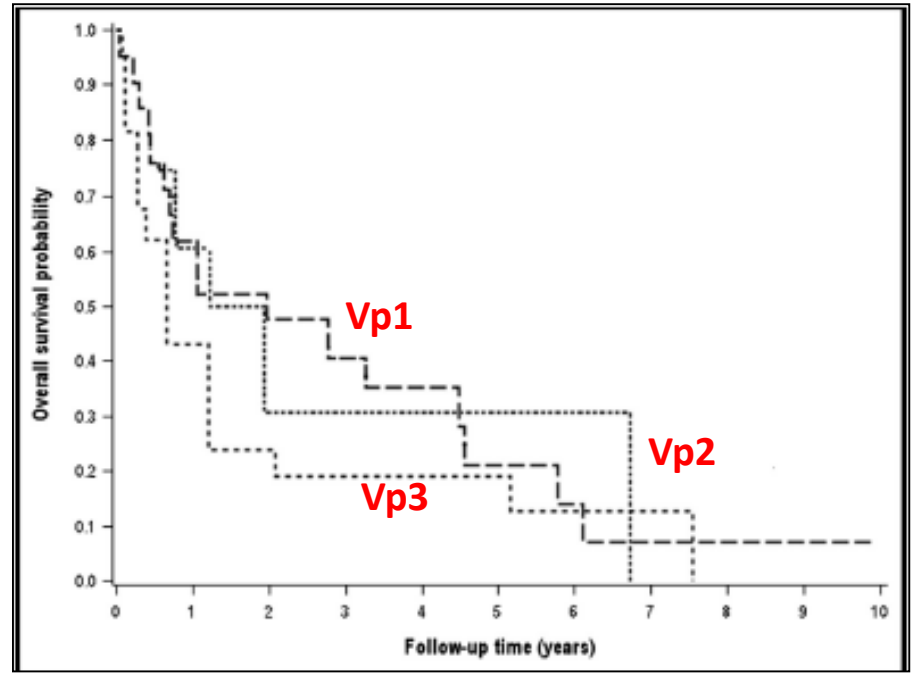
Survival advantage of LR for PVTT: West

62 patients who underwent LR and thrombectomy for HCC

Overall,1, 3, and 5-year survival rates were 53.3%, 30.1%, and 20%, and disease-free survival rates were 31.7%, 20.8%, and 15.6%, respectively



Disease-free survival rates in patients who underwent liver resection with thrombectomy with curative intent for HCC with MVI



Survival rates after thrombectomy for portal vascular tumor thrombus, classified as:

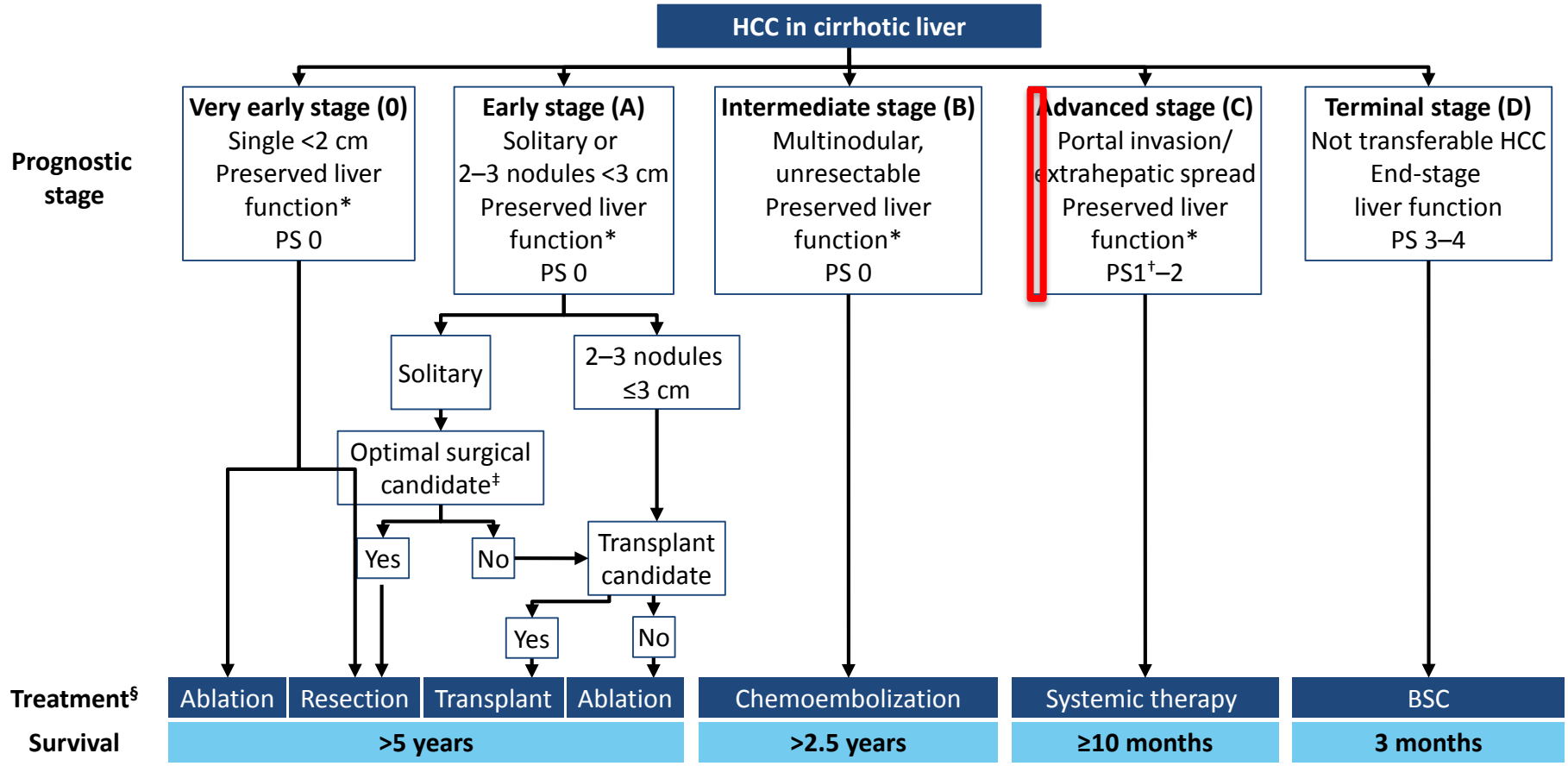
Vp1: tumor thrombus in peripheral portal vein of the third or lower order branch

Vp2: tumor thrombus in the second branch

Vp3: tumor thrombus in the first portal branch or portal vein trunk

Pesi B et al; Am J Surg 2015

Surgery for PVTT patients = advanced



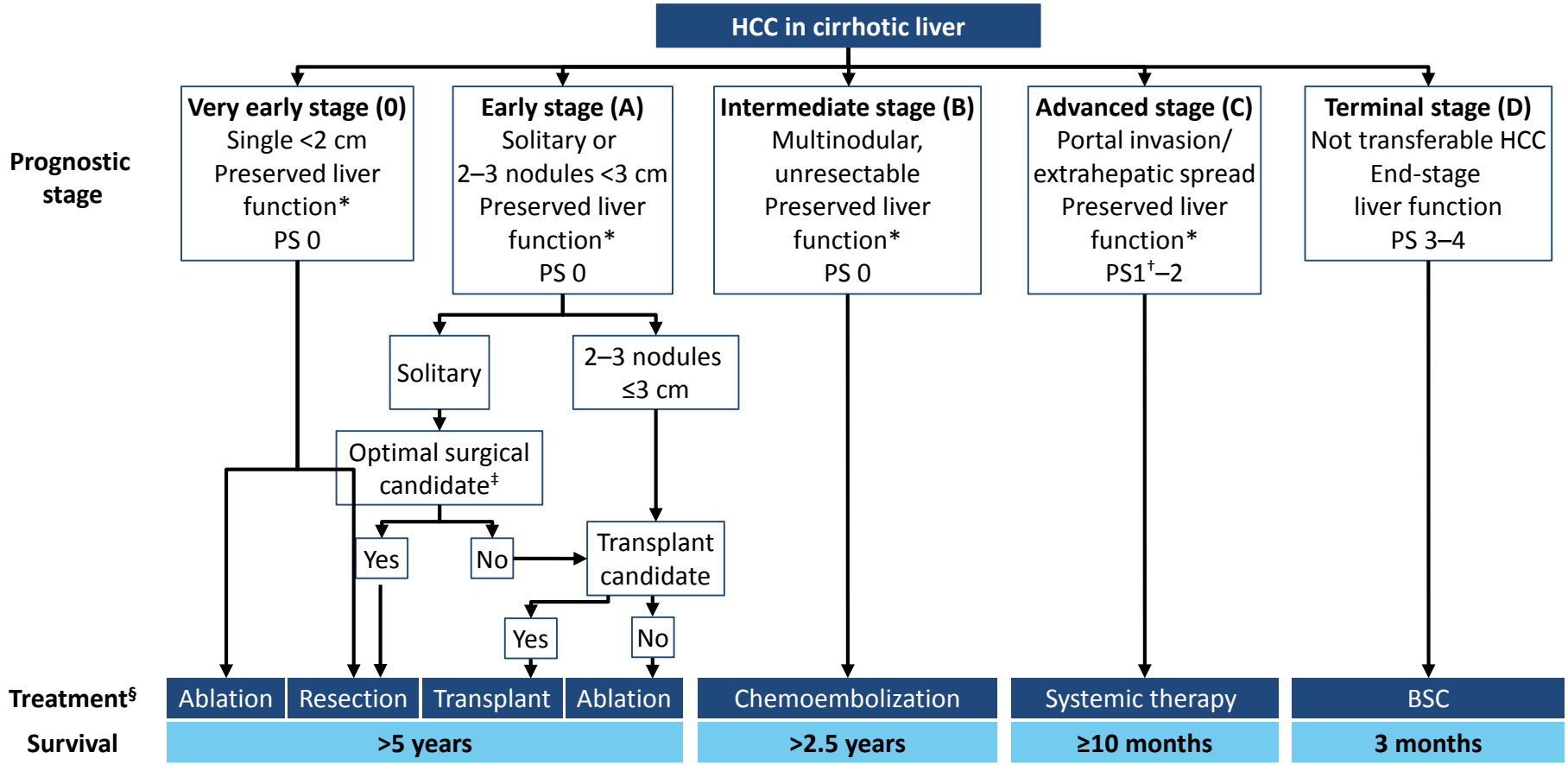
No prospective comparison of LR vs. systemic treatments or radioembolization has ever been reported…Therefore, LR can only be considered for PV1/2 extension of HCC, and only then as an option to be tested within research settings

and not to be considered a standard of practice

EASL HCC Committee, J Hepatology 2018

Applicability: SIRT (TARE)

