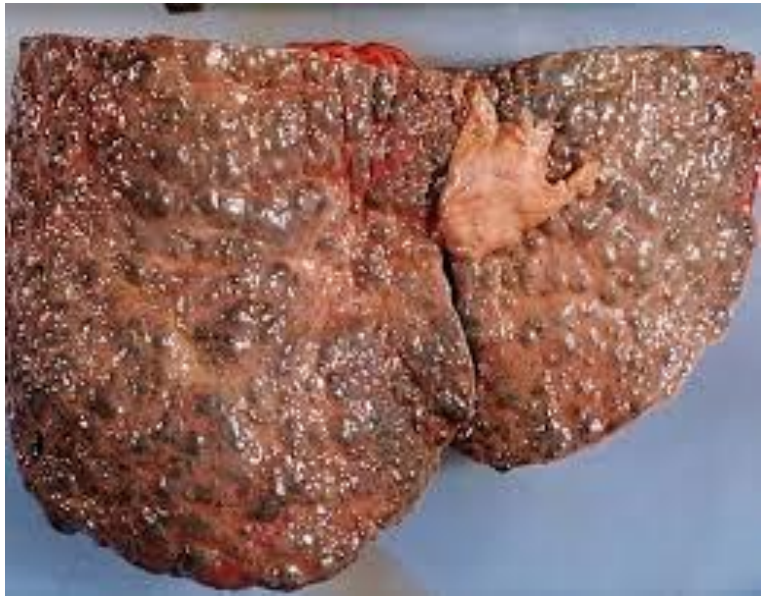
Cirrhosis



Dr Tien Huey Lim

Gastroenterologist

Cirrhosis

- Eighth leading cause of death in the US
- Approximately 50% patients with “compensated” cirrhosis develop ascites within 10 years
- Mortality of patients with ascites = 15% in 1 year
- 44% mortality in 5 years

Complications of Cirrhosis

- Varices
- Ascites
  - SBP
    Hepatic hydrothorax
- Hepatic encephalopathy
- HCC

Child pugh score

2 Minute Medicine®	Child-Pugh Score		2minutemedicine.com
Factor	**1 point**	**2 points**	**3 points**
Total bilirubin (µmol/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

	Class A	**Class B**	**Class C**
Total points	5-6	7-9	10-15
1-year survival	100%	80%	45%

Table I. Child-Pugh score.

MELD score

- Uses objective laboratory results to predict mortality from liver disease
- MELD = 3.78×ln[serum bilirubin (mg/dL)] + 11.2×ln[INR] + 9.57×ln[serum **creatinine** (mg/dL)] + 6.43
- Creatinine
- Bilirubin
- INR

MELD score and 3 month mortality rates

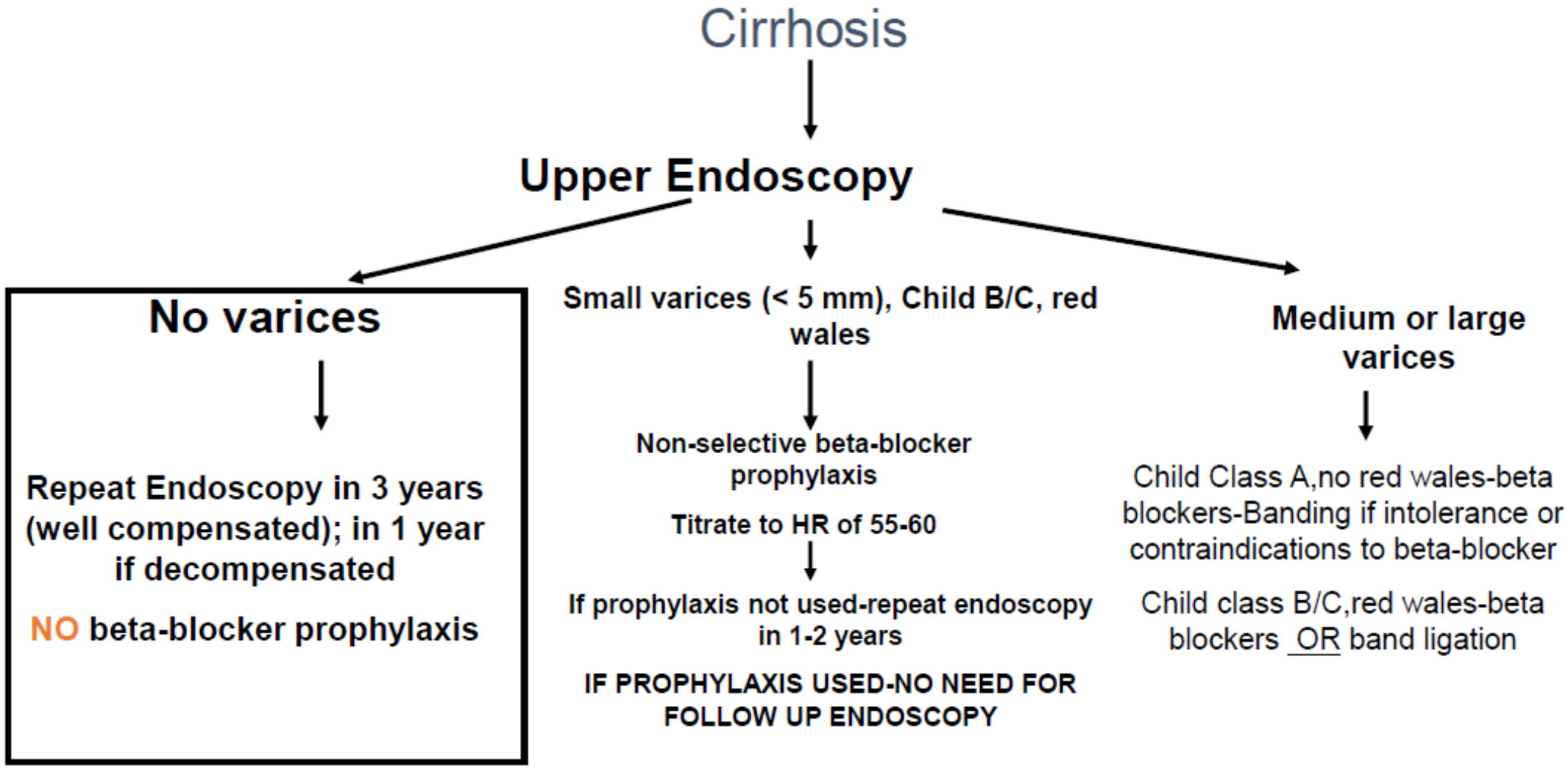
- 40 or more – 71.3% mortality
- 30-39- 52.6% mortality
- 20-29- 19.6% mortality
- 10-19- 6% mortality
- <9- 1.9% mortality

Patient 1: Mrs Fl

- 70 year old female
- Known NASH cirrhosis from liver biopsy in 2007
- T2DM, Dyslipidemia, hypothyroid
- Gastroscopy 2019 showed small gastric varices
- Laminoplasty C4-6, L4/5 decompression 19 May 2020, discharged 3 days later

