ΣΥΓΧΡΟΝΕΣ ΠΡΟΚΛΗΣΕΙΣ ΣΤΗΝ ΑΝΤΙΜΕΤΩΠΙΣΗ ΤΩΝ ΑΣΘΕΝΩΝ ΜΕ ΗΚΚ

Υποσταδιοποίηση Ασθενών προκειμένου να υποβληθούν σε Ηπατεκτομή

ΔΗΜΗΤΡΗΣ Π. ΚΟΡΚΟΛΗΣ
Διευθυντής Χειρουργικής Κλινικής
ΓΑΟΝΑ ”Ο Άγιος Σάββας»

HCC – Current Status and Challenges

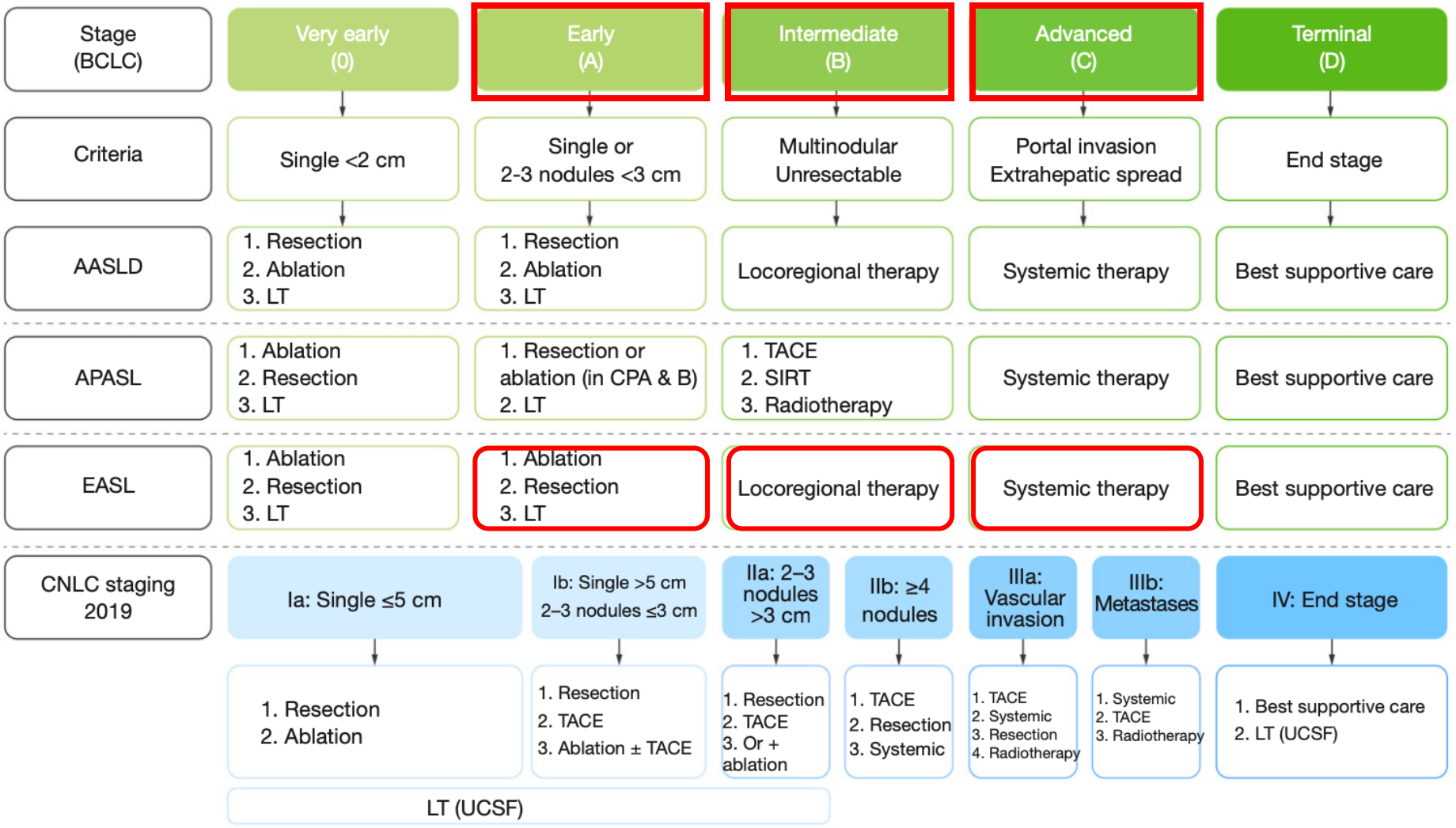
- Most common primary liver cancer
- 6th globally
- 4th leading cause of cancer-death