TARE is not contemplated in guidelines



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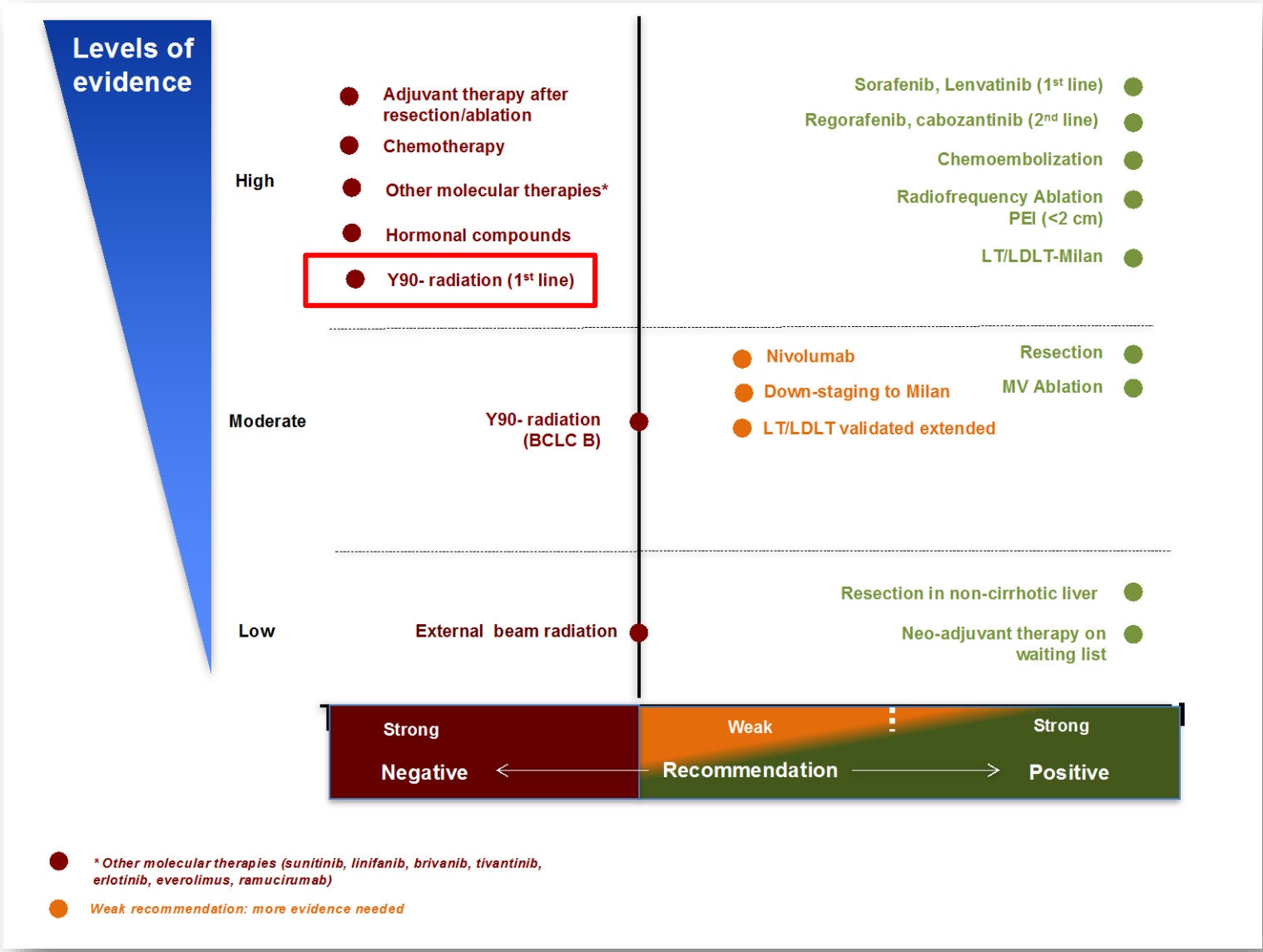
EASL HCC GUIDELINES 2018: the place for TARE



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TARE in the clinical practical guidelines

SIRT vs. sorafenib

One of the most common indications of SIRT is treatment of patients with locally advanced HCC. Two RCTs comparing efficacy and safety in patients treated with SIRT *vs.* sorafenib have completed patient enrolment and have been presented.[556,557] In both studies, designed for superiority of SIRT, the primary endpoint was not reached as no statistically significant differences in OS were observed in intention-to-treat or per-protocol populations. In both studies, tumour response rate was significantly higher with SIRT, although this finding did not translate into longer survival. In both trials, the applicability of Y-90 was limited to 72–77% of patients because of treatment contraindications. In the SIRveNIB trial,[557] progression-free survival and time to progression were significantly higher in the SIRT group than in the sorafenib group in the treated population. In the SARAH trial,[556] the total and median number of treatment-related adverse events per patient were twice as frequent with sorafenib *vs.* SIRT including Grade ≥3 treatment-related adverse events. However, the course of the adverse event (rate of remission in the two arms) was not reported. A head-to-head RCT of SIRT *vs.* sorafenib is ongoing, and the added value of sorafenib in patients treated with SIRT is being evaluated in another RCT (SORAMIC trial). Another phase III clinical trial (STOP-HCC) evaluating yttrium-90 trans-arterial radioembolization (TheraSphere®) prior to sorafenib *vs.* Sorafenib alone in the treatment of patients with unresectable HCC is ongoing. At present, the survival benefit of SIRT compared to sorafenib in advanced HCC is still not proven, and its use either alone or in combination with systemic therapy should only be adopted after multidisciplinary board discussion.

Clinical Practice Guidelines

At present, the survival benefit of SIRT compared to sorafenib in advanced HCC is still not proven, and its use either alone or in combination with systemic therapy should only be adopted after multidisciplinary board discussion

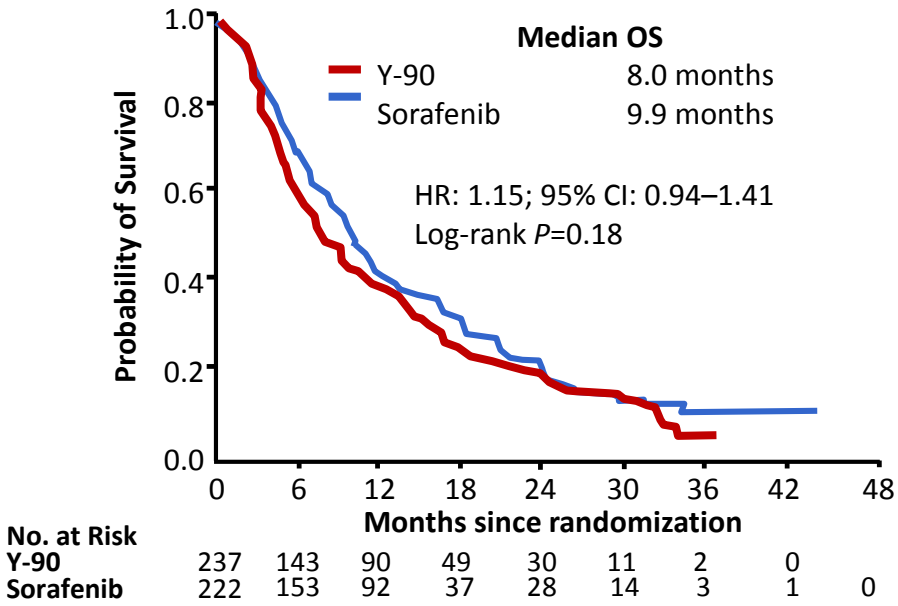
STUDY CONCEPT

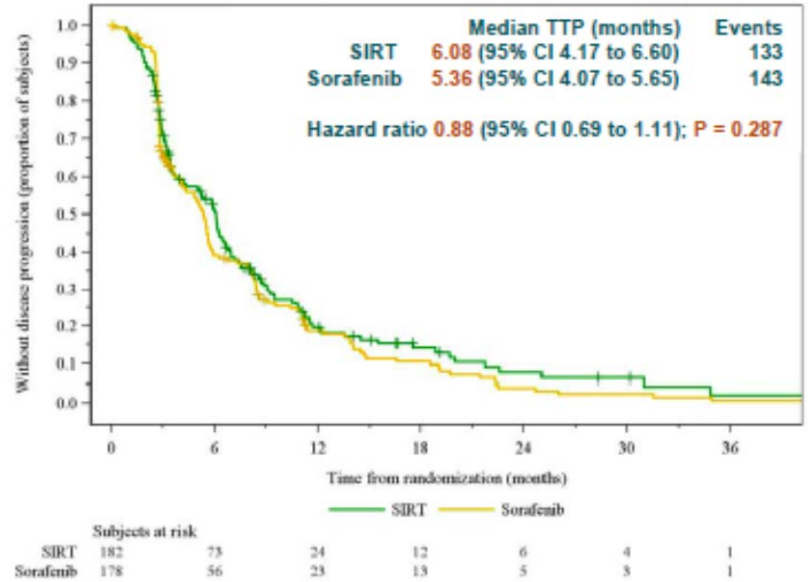
	SARAH	SIRVENIB
Survival comparison	10.7 mos	9.35 mos
Survival advantage	15.0 mos	14.0 mos
HR	0.67	0.71
Power	80%	90%
Pts enrolled	459	360
Primary endpoint	OS	
Secondary endpoints	RR, toxicity and QOL, PFS	

Vilgrain V, Lancet Oncology 2017

Gandhi M, BMC 2016 and data @ ASCO GI 2017

STUDY RESULTS





SARAH

- no difference in OS between RE and sorafenib
- RR: 19% SIRT and 11.6% sorafenib
- fewer G3 side effects with SIRT (40.7%) vs sorafenib (63%)

Vilgrain V, Lancet Oncology 2017

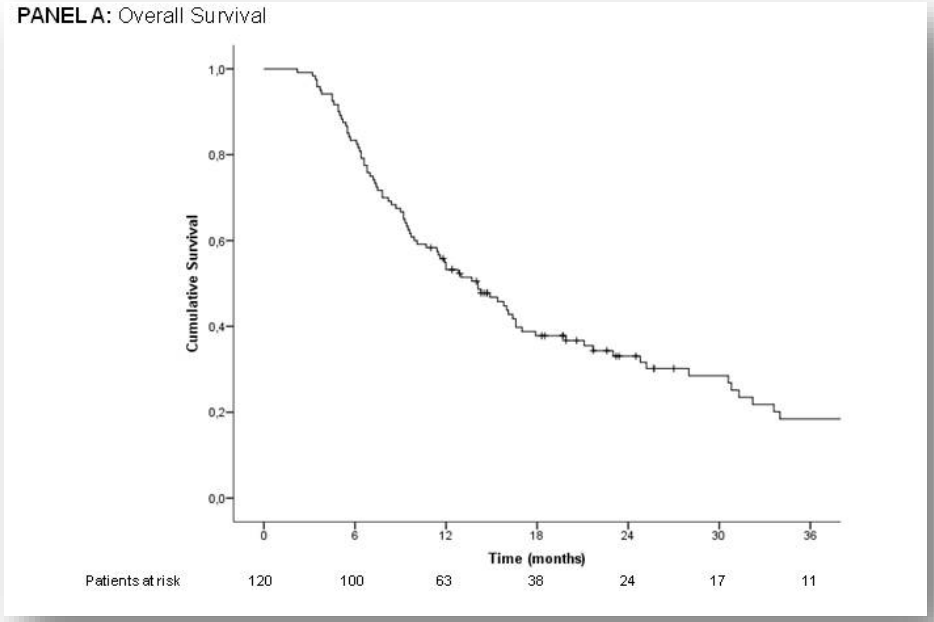
SIRVENIB

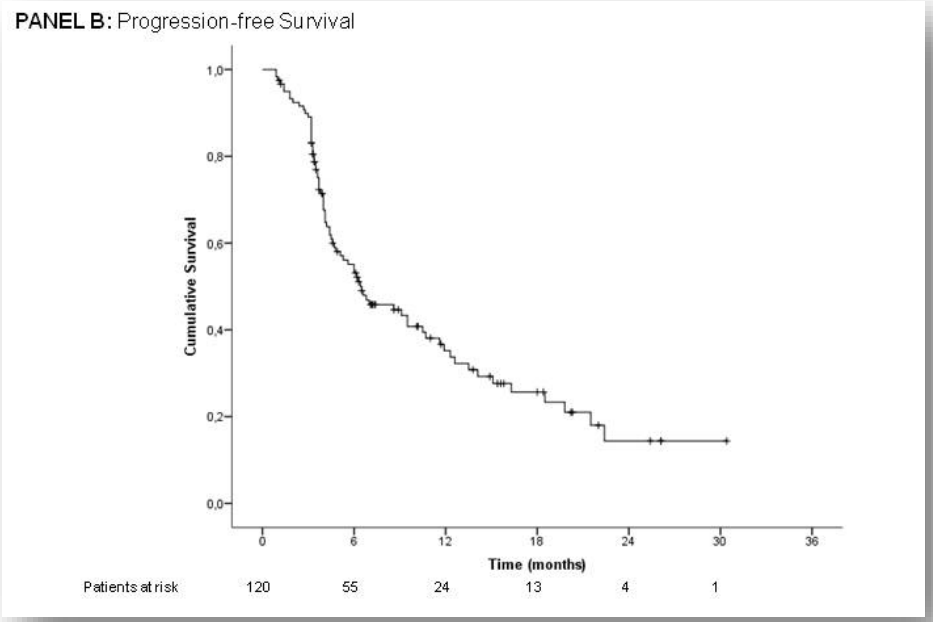
- the study did not meet the primary end point
- RR: 16.5% SIRT and 11.7% sorafenib
- fewer G3 side effects with SIRT (27.7%) vs sorafenib (50.6%)