- Readmitted 10 July 2020 with infected c-spine operative wound (staph aureus)
- Returned to OT for debridement + loose screw removed
- Developed hematemesis 22 July 2020
- Hb 95 → 72
- Gastroscopy 22/7/20: Grade 1 esophageal varices, blood in stomach obscuring views
- Gastroscopy 23/7/20: Esophageal varices banded x3, significant amount of blood in stomach obscuring views

- Gastroscopy 27/7/20: Esophageal varices. Type 2 gastro-esophageal varices which extends along the fundus without bleeding → injected with glue
- Self discharged after this against medical advice (!)
- Represented 29/7/20 after further hematemesis and melena
- BP 90mm systolic, P 100, Hb 52.
- Treated with RBC, terlipressin, transferred to Akl Liver unit for TIPSS procedure



Garcia-Tsao, G. et al. Hepatology 2017;65:310-335

Management of Patients With Moderate/Large Varices That Have Not Bled

Therapy	*Recommended Dose*	*Therapy Goals*	*Maintenance/Follow-Up*

Propranolol	• 20-40 mg orally twice a day
	• Adjust every 2-3 days until treatment goal is achieved
	• Maximal daily dose
	  ○ 320 mg/day in patients without ascites
	  ○ 160 mg/day in patients with ascites
		• Resting heart rate of 55-60 beats per minute
		• Systolic blood pressure should not decrease <90 mm Hg
			• At every outpatient visit make sure that heart rate is on target
			• Continue indefinitely
			• No need for follow-up EGD

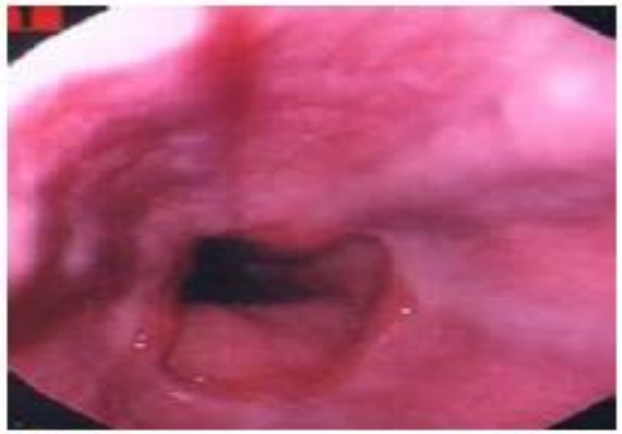
Nadolol	• 20-40 mg orally once a day
	• Adjust every 2-3 days until treatment goal is achieved
	• Maximal daily dose
	  ○ 160 mg/day in patients without ascites
	  ○ 80 mg/day in patients with ascites
		• Resting heart rate of 55-60 beats per minute
		• Systolic blood pressure should not decrease <90 mm Hg
			• At every outpatient visit make sure that heart rate is on target
			• Continue indefinitely
			• No need for follow-up

Carvedilol	• Start with 6.25 mg once a day • After 3 days increase to 6.5 mg twice-daily • Maximal dose: 12.5 mg/day (except in patients with persistent arterial hypertension)	• Systolic arterial blood pressure should not decrease <90 mm Hg	• Continue indefinitely • No need for follow-up EGD
EVL	• Every 2-8 weeks until the eradication of varices	• Variceal eradication (no further ligation possible)	• First EGD performed 3-6 months after eradication and every 6-12 months thereafter

*Any of these four therapies can be used, but current data do not support the use of combination therapy

Garcia-Tsao, G. et al. Hepatology 2017;65:310-335

Esophageal Varices



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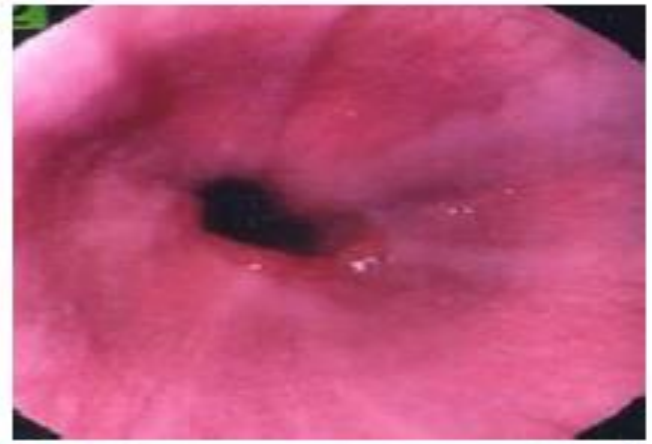