- BCLC 0, A → LR, ABL, LT → OS> 5years
- BCLC B, C(65%) → Non Surg Tx → OS≤20months

Conversion Therapy!!!

HepatoBiliary Surg Nutrition 2022

Stage-dependent Recommendations on the Treatment of HCC



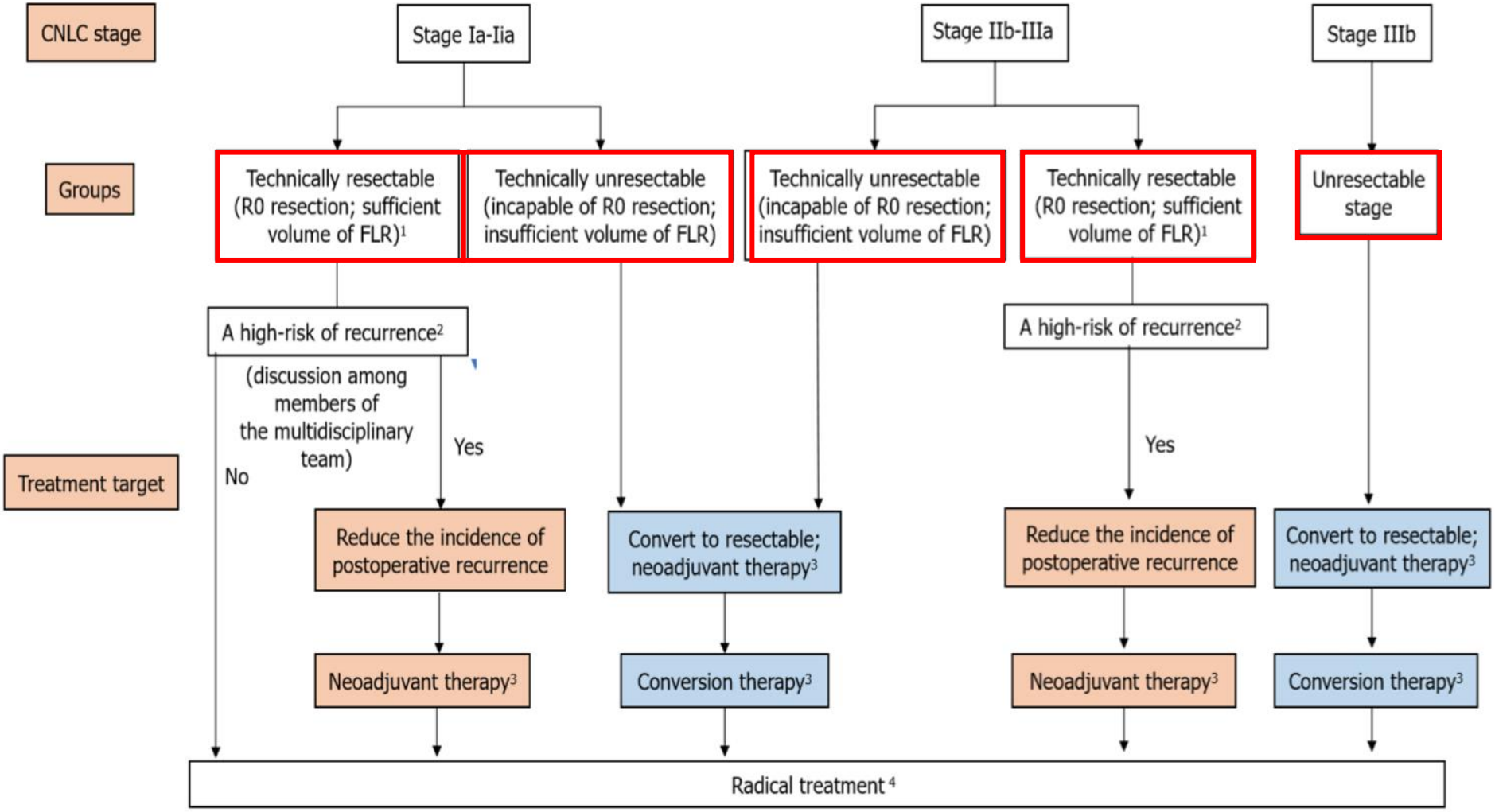
Conversion - Downstaging

- “Unresectable” HCC  “Resectable” HCC

- Unresectable HCC in the sense of SURGERY
    1. Poor pt condition – increased surgical risk
    2. Inappropriate liver function
    3. Insufficient FLR
    4. Low R0 probability

- Unresectable HCC in the sense of ONCOLOGY
    1. Surgically removable
    2. No better outcome than non-Sx
    3. Oncology – Biology First

Roadmap of Conversion Therapy



Selection of Treatment – Timing of Surgery – Adverse effects

World J Gastroent 2021

Systematic and Locoregional Therapies

Conversion Rate

Treatment regimen	Study name/design	Sample size	ORR†, %	PFS†, months	OS, months	Grade ≥3 TRAEs, %	Treatment line
TKI+ PD-1/PD-L1 monoclonal antibody							
Lenvatinib + nivolumab (42)	Phase Ib, single arm	30	54.2	7.39‡	–	60§	First line
Lenvatinib + pembrolizumab (16)	Phase Ib, single arm	100	36	8.6	22.0	67	First line
Apatinib + camrelizumab (18)	Phase II, single arm	70	34	5.7	20.3	77.4¶	First line
Regorafenib + pembrolizumab (43)	Phase Ib, single arm	35	29	–	–	86§	First line