Gandhi M, BMC 2016 and data @ ASCO GI 2017

TARE survival outcome according to prognostic factors

PROGNOSTIC EFFECT OF YTTRIUM-90 RADIOEMBOLIZATION FOR HEPATOCELLULAR CARCINOMA WITH PORTAL VEIN INVASION





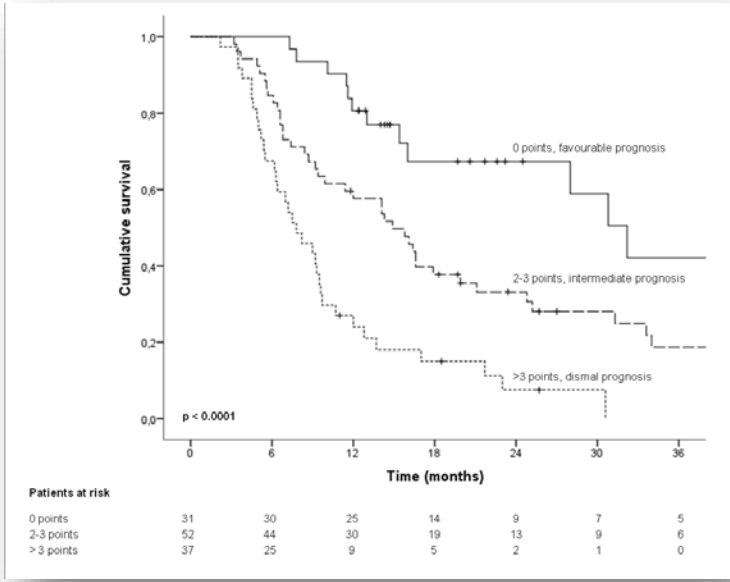
120 patients included

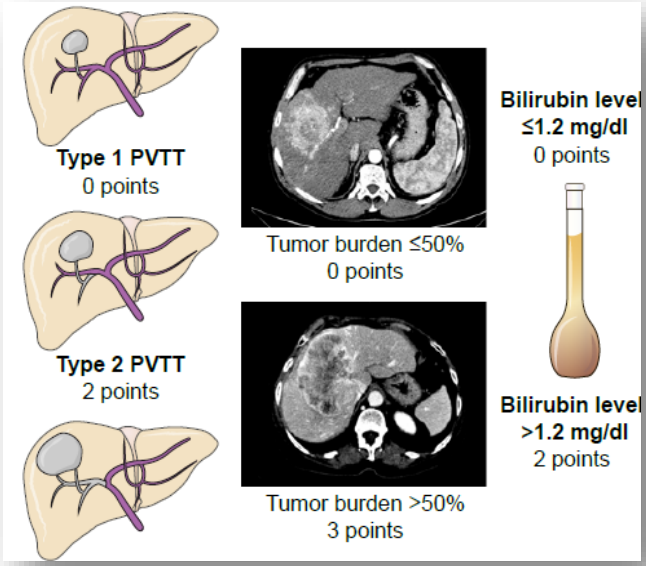
Median OS was 14.1 months (95%CI: 10.7-17.5) and median PFS was 6.5 months

Spreafico C and Mazzaferro V. J Hep, epub

Carefully selecting pts who benefit the most from SIRT

PROGNOSTIC EFFECT OF YTTRIUM-90 RADIOEMBOLIZATION FOR HEPATOCELLULAR CARCINOMA WITH PORTAL VEIN INVASION





3 prognostic categories built on bilirubin, extension of PVTT and tumor burden (only variables independently correlated with OS)

Spreafico C and Mazzaferro V. J Hep, epub

Carefully selecting pts who benefit the most from SIRT

PROGNOSTIC EFFECT OF YTTRIUM-90 RADIOEMBOLIZATION FOR HEPATOCELLULAR CARCINOMA WITH PORTAL VEIN INVASION

Category	Median OS, months (95% IC)	1-yr survival	3-yrs survival	Median PFS, months (95% IC)	HCC progression within 3 months	Liver decompensation within 3 months
0 points (31 pts): favourable prognosis	32.2 (25.9-38.5)	80.6%	42.1%	14.1 (6.9-21.3)	6.5%	3.2%
2-3 points (52 pts): intermediate prognosis	14.9 (10.6-19.2)	57.6%	18.7%	6.2 (4.2-8.2)	9.6%	9.6%
> 3 points (37 pts): dismal prognosis	7.8 (5.4-10.2)	24.0%	0%	4.1 (3.0-5.2)	16.9%	21.6%

OS, PFS and risk of liver decompensation significantly differed along the same prognostic categories

Spreafico C and Mazzaferro V. J Hep, epub

METHODOLOGICAL WEAKENESSES

1. End point
2. Inclusion criteria
3. Dose administration
4. Center selection and skills (sorafenib management, radiological and nuclear medicine skills)
5. Evaluation of AE profile

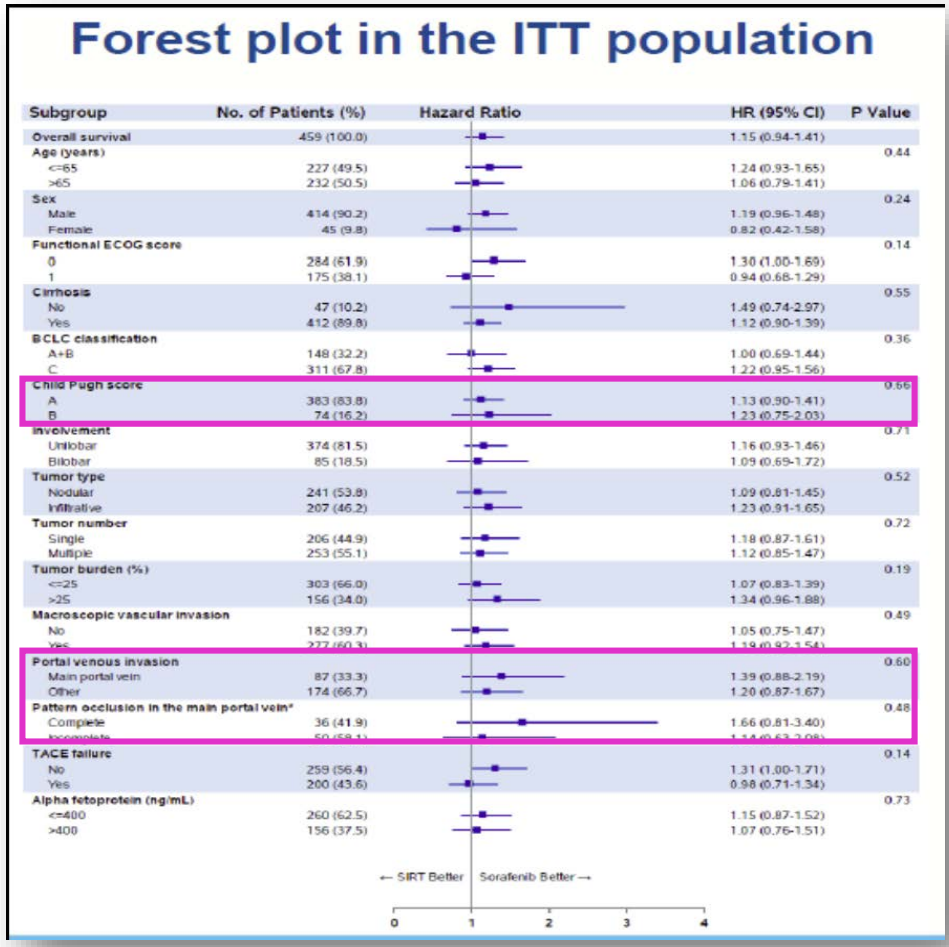
Superiority

Non-inferiority

Results have to be consistent with the study design

-30% patients with trunk (main) PVTT with a device that was initially contraindicated for PVT

- 20% patients Child B



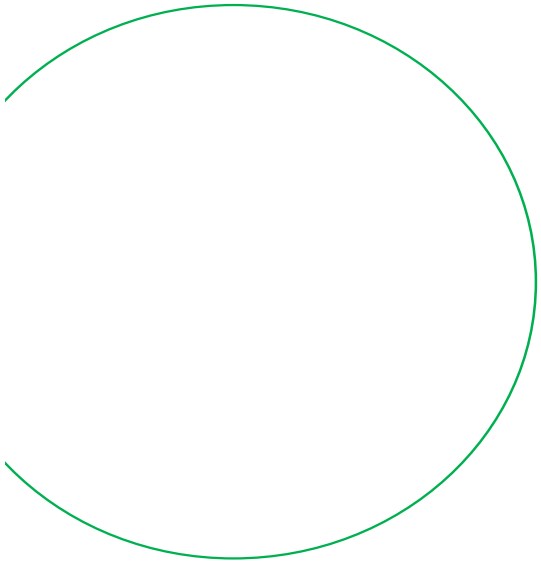
Two populations with a competitive risk of unsuccess (cirrhosis)

http://www.openbriefing.com/OB/Sirtex-Medical-Limited/2017/4/24/SARAH-Clinical-Study-Results-Investor-Presentation/2482.aspx

Vilgrain V, Lancet Oncology 2017

Vilgrain V, Lancet Oncology 2017

SARAH: methodological biases



www.openbriefing.com/OB/Sirtex-Medical-Limited/2017/4/24/SARAH-Clinical-Study-Results-Investor-Presentation/2482.aspx

SARAH: no dosimetric study (BSA method)

In previous studies studies (1-3), almost twice the amount of activity was administered with TheraSphere® compared to that used in the SARAH trial

	SARAH (n=190)	Mazzaferro (n=52) [8]	Garin (n=85) [9]	Biederman (n=69) [10]
BCLC A	3.8%	0	7%	76.2% (Child-Pugh A)
BCLC B	27.8%	32.7%	56.4%	23.8% (Child-Pugh B)
BCLC C	68.4%	67.3%	36.4%	N/A
Mean Activity/Prescribed Dose	1.4 GBq	2.6 GBq or 101 Gy	2.6 GBq or 117 Gy	2.6 GBq and Gy not published
Median Overall Survival	9.9 months	15 months Non-PVT: 18 months PVT: 13 months	18.7 months Non-PVT: 24 months PVT: 12 months	PVT: 9.4 months

WHAT ADVERSE EVENTS WERE MONITORED?