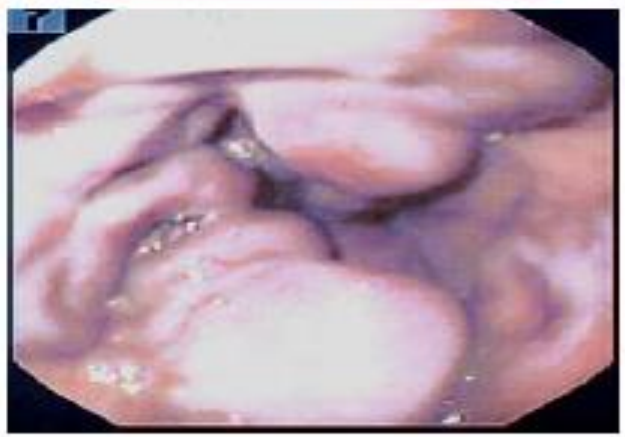

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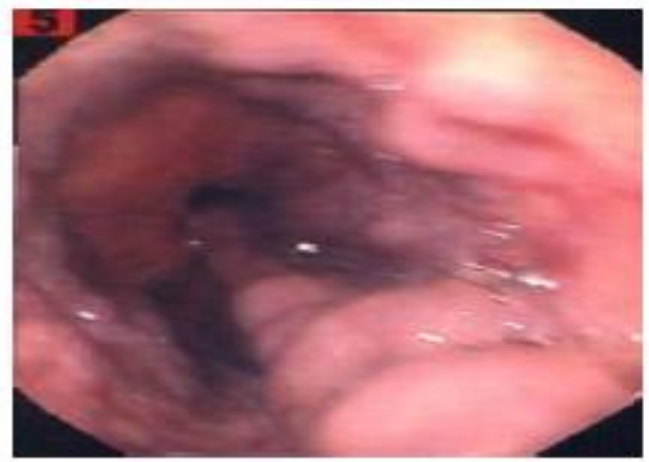
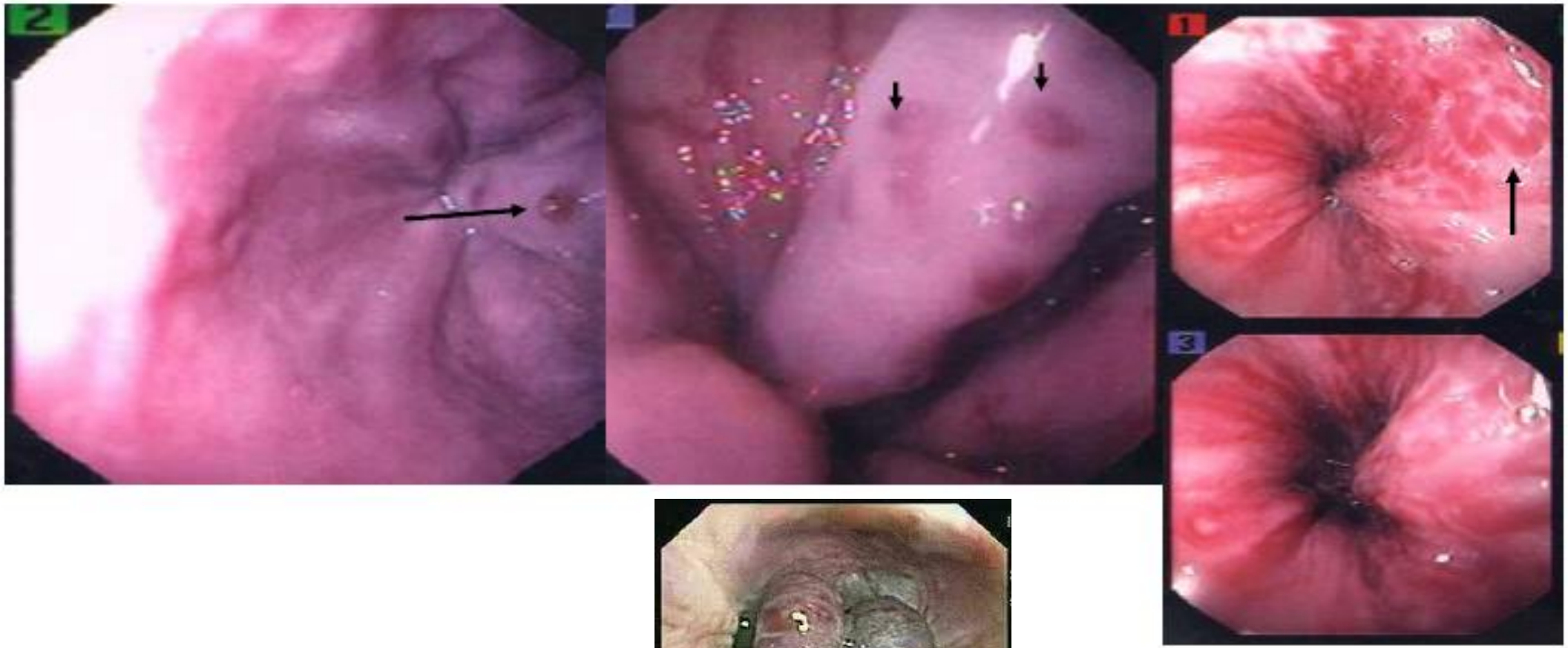
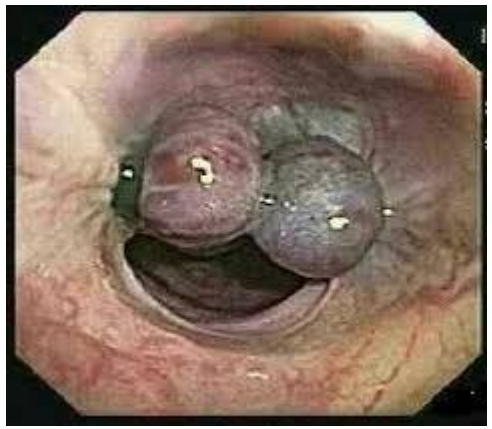


‘Cherry Red’ Spots

‘Red Wales’

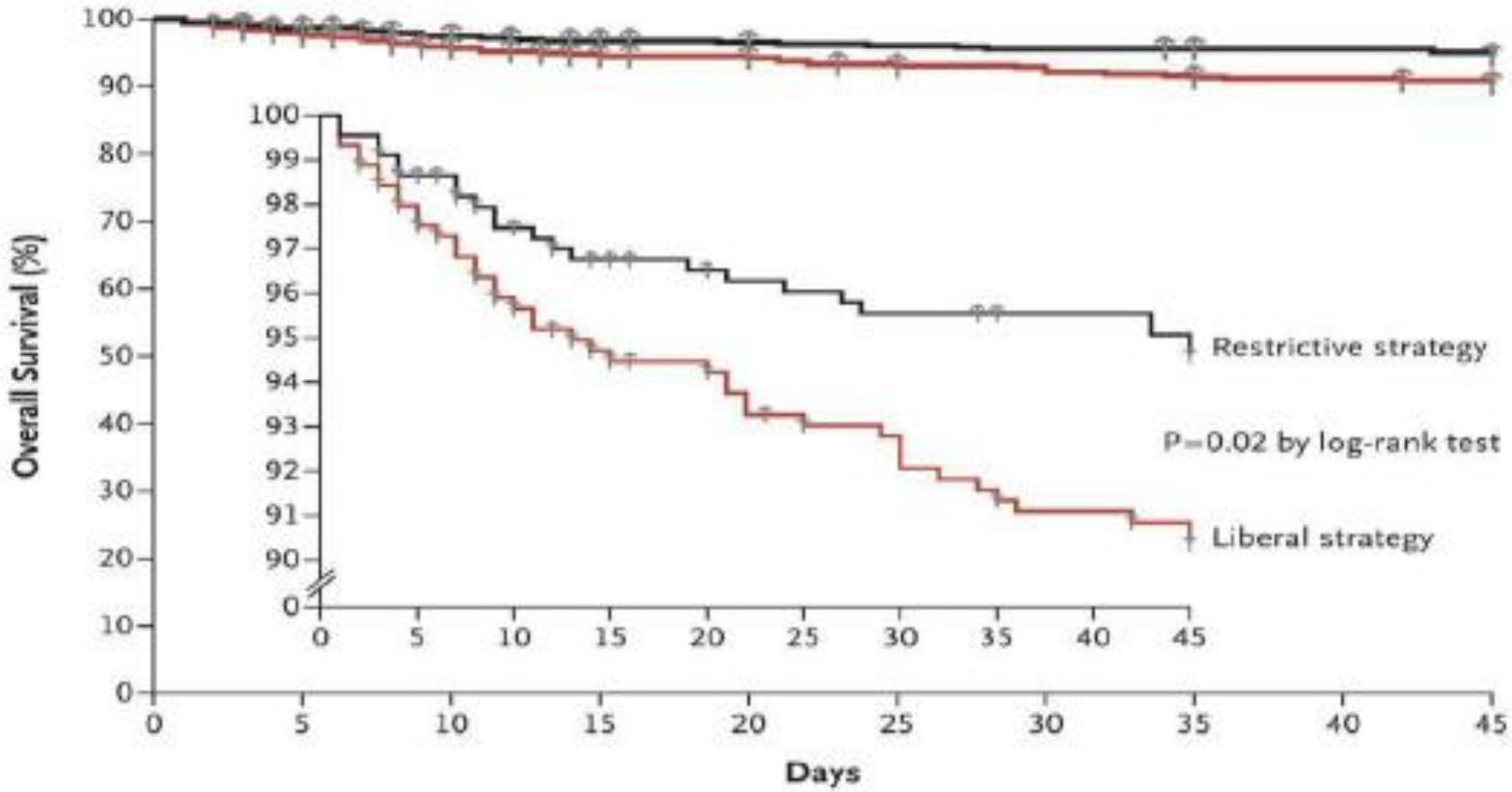




Acute variceal bleed

- Do NOT over transfuse- aim Hb 70-90
- Antibiotic prophylaxis (Cefuroxime) to prevent SBP
- Start terlipressin 1mg q6hrly initially then increase to 2mg q4hrly if required
- Timely gastroscopy +/- variceal banding
- Consider TIPSS if banding fails/early TIPSS to prevent rebleeding in decompensated patients