Cabozantinib + nivolumab + ipilimumab (44)	CheckMate 040: Phase I/II non-randomized	35	29	6.8	NR	71	First line/ second line
Anlotinib + penpulimab (45)	Phase Ib/II, single arm	31	24	–	NE	12.9	First line
Cabozantinib + nivolumab (44)	CheckMate 040: Phase I/II non-randomized	36	19	5.4	21.5	47	First line/ second line
Bevacizumab+ PD-1/PD-L1 monoclonal antibody							
Bevacizumab + toripalimab (46)	CT34: Phase II, multi-center, single arm	54	31.5	9.9	NR	37§	First line
Bevacizumab + atezolizumab (47)	IMbrave150: Phase III, randomized	336	30	6.9	19.2	43	First line
Bevacizumab†† + sintilimab (41)	ORIENT-32: Phase II/III, randomized	380	21	4.6	NR	35	First line
Other options							
Nivolumab + ipilimumab‡‡ (48)	CheckMate 040: Phase I/II non-randomized (sub-analysis)	50	32	–	22.8	53	Second line
Camrelizumab + FOLFOX4 (49)	Phase II, single arm	34	29.4	7.4	11.7	85.3	First line
Durvalumab + tremelimumab§§ (50)	Phase II, randomized	74	24	2.17	18.7	35.1	Second line
HAIC with FOLFOX regimen (51)	Phase III, randomized	159	45.9	9.63	–	19¶¶	First line
HAIC with FOLFOX regimen + sorafenib (20)	Randomized	125	40.8	7.03	13.4	53.2	First line
TACE (51)	Phase III, randomized	156	17.9	5.4	–	30¶¶	First line
DEB-TACE + sorafenib (52)	Phase III, randomized	157	36	9.93†††	21†††	NR	First line
DEB-TACE + placebo (52)	Phase III, randomized	156	31	7.8†††	19.9†††	NR	First line