Table 3. Incidence of Drug-Related Adverse Events (Safety Population).*

Adverse Event	Sorafenib (N=297)			Placebo (N=302)			P Value	
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3 or 4
	percent							
Overall incidence	80			52				
Constitutional symptoms								
Fatigue	22	3	1	16	3	<1	0.07	1.00
Weight loss	9	2	0	1	0	0	<0.001	0.03
Dermatologic events								
Alopecia	14	0	0	2	0	0	<0.001	NA
Dry skin	8	0	0	4	0	0	0.04	NA
Hand–foot skin reaction	21	8	0	3	<1	0	<0.001	<0.001
Pruritus	8	0	0	7	<1	0	0.65	1.0
Rash or desquamation	16	1	0	11	0	0	0.12	0.12
Other	5	1	0	1	0	0	<0.001	0.12
Gastrointestinal events								
Anorexia	14	<1	0	3	1	0	<0.001	1.00
Diarrhea	39	8	0	11	2	0	<0.001	<0.001
Nausea	11	<1	0	8	1	0	0.16	0.62
Vomiting	5	1	0	3	1	0	0.14	0.68
Voice changes	6	0	0	1	0	0	<0.001	NA
Hypertension	5	2	0	2	1	0	0.05	0.28
Liver dysfunction	<1	<1	0	0	0	0	0.50	0.50
Abdominal pain not otherwise specified	8	2	0	3	1	0	0.007	0.17
Bleeding	7	1	0	4	1	<1	0.07	1.00

- Postradioembolization syndrome, **20% to 55%**
- Radio-induced liver disease, **4 % to 20%**
- Biliary complications, **< 10%**
- Gastrointestinal complications, **< 5%**
- Liver decompensation, **10.8% at 3 months and 31.6% at 6 months**

Llovet JM, NEJM 2008
Mazzaferro V, Hepatology 2013

WEAKNESSES IN ADVERSE EVENTS REPORTING

Treatment-related AEs	SIRT	Sorafenib
All	1297	2837
⩾ Grade 3	230	411

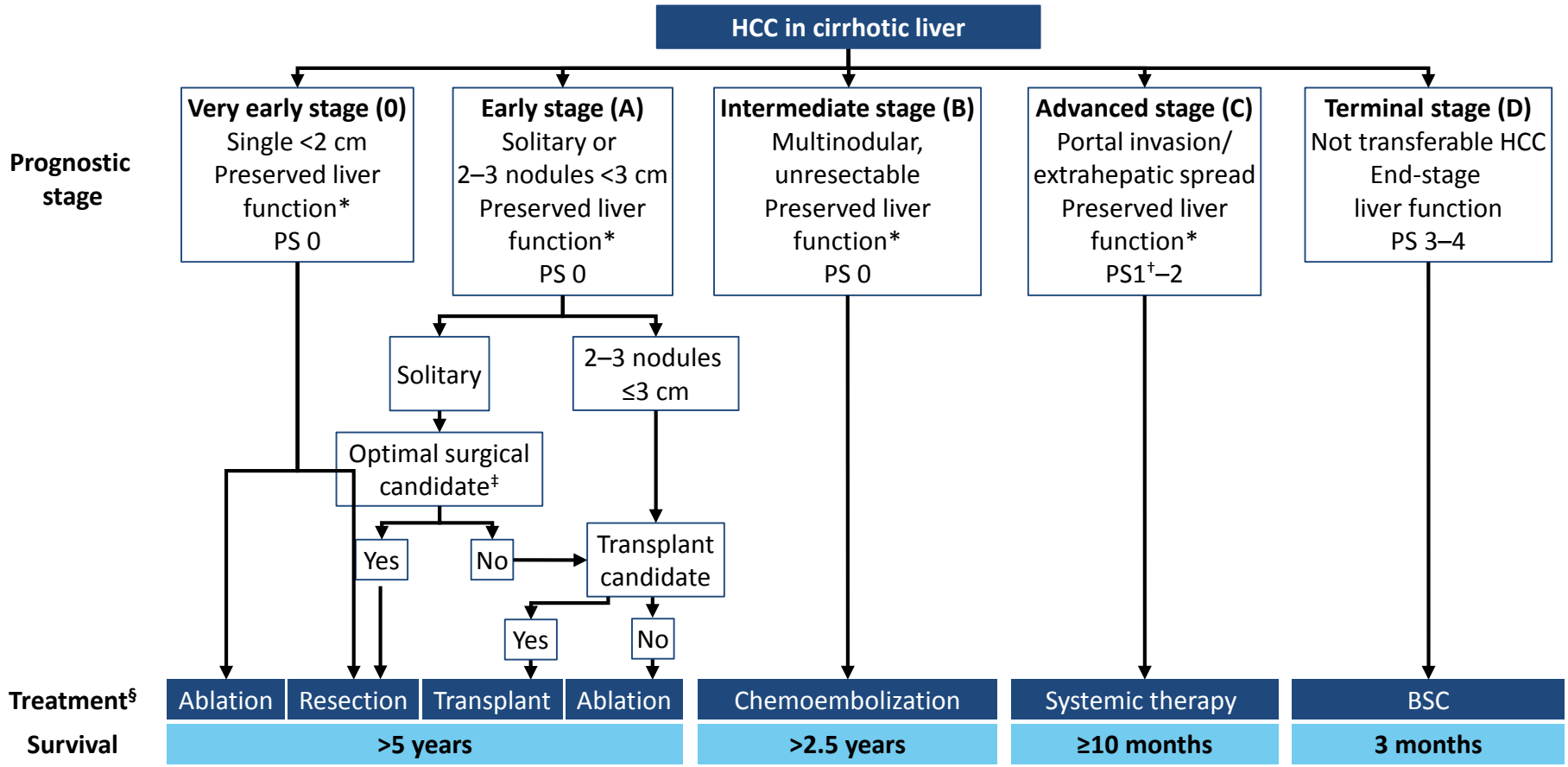
TREATMENT RELATED G3 AES WERE LOWER IN THE SIRT GROUP

Treatment-related AES	SIRT Nb of patients (⩾G 3)	Sorafenib Nb of patients (⩾G 3)
Fatigue	94 (20)	140 (41)
Weight loss	14 (0)	46 (6)
Alopecia	0 (0)	35 (0)
Hand foot skin reaction	1(1)	45 (12)
Pruritus	7 (1)	19 (1)
Diarrhea	29 (3)	146 (30)
Abdominal pain	46 (6)	63 (14)
Hypertension	6 (0)	28 (5)

230/1297= 17.7%
411/2837= 14.5%

Vilgrain V, Lancet Oncology 2017

Applicability of systemic treatments



EASL HCC Committee, J Hepatology 2018

Clinical Practice Guidelines

Systemic therapies

Recommendations

- Sorafenib is the standard first-line systemic therapy for HCC. It is indicated for patients with well-preserved liver function (Child-Pugh A) and with advanced tumours (BCLC–C) or earlier stage tumours progressing upon or unsuitable for loco-regional therapies (**evidence high; recommendation strong**).
- Lenvatinib has been shown to be non-inferior to sorafenib and is also recommended in first-line therapy for HCC given its approval. It is indicated for patients with well-preserved liver function (Child-Pugh A class), good performance status and with advanced tumours – BCLC-C without main portal vein invasion – or those tumours progressing upon or unsuitable for loco-regional therapies (**evidence high; recommendation strong**).
- There are no clinical or molecular biomarkers established to predict response to first or second-line systemic treatments (**evidence moderate**).
- Regorafenib is recommended as second-line treatment for patients tolerating and progressing on sorafenib and with well-preserved liver function (Child-Pugh A class) and good performance status (**evidence high; recommendation strong**). Recently, Cabozantinib has

Sorafenib
safe applicability in selected Child Pugh B

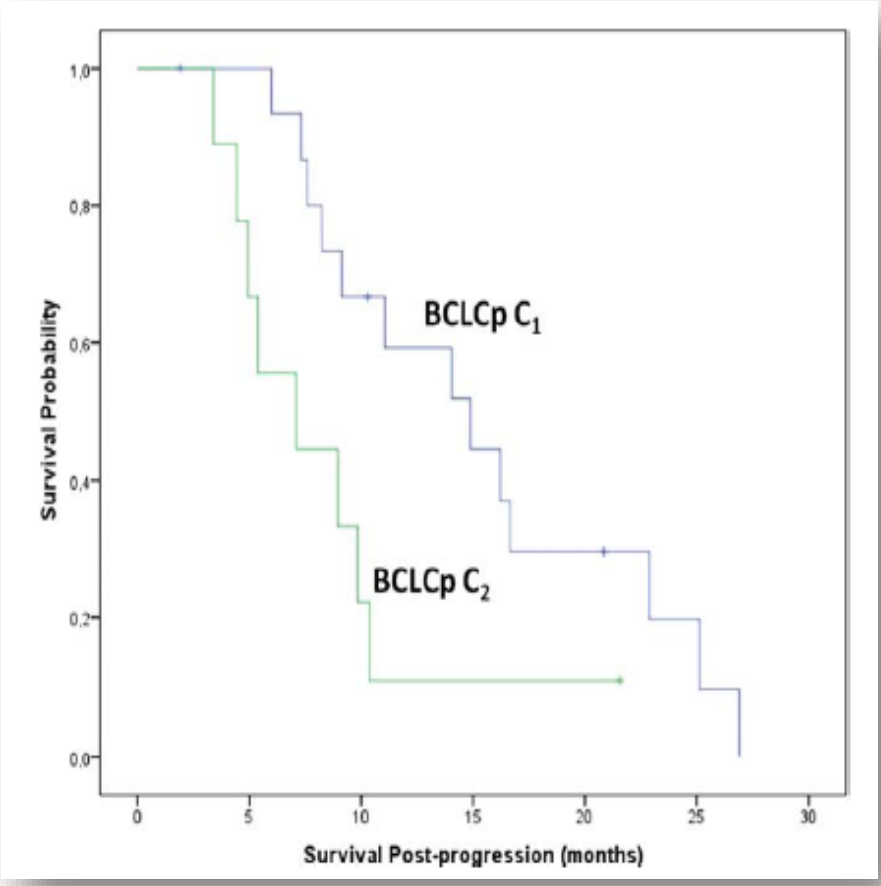
Lenvatinib
difficult applicability of a drug with advanced criteria exclusion, no second line treatment and higher reported serious AE

Regorafenib
recommended at whatever progression?
Clinical judgment of tumor progression based on availabilty of second line

EASL HCC Committee, J Hepatology 2018

mRECIST (radiological progression) or pattern of progression

BCLCp classification



Patients who progress to or within a C stage:

- BCLCp-C_1: with progression due to growth of existing nodules or new intrahepatic sites (14.9 months)
- BCLCp-C_2: with progression due to new extrahepatic lesion and/or vascular invasion (7.1 months)

BCLC, Barcelona Clinic Liver Cancer; BCLCp, BCLC upon progression.