Survival, According to Transfusion Strategy

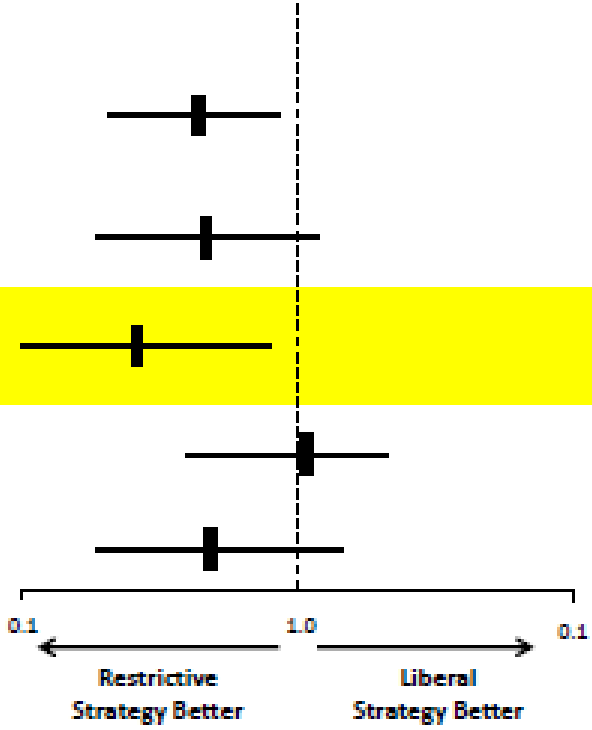


No. at Risk										
Restrictive strategy	444	429	412	404	401	399	397	395	394	392
Liberal strategy	445	428	407	397	393	386	383	378	375	372

Villanueva C, et al. *N Engl J Med* 2013;368:11-21

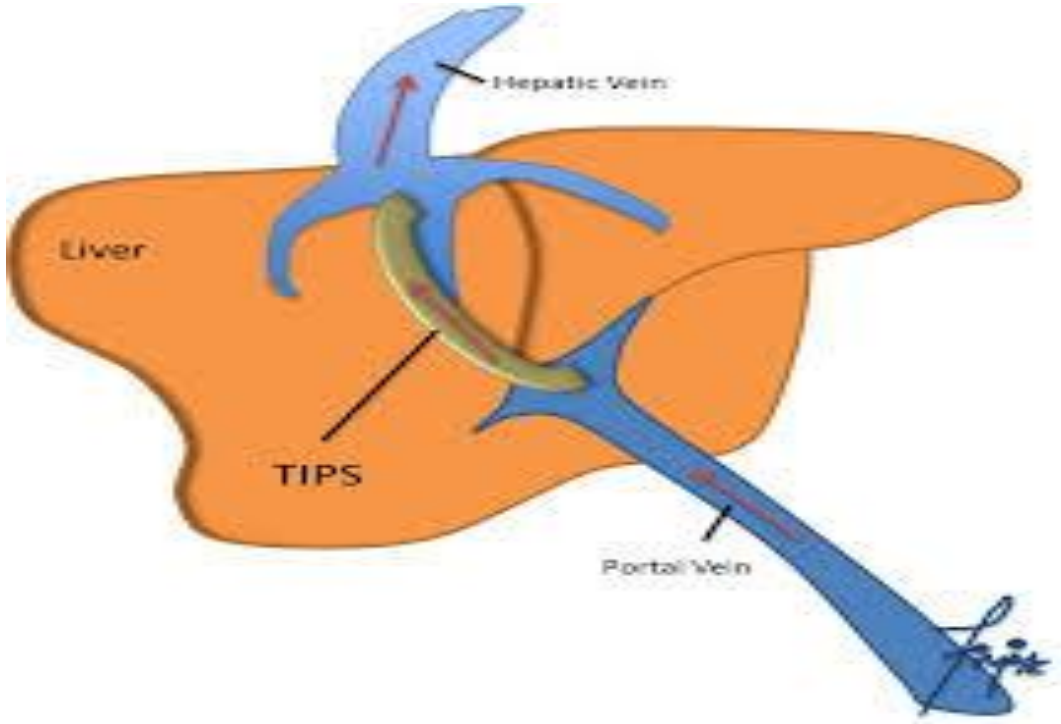
Death by 6 Weeks, According to Subgroup

Subgroup	Restrictive Strategy	Liberal Strategy	Hazard Ratio (95% CI)	P-value
	# of patients/total # (%)			
Overall	23/444 (5)	41/445 (9)	0.55 (0.33-0.92)	0.02
Patients with cirrhosis	15/139 (11)	25/138 (18)	0.57 (0.30-1.08)	0.08
Child-Pugh class A or B	5/113 (4)	13/109 (12)	0.30 (0.11-0.85)	0.02
Child-Pugh class C	10/26 (38)	12/29 (41)	1.04 (0.45-2.37)	0.91
Bleeding from varices	10/93 (11)	17/97 (18)	0.58 (0.27-1.27	0.18