Downstaging and Resection of Initially Unresectable Hepatocellular Carcinoma with Tyrosine Kinase Inhibitor and Anti-PD-1 Antibody Combinations

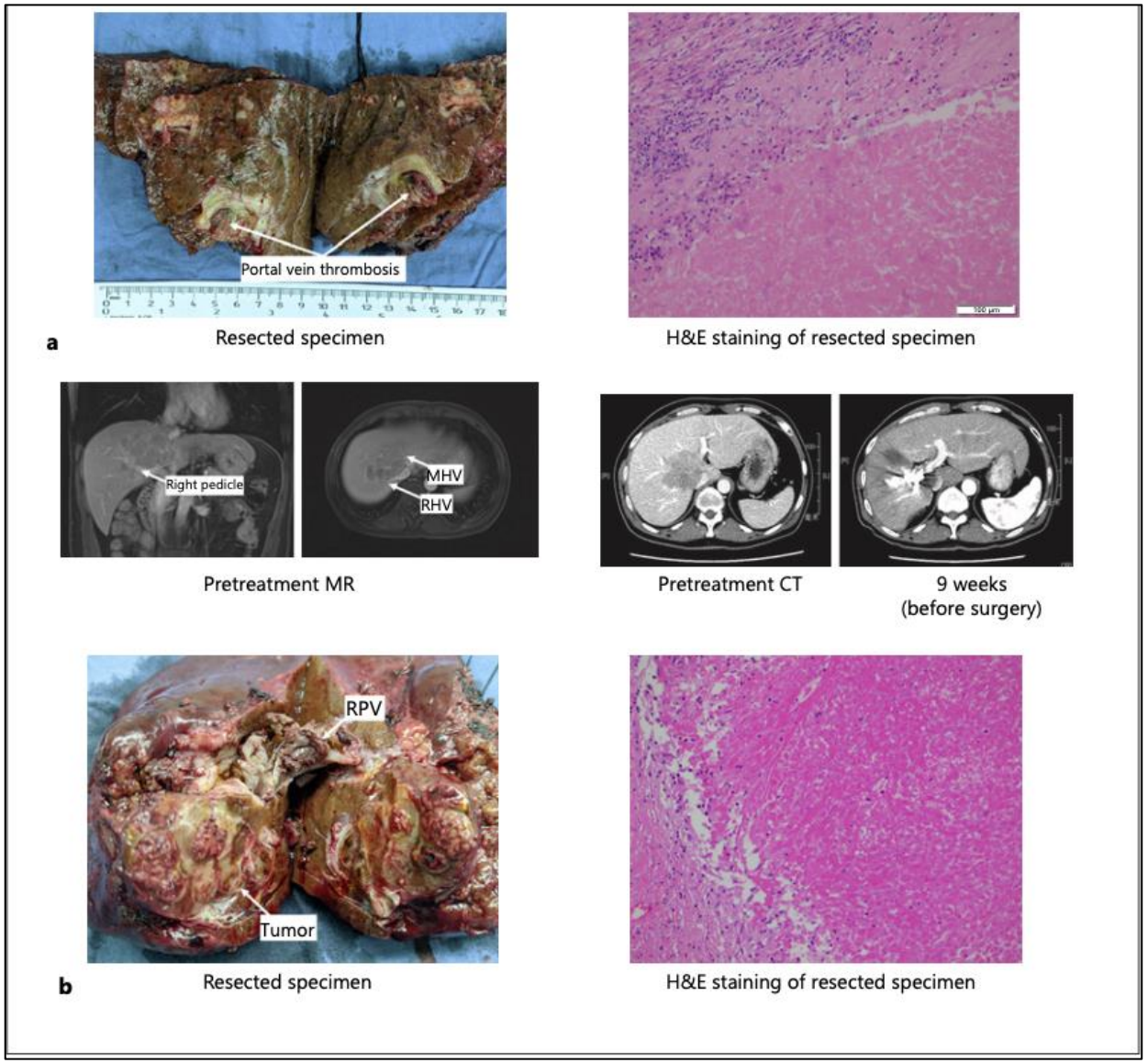
Liver Cancer 2021

T3 ⇨ T2

16% R0 resection

60% pCR

↑ Liver abscess
Bile leak