Reig M et al. Hepatology 2013;58:2023–31.

mRECIST as they were intended to be

RECIST — learning from the past to build the future

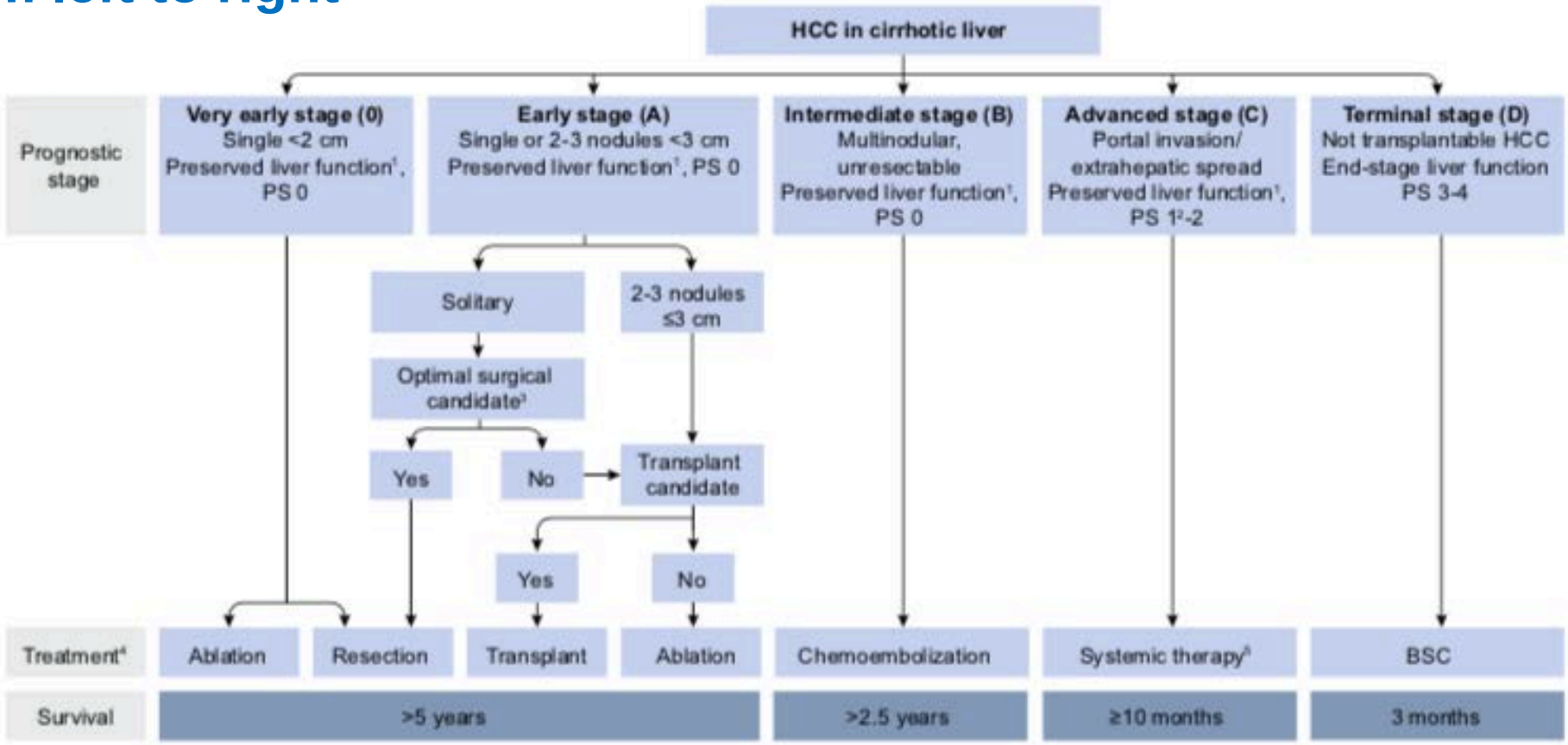
Saskia Litière, Sandra Collette, Elisabeth G. E. de Vries, Lesley Seymour and Jan Bogaerts

Indeed, RECIST was meant as a tool for clinical trials, not to replace common-sense clinical decision-making. Both in clinical trials and in clinical practice, treatment protocols can consider treatment beyond (RECIST) progression, if it provides clinical benefit to a particular patient.

Litière et al. Nat Rev Clin Oncol 2017;14:187-192

Applicability: stage migration

from left to right



The **stage migration strategy** is a therapeutic choice by which a treatment theoretically recommended for a particular stage is selected as best 1st line treatment option for an earlier stage

EASL HCC Committee, J Hepatology 2018

from right to left

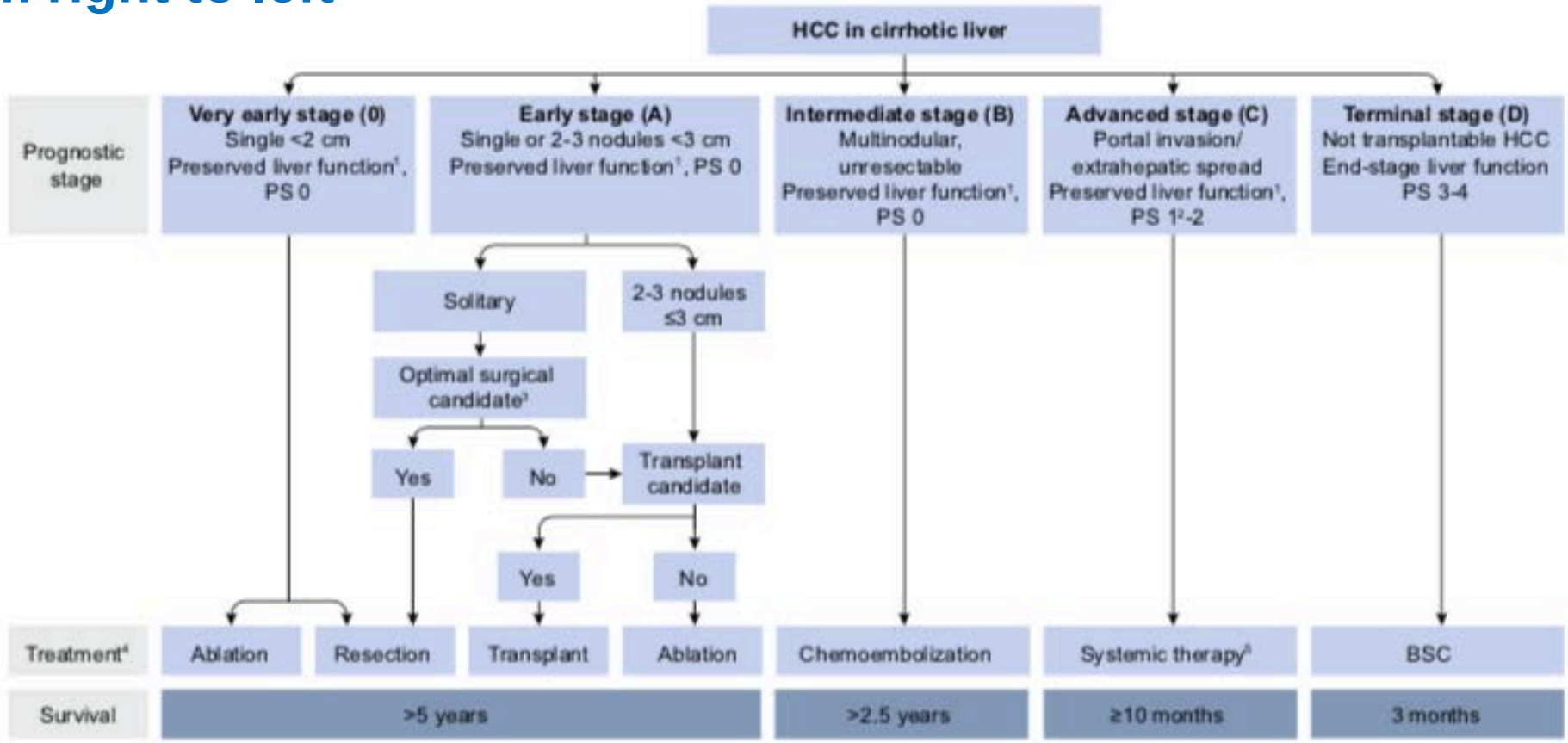
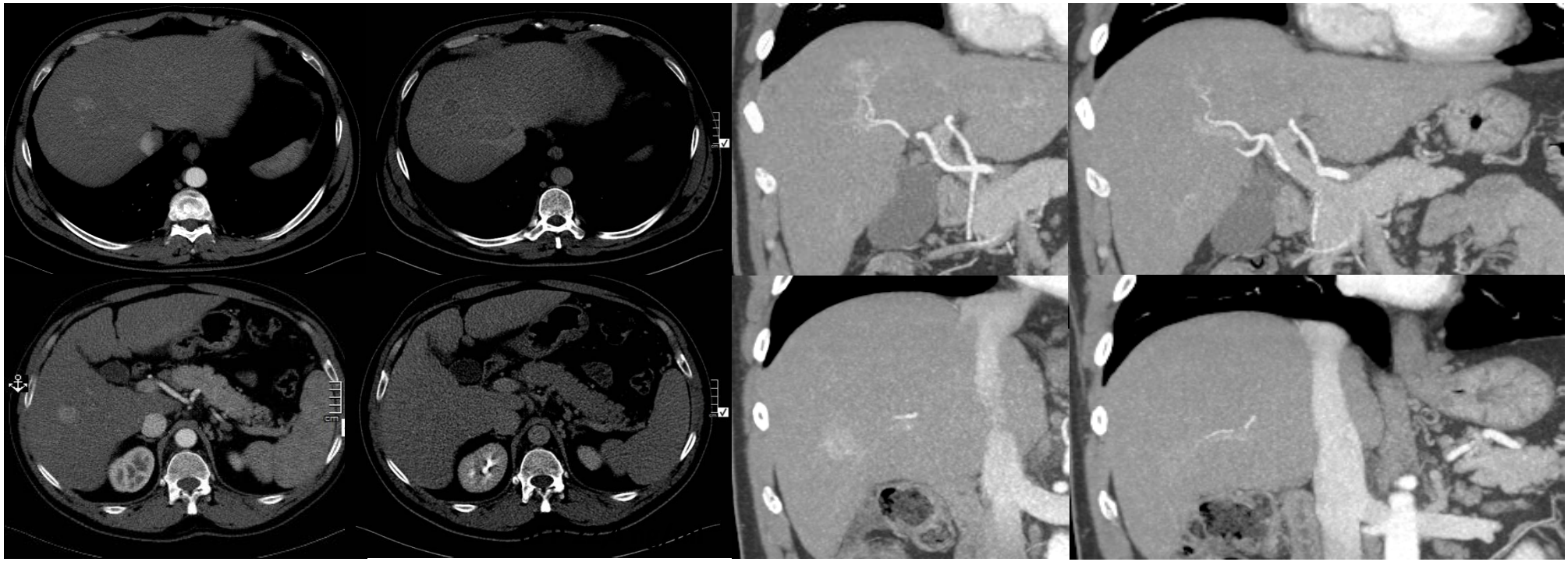


Fig. 3. Modified BCLC staging system and treatment strategy. [1]"**Preserved liver function**" refers to Child-Pugh A without any ascites, considered conditions to obtain optimal outcomes. This prerequisite applies to all treatment options apart from transplantation, that is instead addressed primarily to patients with decompensated or end-stage liver function. [2]**PS 1** refers to tumour induced (as per physician opinion) modification of performance capacity. [3]**Optimal surgical candidacy** is based on a multiparametric evaluation including compensated Child-Pugh class A liver function with MELD score <10, to be matched with grade of portal hypertension, acceptable amount of remaining parenchyma and possibility to adopt a laparoscopic/minimally invasive approach. The combination of the previous factors should lead to an expected perioperative mortality <3% and morbidity <20% including a postsurgical severe liver failure incidence <5%. [4]The **stage migration strategy** is a therapeutic choice by which a treatment theoretically recommended for a different stage is selected as best 1st line treatment option. Usually it is applied with a left to right direction in the scheme (*i.e.* offering the effective treatment option recommended for the subsequent more advanced tumour stage rather than that forecasted for that specific stage). This occurs when patients are not suitable for their first line therapy. However, in highly selected patients, with parameters close to the thresholds defining the previous stage, a right to left migration strategy (*i.e.* a therapy recommended for earlier stages) could be anyhow the best opportunity, pending multidisciplinary decision. [5]As of 2017 sorafenib has been shown to be effective in first line,

SP ♂ 1959

Comorbidità	BPCO
2007	ambulatorio epatologia: epatopatia cronica HCV- (genotipo 1a) e potus-correlata proposta terapia antivirale (IFN+ribavirina), rifiutata
luglio 2012	dolori addominali → eco addome: 2 lesioni epatiche ambulatorio epatologia: fibroscan 15 Kpa, cirrosi Child A, HCV RNA>500000 UI,
luglio 2012	TC addome: HCC bifocale in S8 di 24 mm e S5-6 di 21 mm αFP 22.4 ng/ml