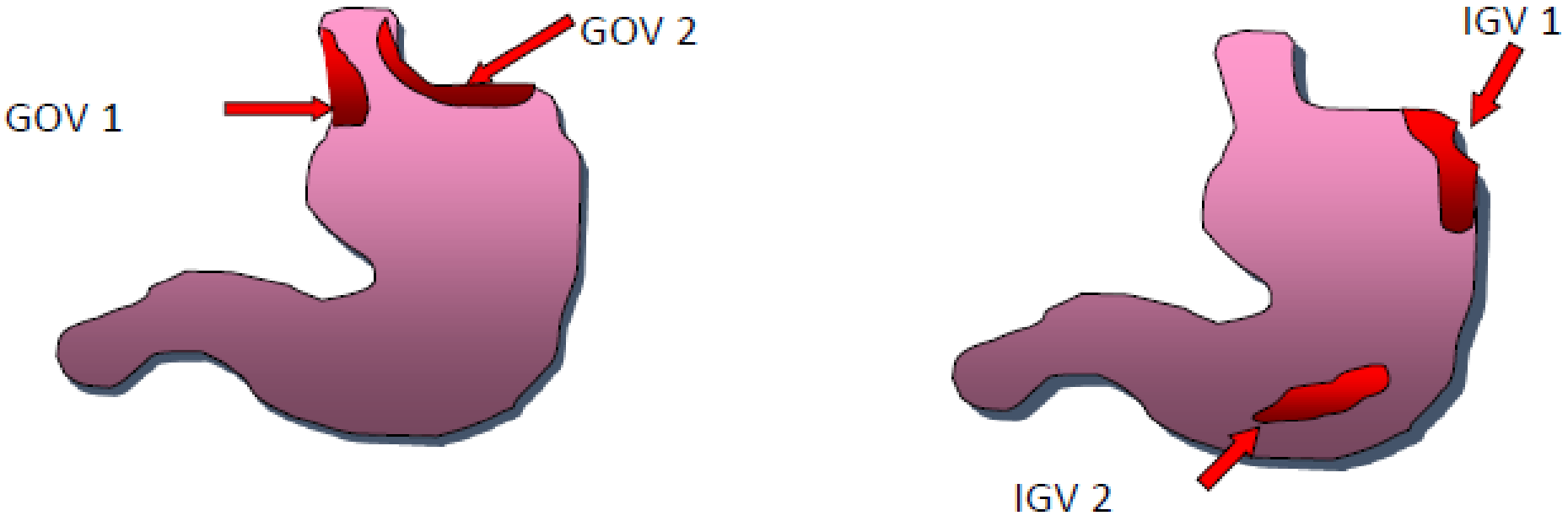


Villanueva C, et al. *N Engl J Med* 2013;368:11-21

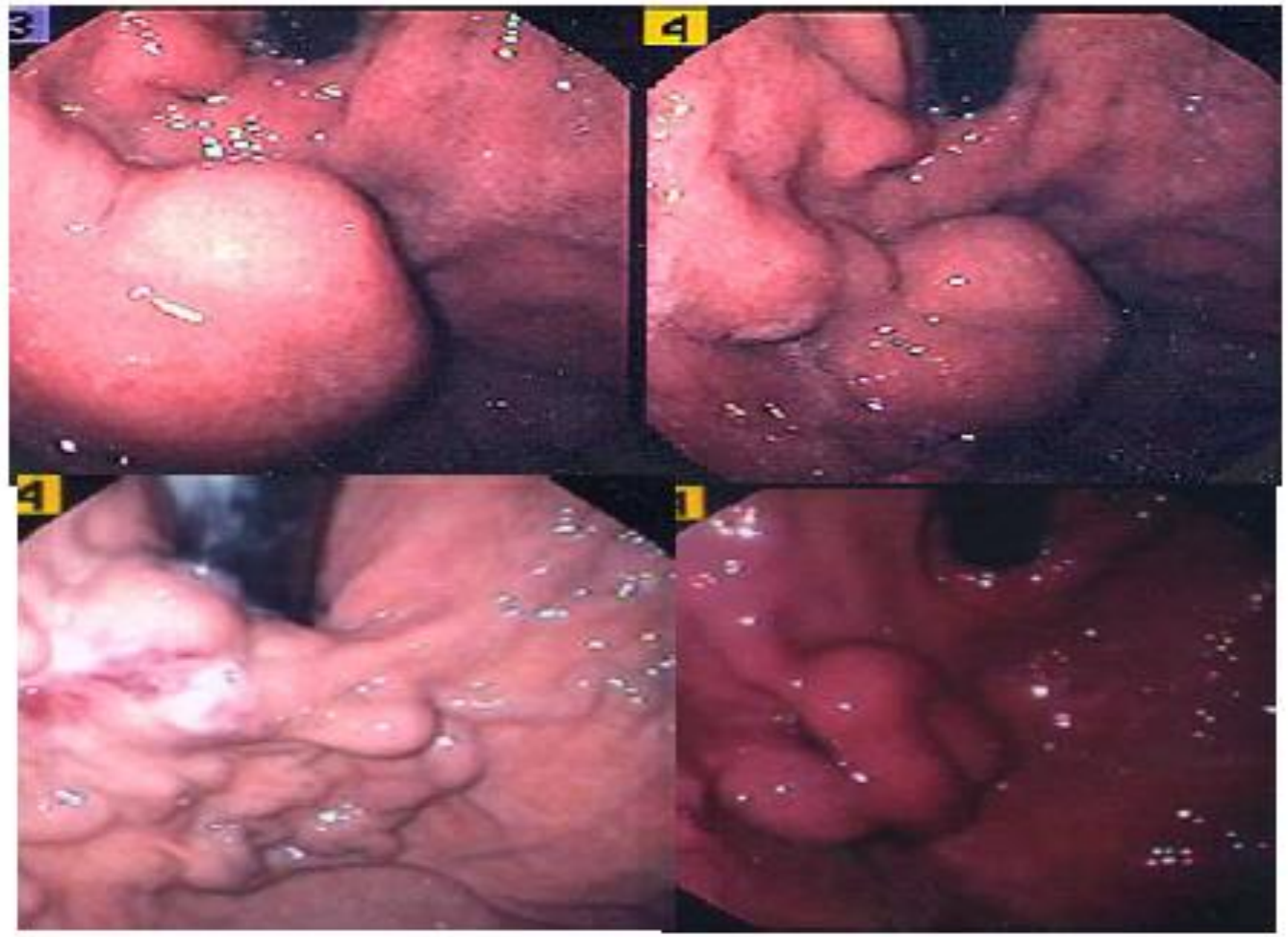
TIPSS



Sarin Classification of Gastroesophageal Varices



Large Fundal Varices



Prevention of hemorrhage from gastric varices

- Non selective beta blockers can be used to prevent bleeding from GOV2 and IGV1
- Evidence not as strong as in esophageal varices

- Glue injection or TIPSS for acute bleed

Patient 2- WD

- 73 year old retired man
- PMHx: HT, IGT, increased BMI
- Drinks 4 units ETOH per day for the past 50 years
- Presented in Jan 2015 with increased abdominal girth
- USS confirmed cirrhosis and large volume ascites
- Bili 29, GGT 199, ALP 174, AST 54, ALT 23, platelet 252
- Na 132, Albumin 25, INR 1.1

- Started on spironolactone and frusemide but weight unchanged
- Large volume paracentesis: 10.5L drained
- Discharged on Spironolactone 100mg daily, frusemide 40mg daily
- Readmitted March 2015 with Na 124, K 5.4, large volume ascites
- Spironolactone stopped
- Drained 8 litres
- Throughout 2015, required paracentesis every 4 weeks

- Dec 2015 developed SBP (streptococcus G on aspirate)
- Significantly troubled by large umbilical hernia (intermittent spontaneous discharge of 2-3L of fluid from umbilical wound)
- Child pugh score 10/15 Dec 2015
- Continues to drink but cut down to 1 beer/day
- Gradually recompensated
- By June 2016, child pugh score 8/15 (no longer requiring paracentesis, ascites well controlled on small dose spironolactone)

2017-2019

- Well, child pugh score 6/15, diuretic controlled ascites
- Umbilical hernia no longer a problem

2020

- 2 new lesions detected on screening USS – 15mm and 8mm in right lobe of liver
- Not a surgical candidate
- Referred for clinical trials but patient declined participation

Ascites- management

- Low sodium intake: 88mmol/d (2g of salts/d)
- Diuretics: aldosterone antagonist
  - Stepwise increase 100mg daily up to 400mg daily every 3 days
  - Add frusemide 40mg daily up to 160mg daily
  - Monitor for hypoNa, renal impairment, hyperK
  - Aim for body weight reduction >1kg per week until ascites controlled

Discontinue NSAIDs, beta blockers, ACE inhibitors
Serial therapeutic paracentesis
TIPSS
Consider liver transplantation

Practical points

- Cessation of alcohol intake can dramatically improve degree of liver failure, despite continued presence of HCV +/- NASH (75% 3 year survival vs 0% in those who continue drinking)
- Refractory ascites can revert to diuretic sensitive and can even disappear
- Rapid return to clinic may reduce readmission rates by frequent adjustment of doses of diuretics and prevent dehydration

Veldt. Hepatol 2002;36:93-8.