PostOp Bleeding

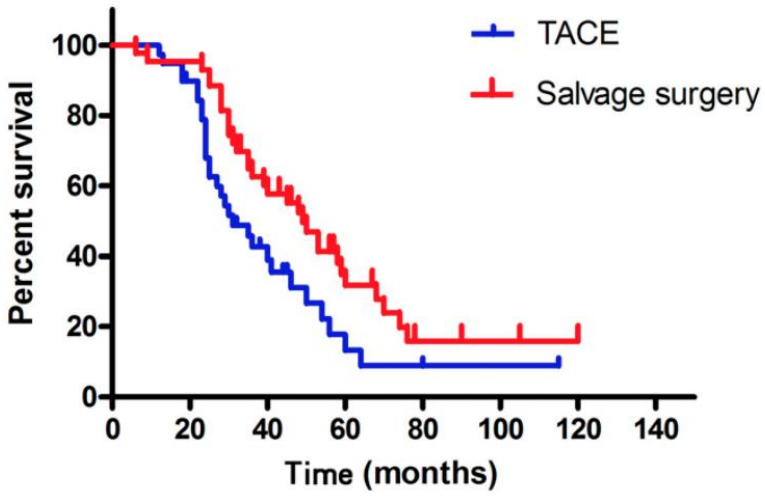


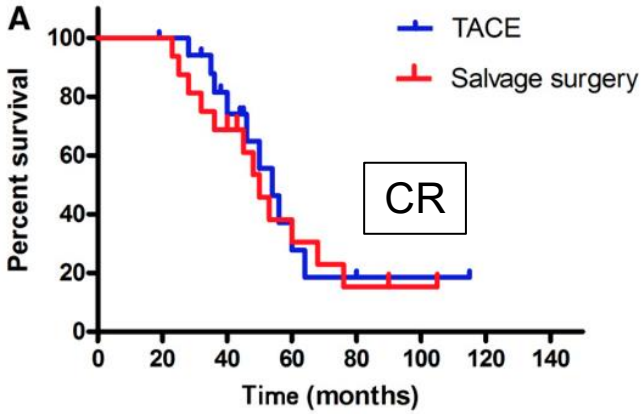
Is Salvage Liver Resection Necessary for Initially Unresectable Hepatocellular Carcinoma Patients Downstaged by Transarterial Chemoembolization? Ten Years of Experience