SP ♂ 1959

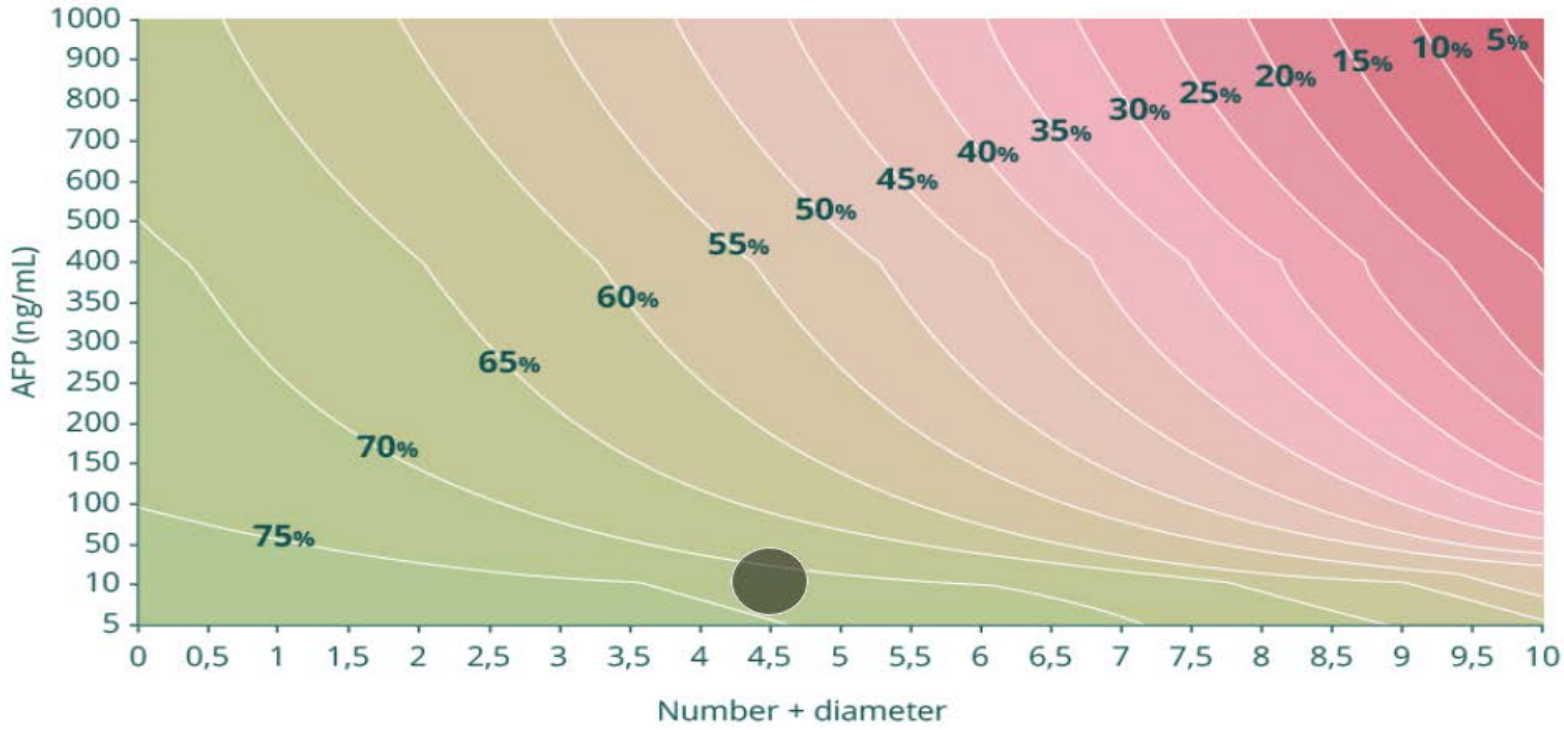
http://www.hcc-olt-metroticket.org/

Pre-operative radiology + alpha-fetoprotein

Size of the largest vital tumor	Number of vital nodules	AFP (ng/mL)
2.4 cm	2	22

5-year predicted survival after liver transplantation: 73.5%

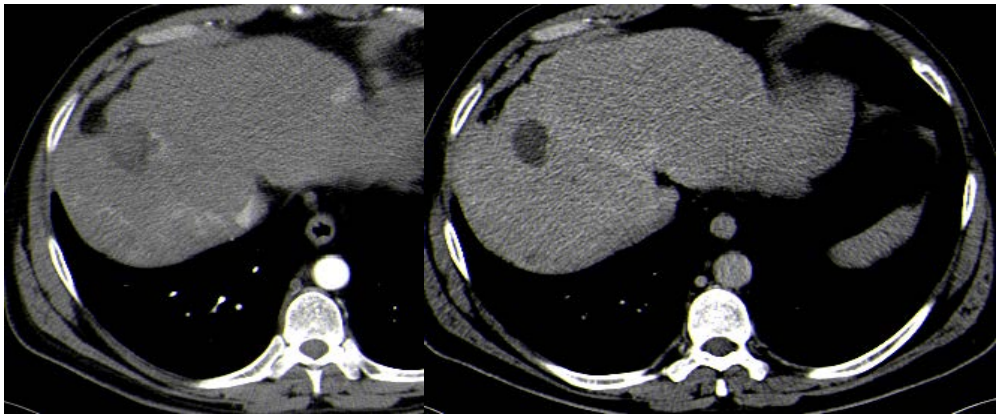
95% confidence interval: 72.7 - 74.3%

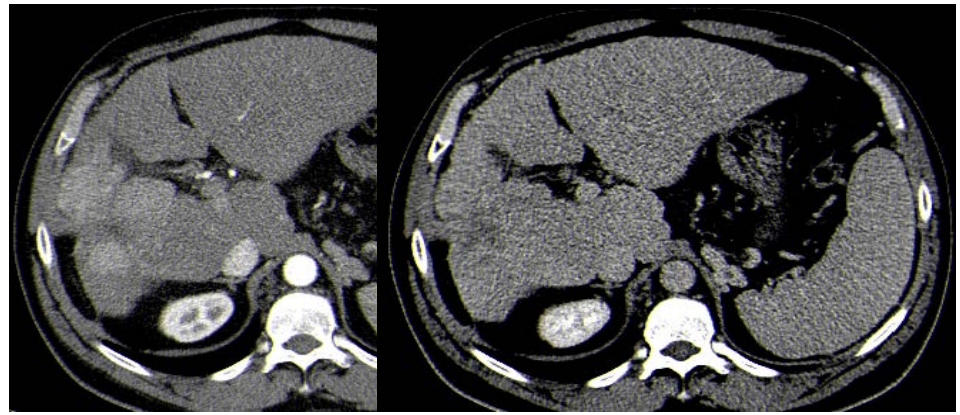


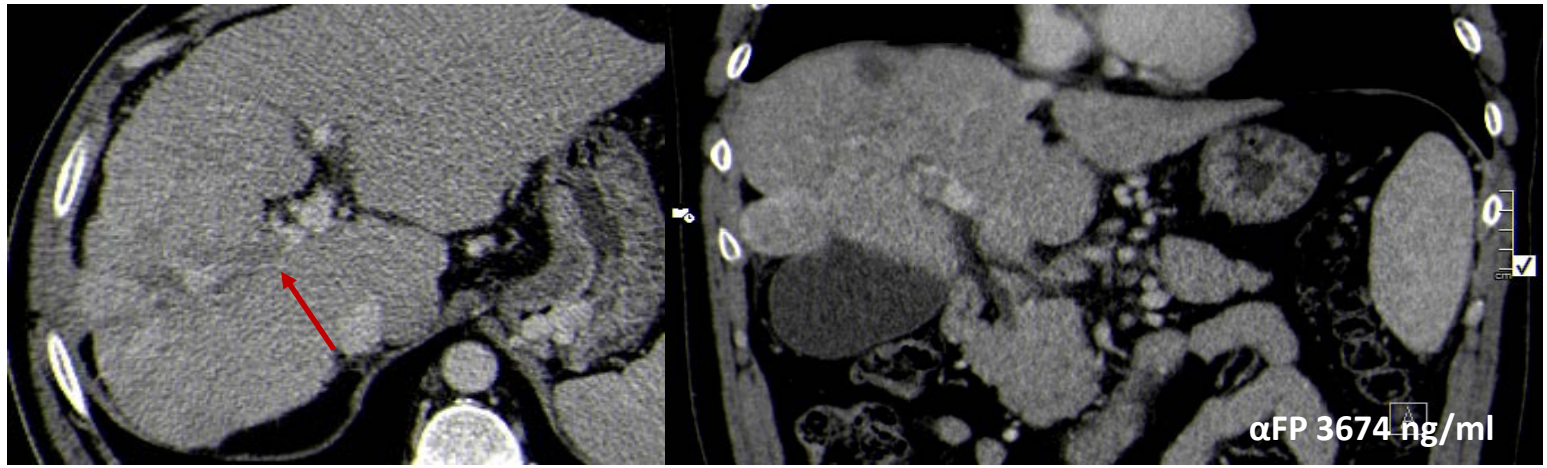
SP ♂ 1959: TACE, RFA SU RESISUO DI MALATTIA, RFA SU DUE NUOVI NODULI (COMPLICANZA SETTICA)

gennaio 2015

Ripresa multifocale di malattia con associata trombosi portale destra
(AFP da 22.5 a 3674 ng/mL)