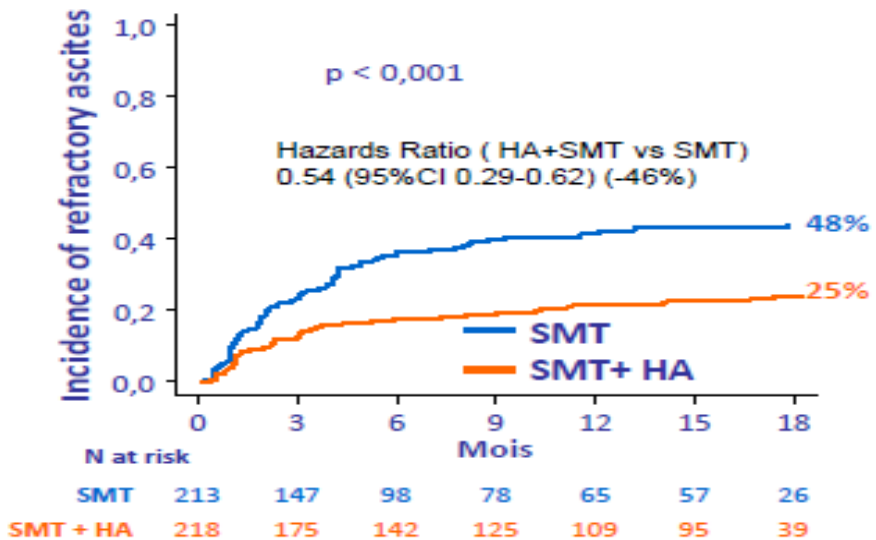
Refractory ascites

- Urine sodium <30mmol in spot urine despite diuretics
- Large volume paracentesis with albumin cover
- TIPSS

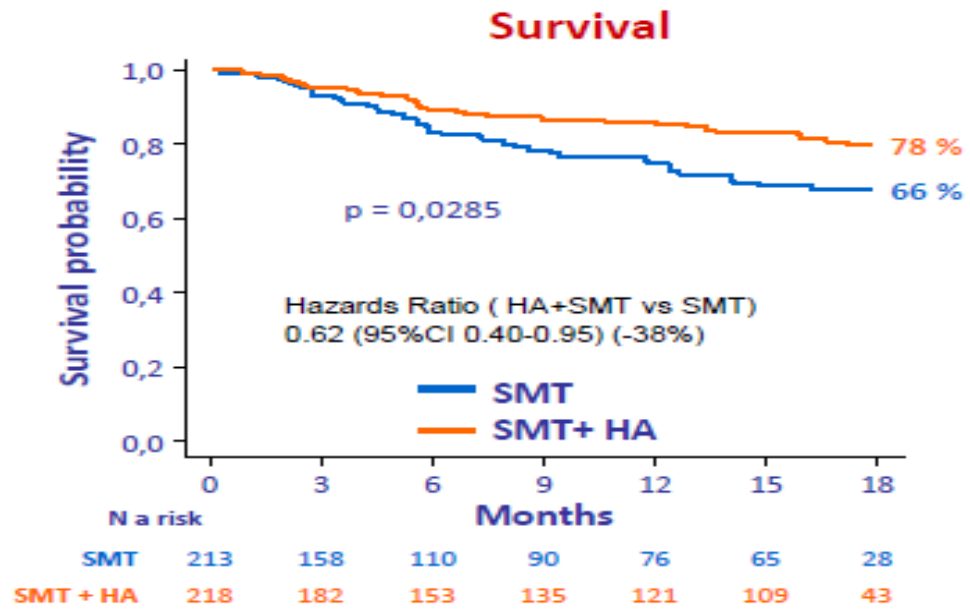
Albumin for prevention of refractory ascites:
(The Answer study)

- Patients with cirrhosis and uncomplicated ascites treated at least with anti-mineralocorticoide drug 200mg/d + furosemide 25 mg/d
  - Stratification on need of paracentesis in last moths and serum NA ≤/> 135 mmol/L
- Randomization 1:1
  - Standard Medical treatment (SMT) **N= 213**
  - SMT + **Albumin 40g x2/weeks for 2 weeks then 40g/w for 18 months N = 218**