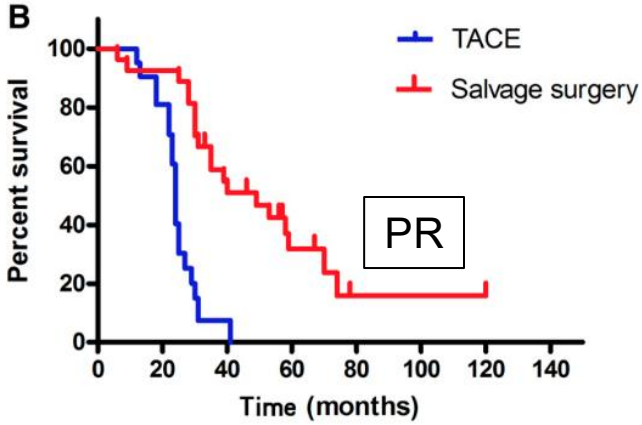
The Oncologist 2016

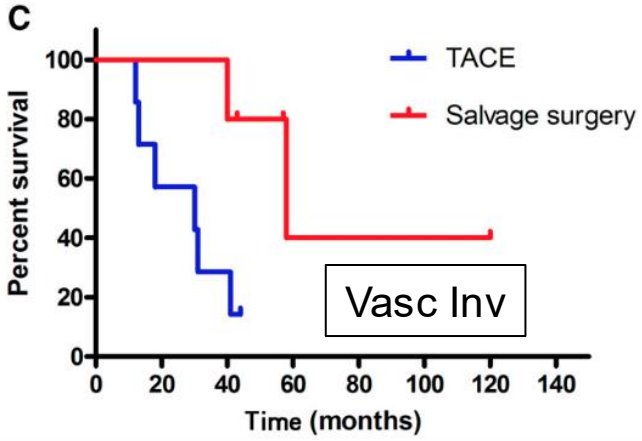
831 Chinese pts HCC
82 PR after TACE

OS after Sx	49months	
OS without Sx	31	(p<0.027)
	26%	
5yr OS	10%	

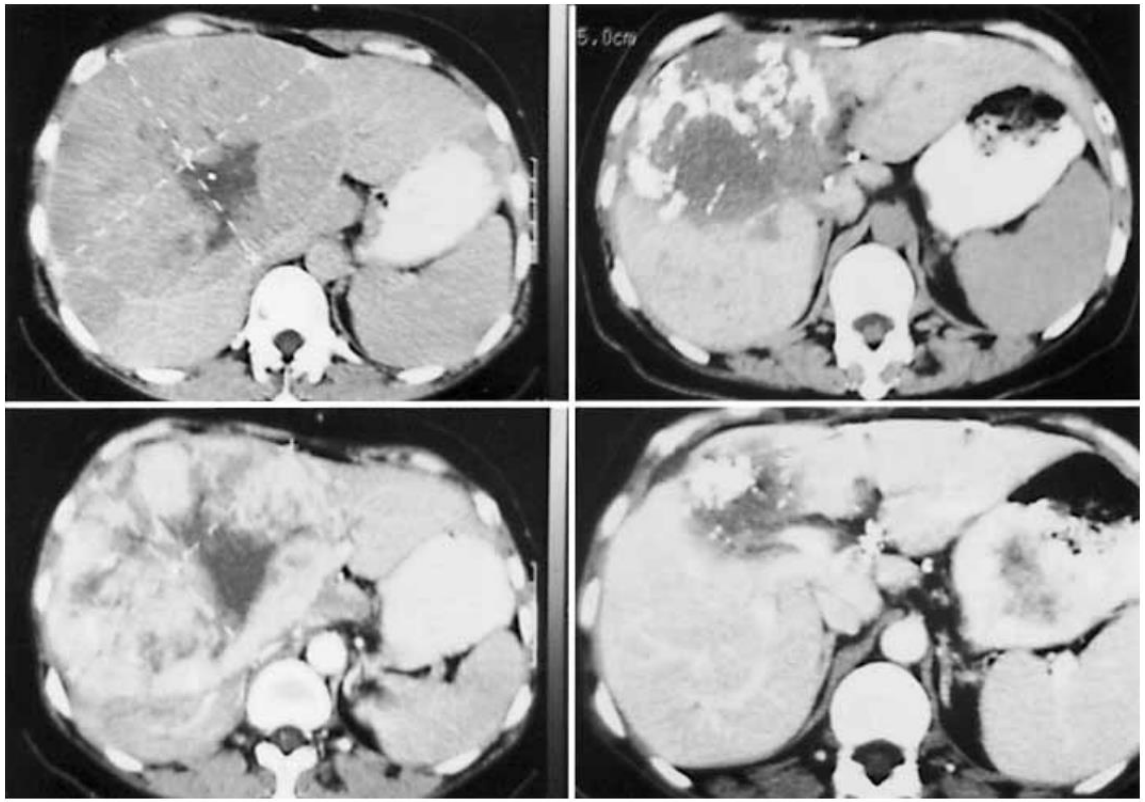








Improved Survival with Resection after Transcatheter Arterial Chemoembolization (TACE) for Unresectable Hepatocellular Carcinoma