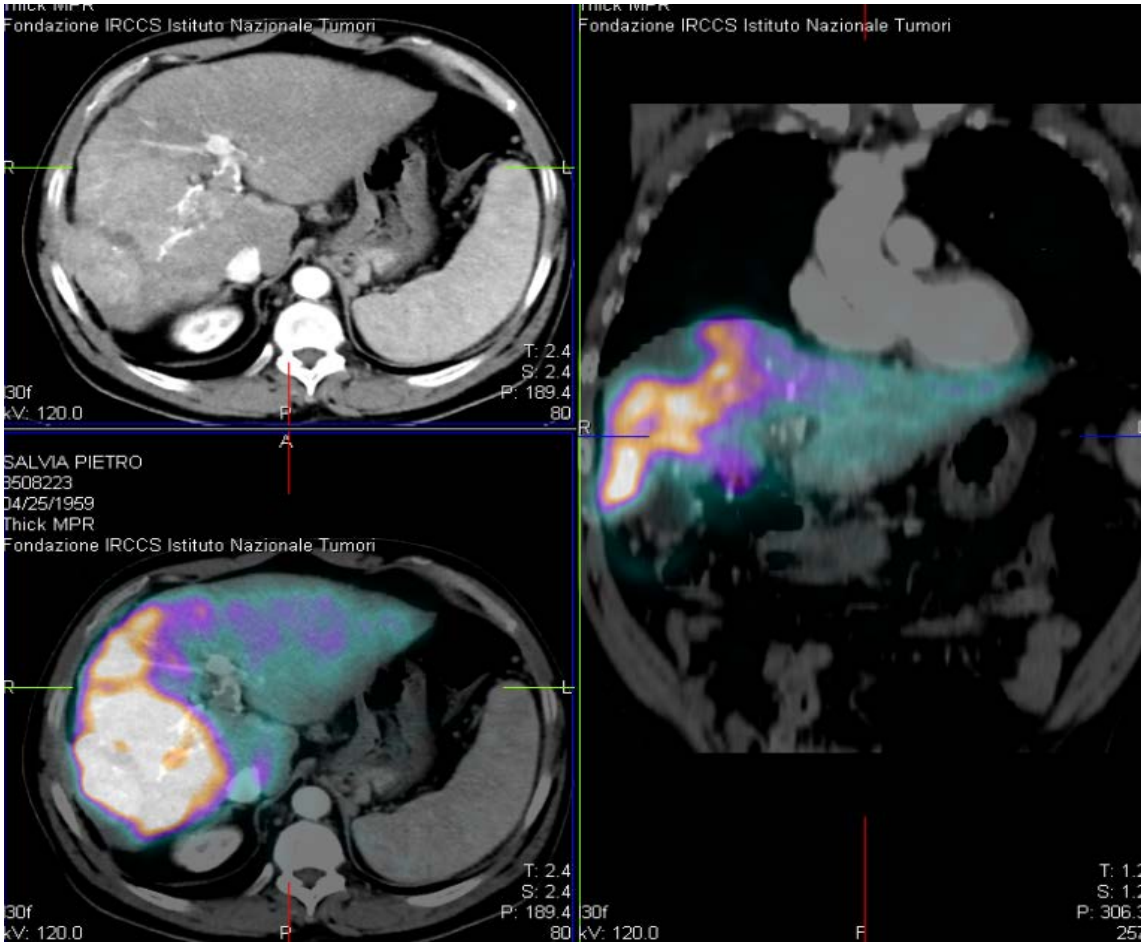


SP ♂ 1959

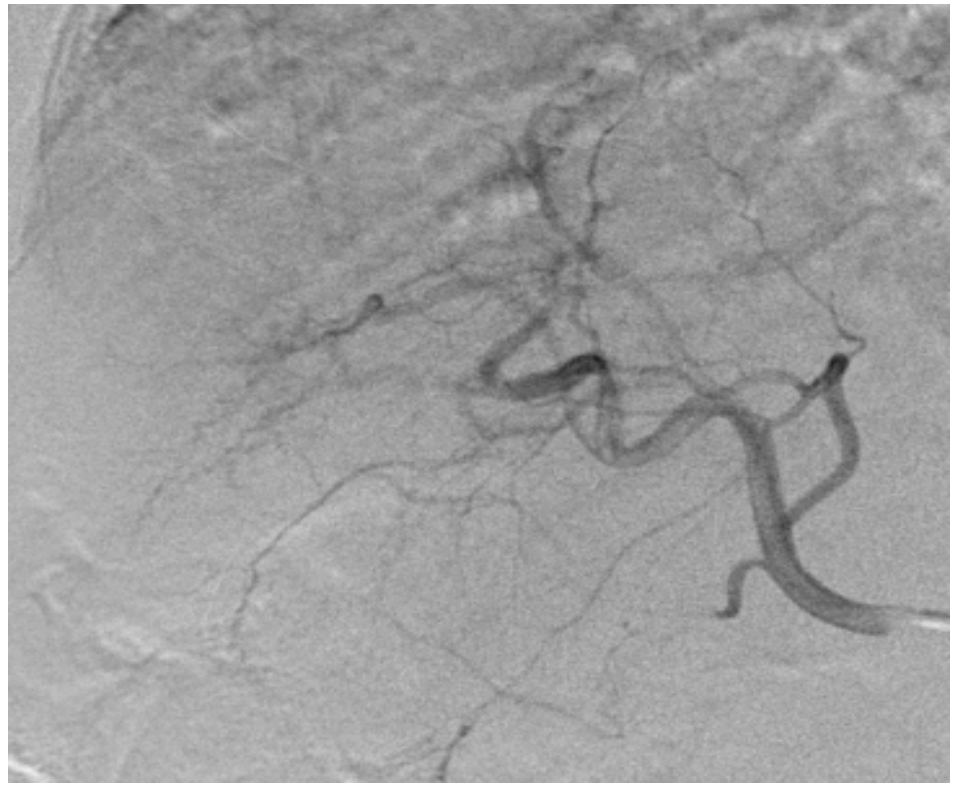
maggio 2015 inizio sorafenib, αFP 22356 ng/ml

maggio 2015 valutazione per TARE Istituto Nazionale dei Tumori

giugno 2015 angioscintigrafia



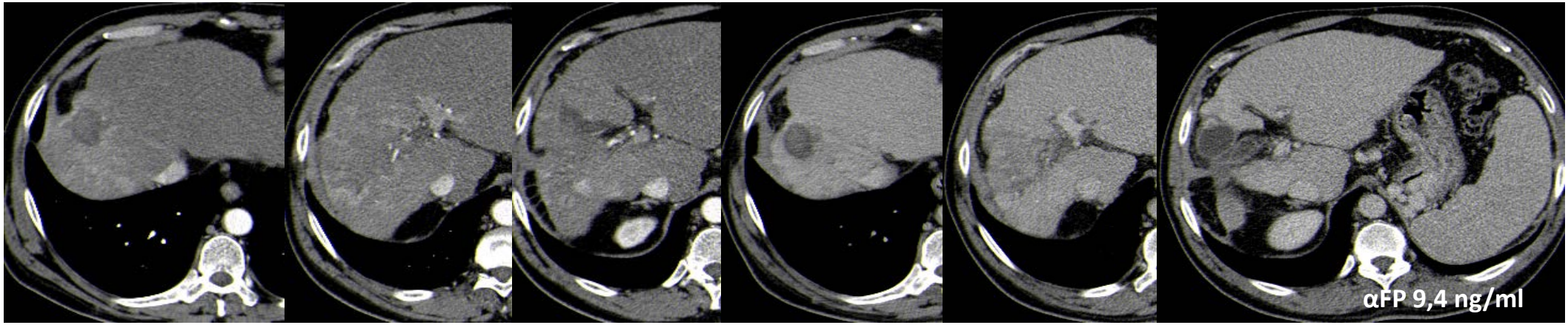
luglio 2015 TARE lobo destro



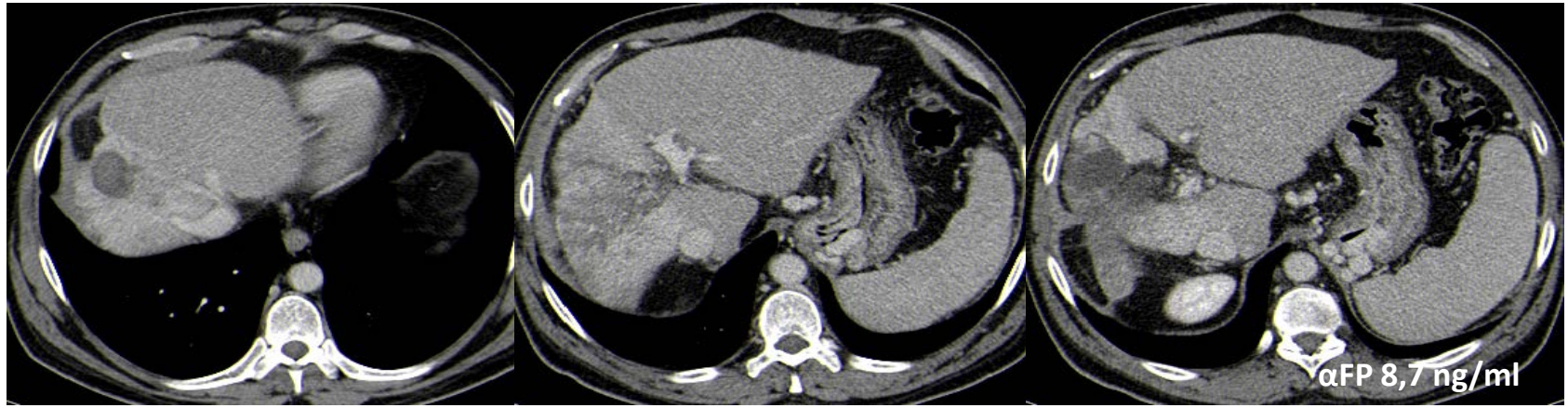
Prosegue Sorafenib 400 mg/die

SP ♂ 1959

settembre 2015 TC controllo a 2 mesi da TARE: risposta radiologica pressoché completa, atrofia del lobo epatico destro con persistente pervietà del ramo portale principale



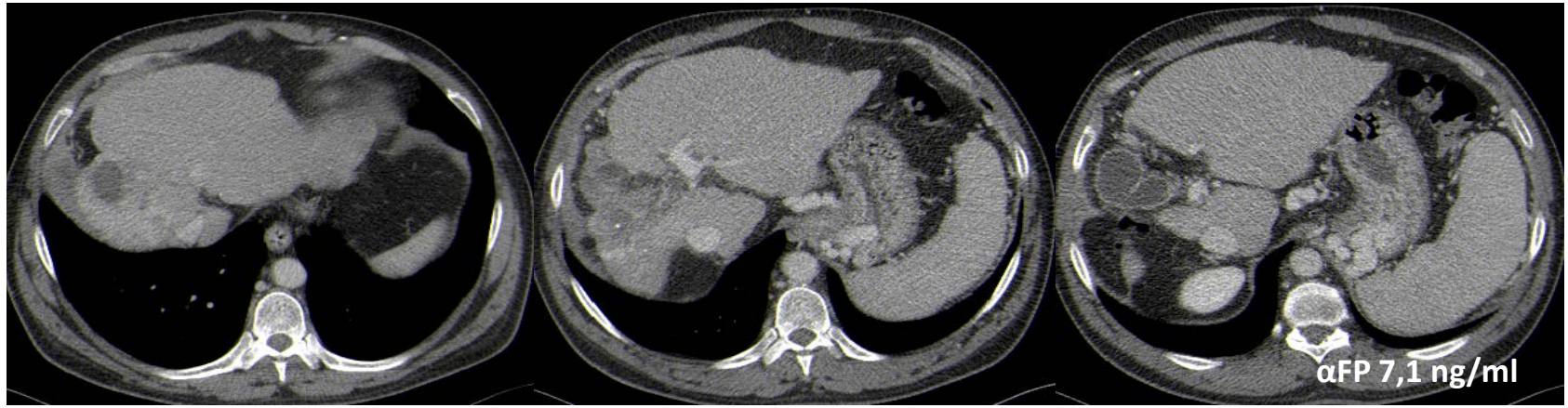
gennaio 2016 TC controllo a 6 mesi da TARE



marzo 2016 sospeso sorafenib, inizia terapia eradicante (ledipasvir, sofosbuvir)

SP ♂ 1959

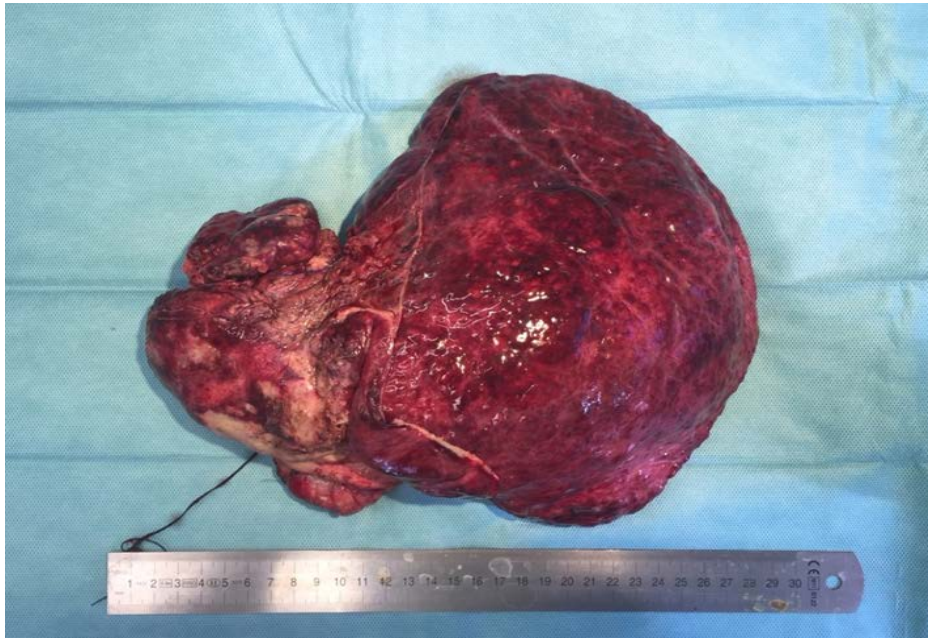
ottobre 2016 TC controllo a 15 mesi da TARE; SVR