Incidence of refractory ascites



Survival



Bernardi M et al. EASL 2017, Abs. LBO-08

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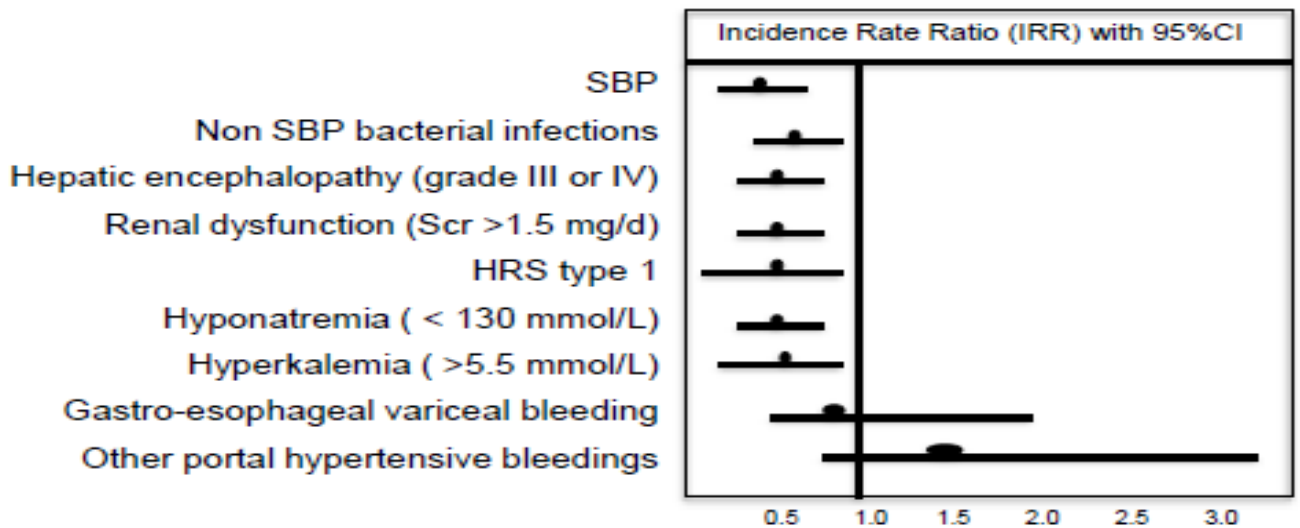
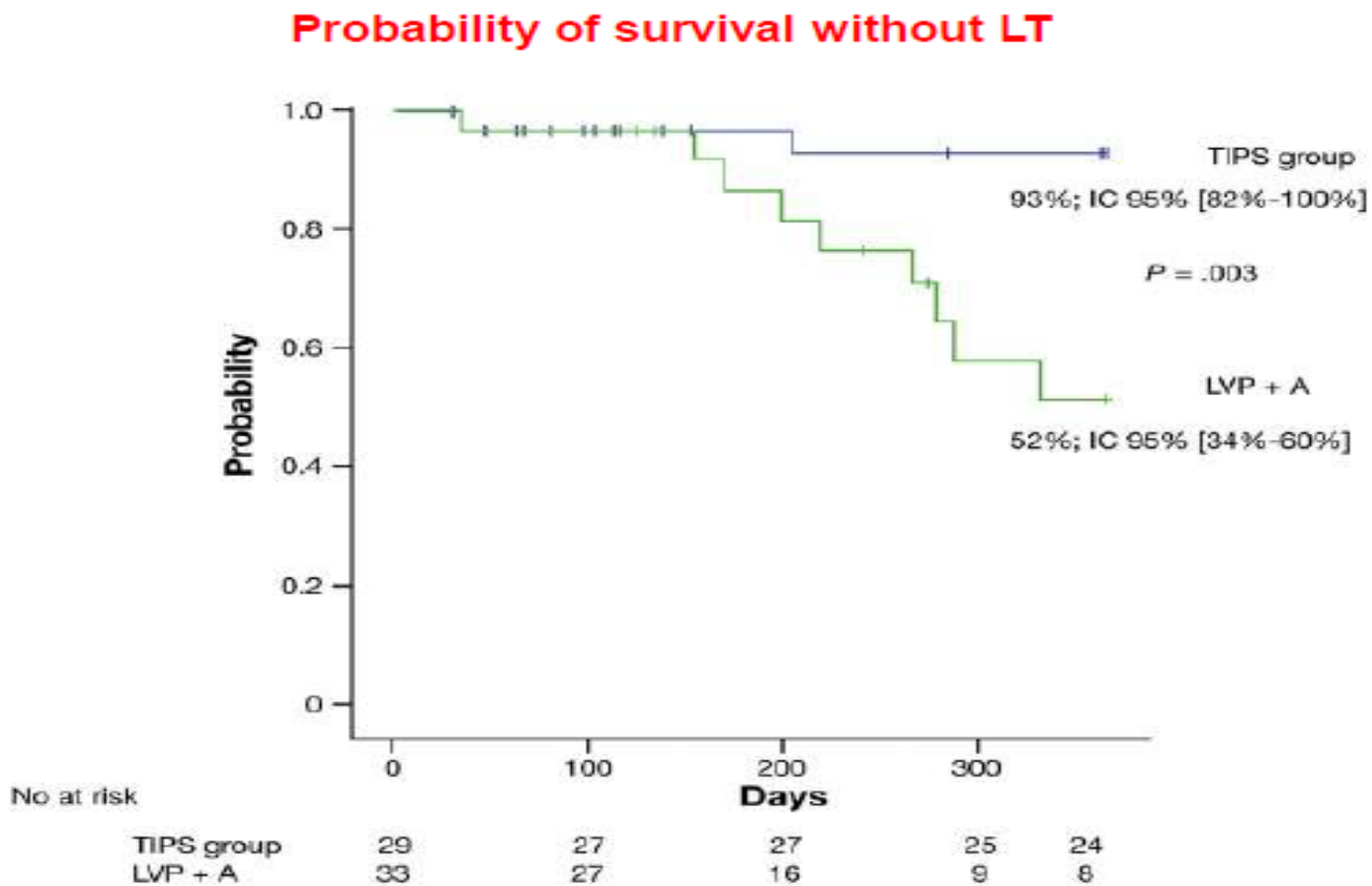
Incidence of complications



Bernardi M et al. EASL 2017, Abs. LBO-08

Transjugular Intrahepatic Portosystemic Shunts

- RCT 62 patients with cirrhosis and at least 2 LVP within at least 3 weeks



Bureau C et al. Gastroenterology 2017; 152: 157-163

Clinical outcome at 1 year

Outcome	TIPS (n = 29)	LVP+A (n = 33)
No. of paracenteses per patient, mean ± SD	1 ± 1	10 ± 7***
Volume extracted, *L/patient*, mean ± SD	6 ± 10	64 ± 47***
Albumin infusion, *g/patient*, mean ± SD	39 ± 70	550 ± 458***
Days in hospital, mean ± SD	17 ± 28	35 ± 40*
Patients with OHE, n	10	11
Episodes of OHE per patient, n, mean ± SD	1.6 ± 0.7	1.7 ± 0.8
Patients with OHE grade >2, n	4	7
Patients with PHT-related bleeding, n	0	6**
Patients with hernia-related complication, n	0	6**
Patients with HRS, n	0	1
Patients with SBP, n	0	2
Patients with sepsis, n	5	9
HCC, n	0	1

HCC, hepatocellular carcinoma; HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis.
*$P < .05$; **$P < .01$; ***$P < .001$.

TIPSS- complications

- TIPS stenosis: 70% bare TIPS vs 11% covered stents
- HE new or worsening : 20-30%
  - Older age is a risk factor
- Intravascular hemolysis with bare stent (10%)
- Others:
  - Cardiac failure 2.5%
  - Renal failure 4.3%
  - Liver failure 1.9%

Salerno F et al. Liver Int 2010

Contraindication to TIPS

- Congestive heart failure
- Pulmonary hypertension
- Complete portal vein thrombosis
- Recurrent overt encephalopathy
- HCC
- Child pugh score >12
- Serum creatinine >250umol/L
- Uncontrolled sepsis
- **TIPS use available for less than 40% of patients**

Spontaneous bacterial peritonitis (SBP)

- Up to 12% of cirrhotic patients requiring admission in older series
- Rates lower now with antibiotic prophylaxis in high risk groups
- Consider in patients with signs and symptoms of fever, abdominal pain, renal failure, encephalopathy
- Diagnosis = >250 WCC in ascitic fluid with predominantly polymorphs
- Treatment = 2nd or 3rd generation cephalosporins for at least 5 days

Prophylaxis for SBP

- Consider for patients with: (class I, level A evidence)
  - low protein ascites (<15g/dL)
  - previous episode of SBP
  - low Na <130
  - Creat >106umol/L
  - decompensated liver disease (child pugh score >9)
- Norfloxacin 400mg daily
- Cotrimoxazole 480mg bd

Hepatic hydrothorax

- Large pleural effusion (usually unilateral and right sided) in a patient with cirrhosis and ascites
- First line treatment: diuretics and sodium restriction
- Therapeutic thoracocentesis for symptoms
- Chest tube insertion contraindicated (increases morbidity and mortality)
- TIPSS is 2nd line treatment

Hepatic encephalopathy

- “Brain dysfunction caused by liver insufficiency and/or portosystemic shunting; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.” (Ferenci, Hepatology 2002;35:716-21.)
- Overt HE occurs in 30-40% in cirrhotics at some point
- Minimal HE in 20-80% cirrhotics
- TIPSS increase risk of HE

Table 2. WHC and Clinical Description

WHC Including MHE	ISHEN	Description	Suggested Operative Criteria	Comment
Unimpaired		No encephalopathy at all, no history of HE	Tested and proved to be normal	
Minimal	Covert	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations	No universal criteria for diagnosis. Local standards and expertise required
Grade I		• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioral decay with respect to his or her standard on clinical examination or to the caregivers	Clinical findings usually not reproducible
Grade II	Overt	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time (at least three of the followings are wrong: day of the month, day of the week, month, season, or year) ± the other mentioned symptoms	Clinical findings variable, but reproducible to some extent
Grade III		• Somnolence to semistupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city, or place) ± the other mentioned symptoms	Clinical findings reproducible to some extent
Grade IV		Coma	Does not respond even to painful stimuli	Comatose state usually reproducible

All conditions are required to be related to liver insufficiency and/or PSS.