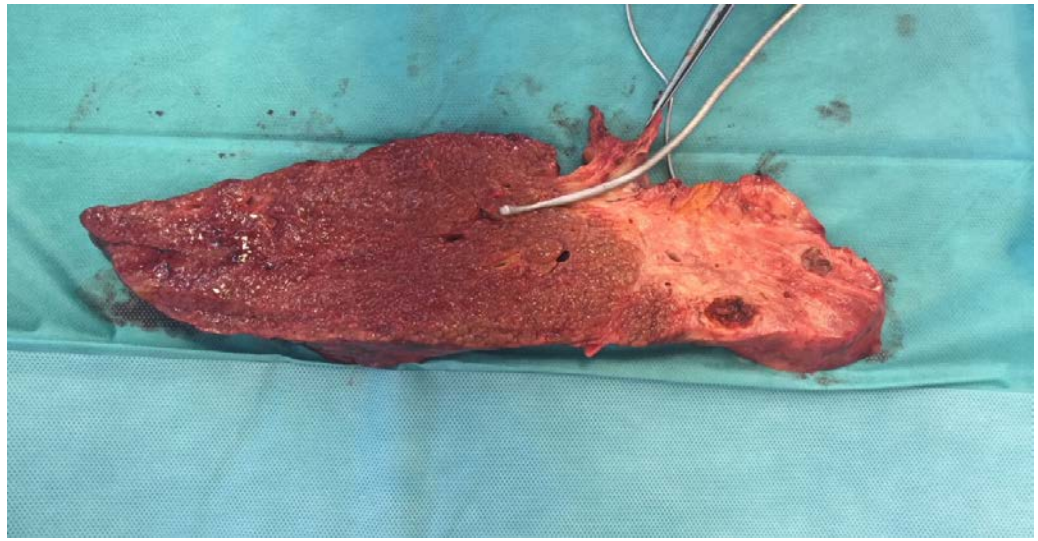


febbraio 2017 inserimento in lista trapianto, αFP 6,5 ng/ml

SP ♂ 1959

6 marzo 2017 trapianto di fegato

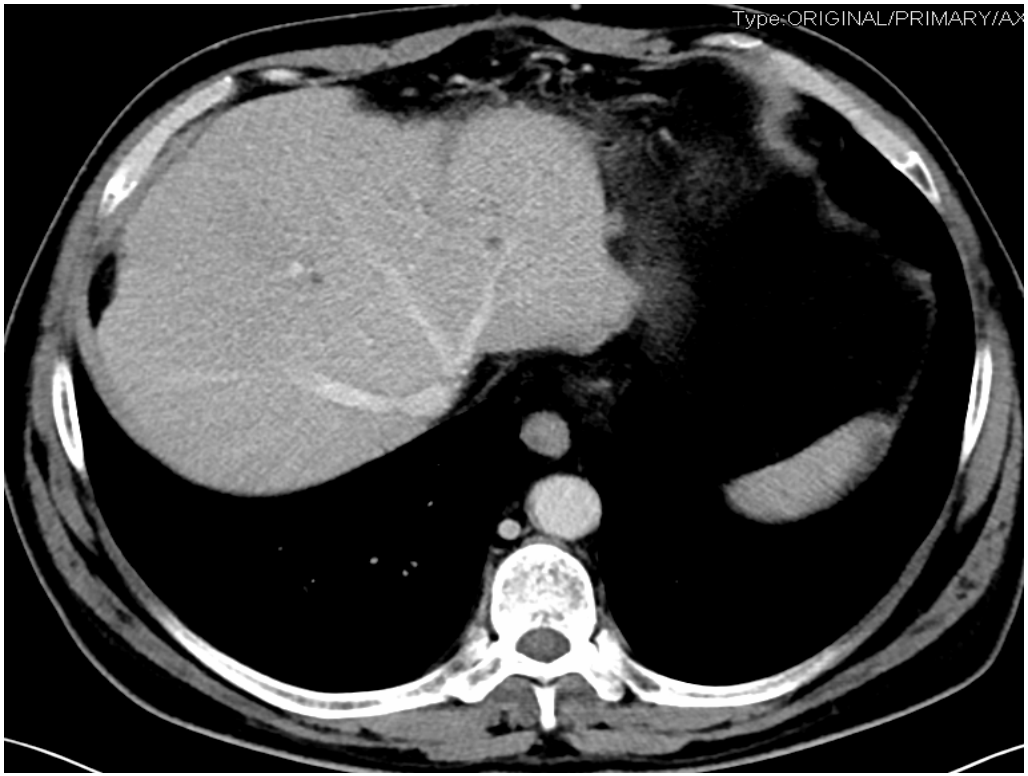


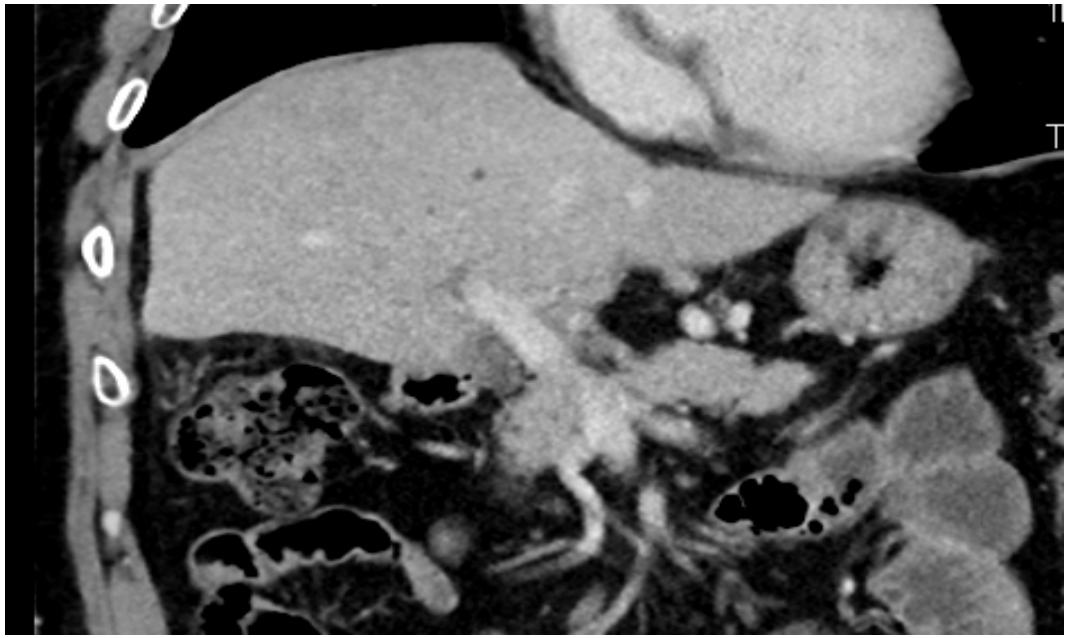


Esame istologico: due noduli necrotici e fibrotici associati a marcata atrofia del lobo destro ed ad aree di trombosi fibrosa di strutture vascolari portali destre compatibili con esiti di chemio- e radioembolizzazione. Non evidenza di neoplasia vitale residua (necrosi da sorafenib). Cirrosi con noduli rigenerativi.

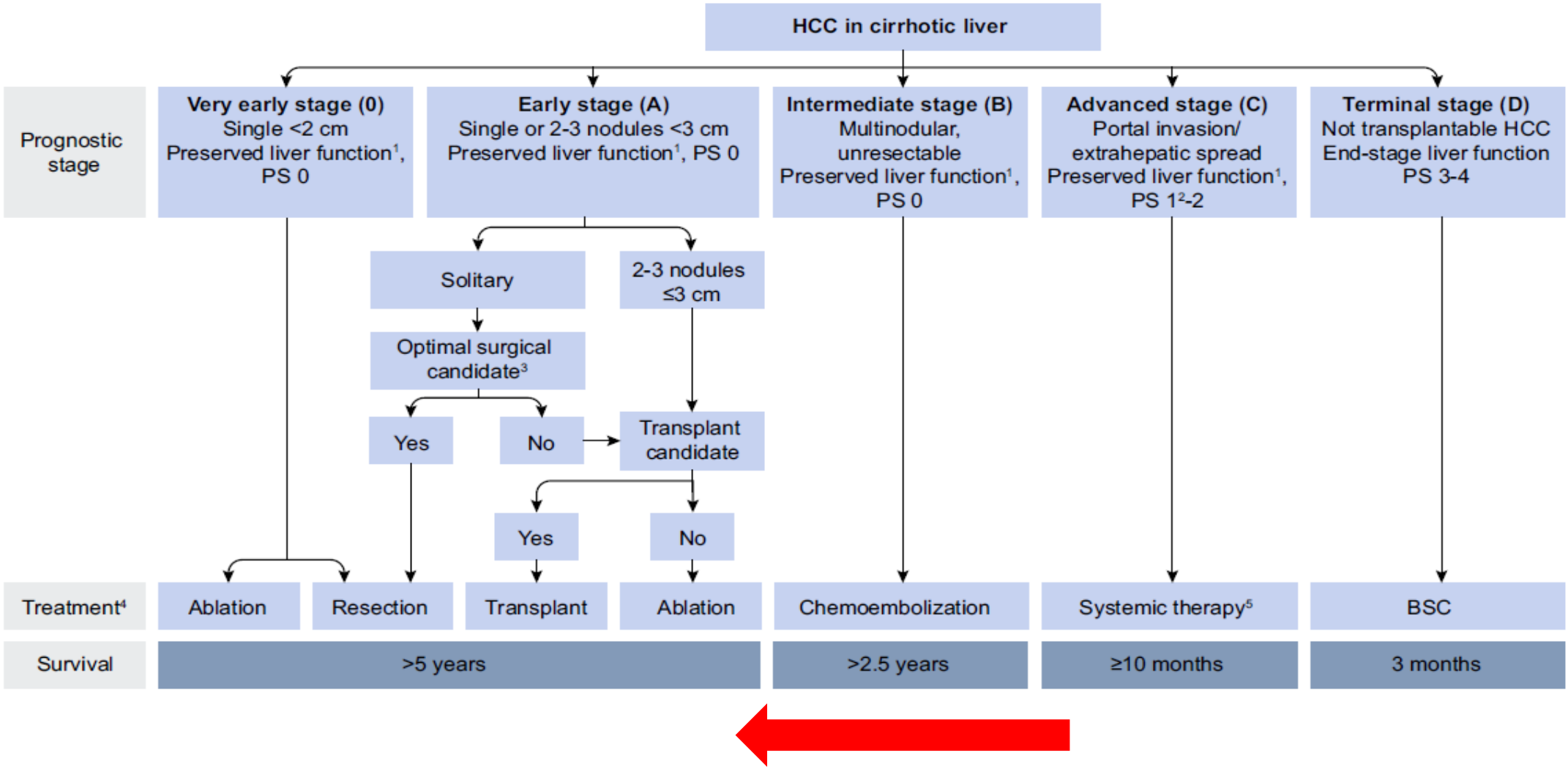
SP ♂ 1959

Luglio 2018 TC controllo a 19 mesi post trapianto epatico





SP ♂ 1959



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Are guidelines a dogma?

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Is a non application a deviation?

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NO, it is probably personalized medicine
ONLY if focused on the best treatment decision in a setting in which ALL therapeutic options are available/contemplated

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The role of guidelines

Societal guideline committees play an important role in synthesizing the knowledge base and classifying the strength of evidence for new treatments; their endorsements strongly affect practice. Ultimately, however, physicians at the point of care bear the final responsibility for accurately interpreting clinical trial results and for integrating regulatory and guideline recommendations in order to make the best treatment decisions for each patient in their care.

SJ Pocok and GW Stone NEJM 2016;375:971-979

Clinical Practice Guidelines

Update process

Because of the increasing number of publications, guidelines need to be continually updated to reflect the recent state of evidence. After 2023, these guidelines will expire. Should important changes occur in the meantime, such as newly available interventions, new important evidence or withdrawal of drug licensing, the information contained in the guidelines will be outdated earlier. In these cases, an update issue of the guidelines is needed earlier. EASL (cpg@easloffice.eu) will decide if an earlier initiation of an update is required.

EASL HCC Committee, J Hepatology 2018

« Il nous faut de l'audace, encore de l'audace, toujours de l'audace! »

« We must dare, and dare again, and go on daring! »

Assemble legislative, Paris, Sept 2nd, 1792

Georges Jacques Danton