Precipitating factors for HE

- Infections
- GI bleeding
- Diuretic overdose
- Electrolyte disorder
- Constipation
- Unidentified

Diagnosis of HE

- Sophisticated psychomotor tests for minimal HE
- Clinical criteria for overt HE
- Blood ammonia level (useful only if normal as it excludes HE)

Management of HE

- Initiation of care for patients with altered level of consciousness
- Rule out alternative causes of altered LOC
- Find and treat reversible causes
- Start empirical treatment
  - Lactulose- aiming for 2-3 bowel motions per day
  - Rifaximin (non absorbable antibiotic)
  - BCAAs
  - L-ornithine-L-aspartate

Rifaximin (via special authority)

- For patients with HE despite adequate trial of good doses of lactulose
- Good data from multiple trials supporting its use in addition to lactulose
- Well tolerated
- No solid data to support use of monotherapy with rifaximin

LOLA

- Interrupts the ammonia cycle
- RCT with IV LOLA on patients with persistent HE showed improvement psychometric testing + ammonia levels
- Oral supplementation is ineffective

Hepatocellular carcinoma (HCC)

Impact of coffee on HCC development

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

Recommendations	Level of evidence	Grade of recommendation
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

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Surveillance in patients at high risk of HCC

- Surveillance is recommended in specific target populations

Recommendations	Level of evidence	Grade of recommendation
• Cirrhotic patients, **Child-Pugh stage A and B**	Low	Strong
• Cirrhotic patients, **Child-Pugh stage C awaiting LTx**	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

- Interval should be dictated by rate of tumour growth and tumour incidence in target population
  - **6-month interval is reasonable and cost-effective**
    - **3 months**: no clinical benefit
    - **12 months**: fewer early stage diagnoses and shorter survival

*Patients at low HCC risk left untreated for HBV and without regular six months surveillance must be reassessed at latest on a yearly basis to verify progression of HCC risk. †PAGE-B score is based on decade of age (16–29 = 0, 30–39 = 2, 40–49 = 4, 50–59 = 6, 60–69 = 8,≥70=10), gender (M = 6, F = 0) and platelet count (≥200,000/µl = 0, 100,000–199,999µl = 1, <100,000 = 2): a total sum of ≤9 is considered at low risk of HCC (almost 0% HCC at five years) a score of 10–17 at intermediate risk (3% incidence HCC at five years) and ≥18 is at high risk (17% HCC at five years)

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Uncertainties in surveillance strategy

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

Recommendations	Level of evidence	Grade of recommendation
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 six months**	Moderate	Strong
Tumour **biomarkers** for accurate early detection are **still lacking**[a]	Low	-
Patients on the **waiting list for LTx** should **undergo surveillance for HCC** • To detect and manage tumour occurrence or tumour response • To help **define priority policies** for transplantation	Low	Strong

[a]Available data show that the biomarkers tested (i.e. AFP, AFP-L3 and DCP) are suboptimal in terms of cost-effectiveness for routine surveillance of early HCC
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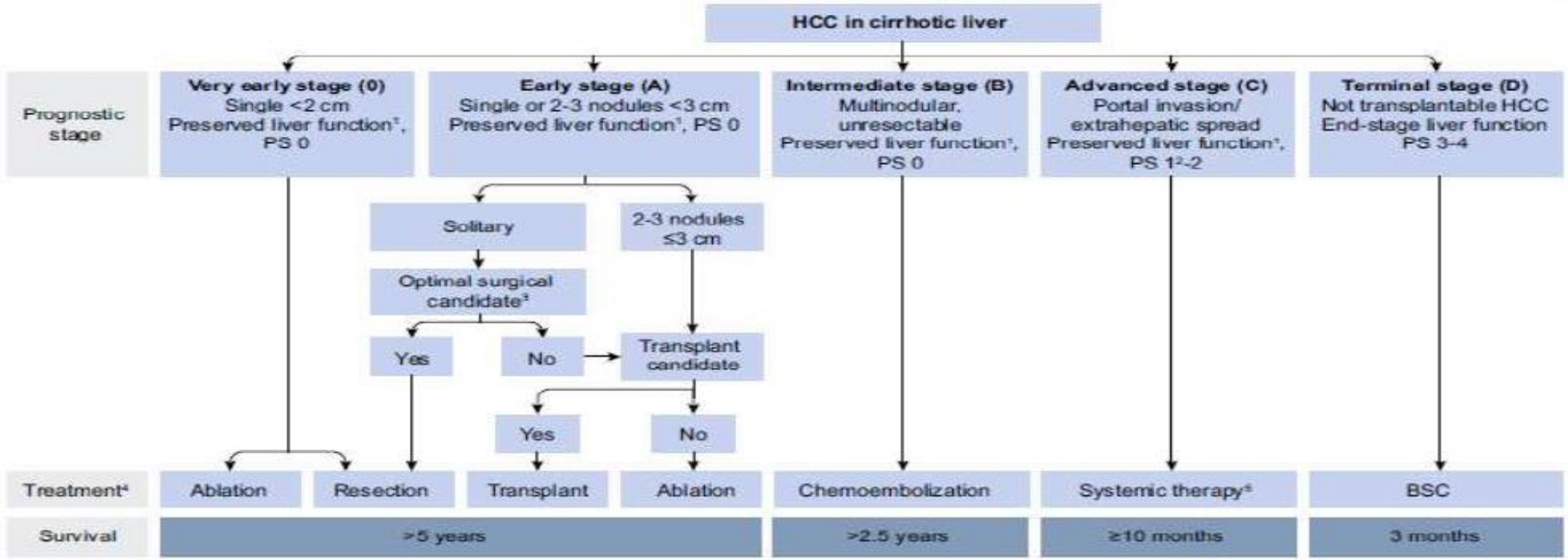
Modified BCLC staging system and treatment strategy



[1]Child-Pugh A without ascites. Applies to all treatment options apart from LTx. [2]PS 1; tumor induced modification of performance capacity. [3]Multiparametric evaluation: compensated Child-Pugh class A liver function with MELD score <10, matched with grade of portal hypertension, acceptable amount of remaining parenchyma and possibility to adopt a laparoscopic/minimally invasive approach. [4]The stage migration strategy applies. [5]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 in OS. Nivolumab has been approved in second line by FDA but not EMA based on uncontrolled phase II data. Please see notes for full details.

EASL CPG HCC J Hepatol 2018

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Conclusions

- Many different complications of cirrhosis
- Aim is to try to treat any reversible causes to prevent cirrhosis progression (HBV, HCV, ETOH, ?NASH)
- Regular monitoring to detect and manage complications early