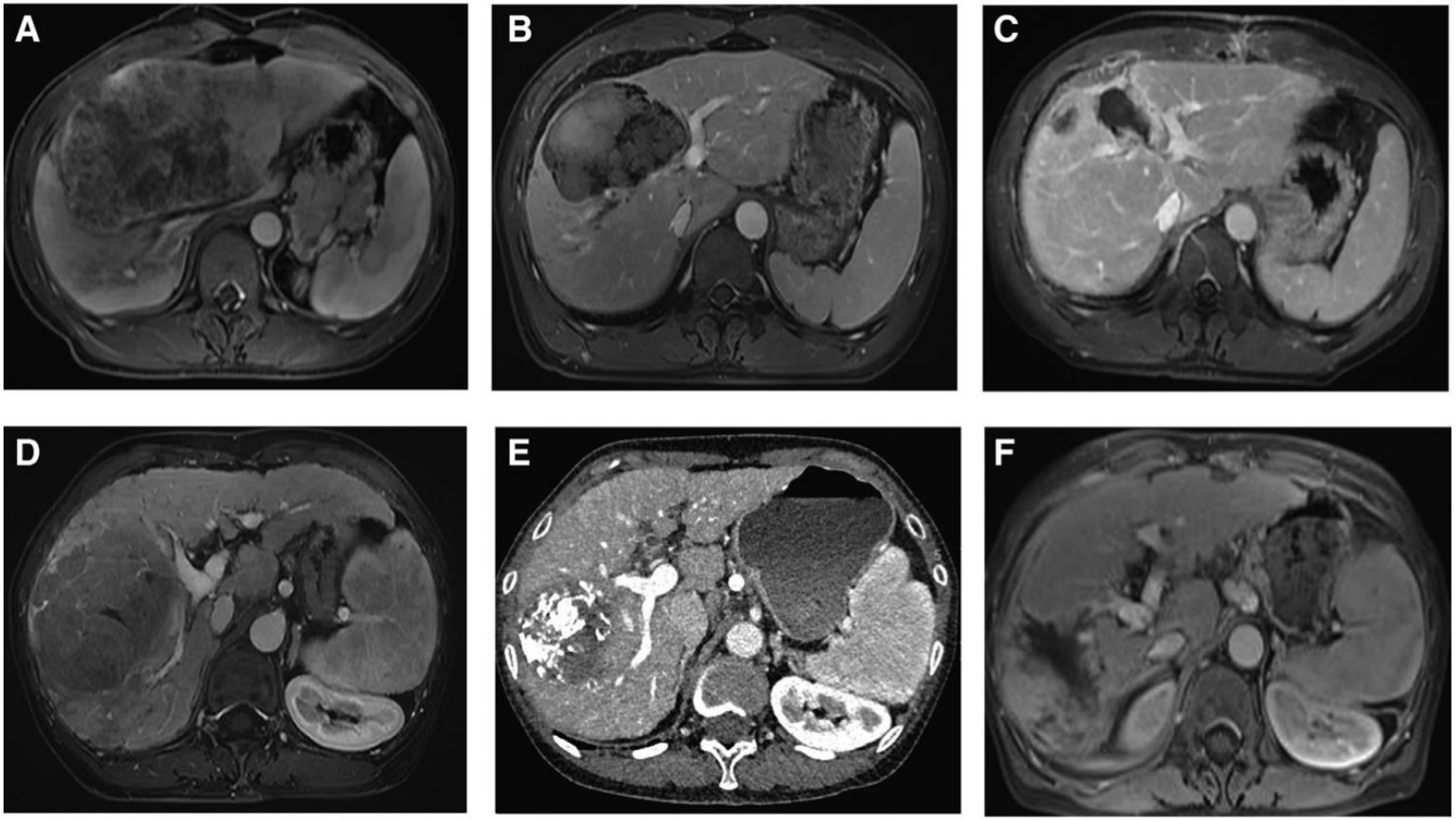
OS after TACE conversion Hepatectomy

1-yr	80%
3-yr	65%
5-yr	56%

Dig Surg 1998

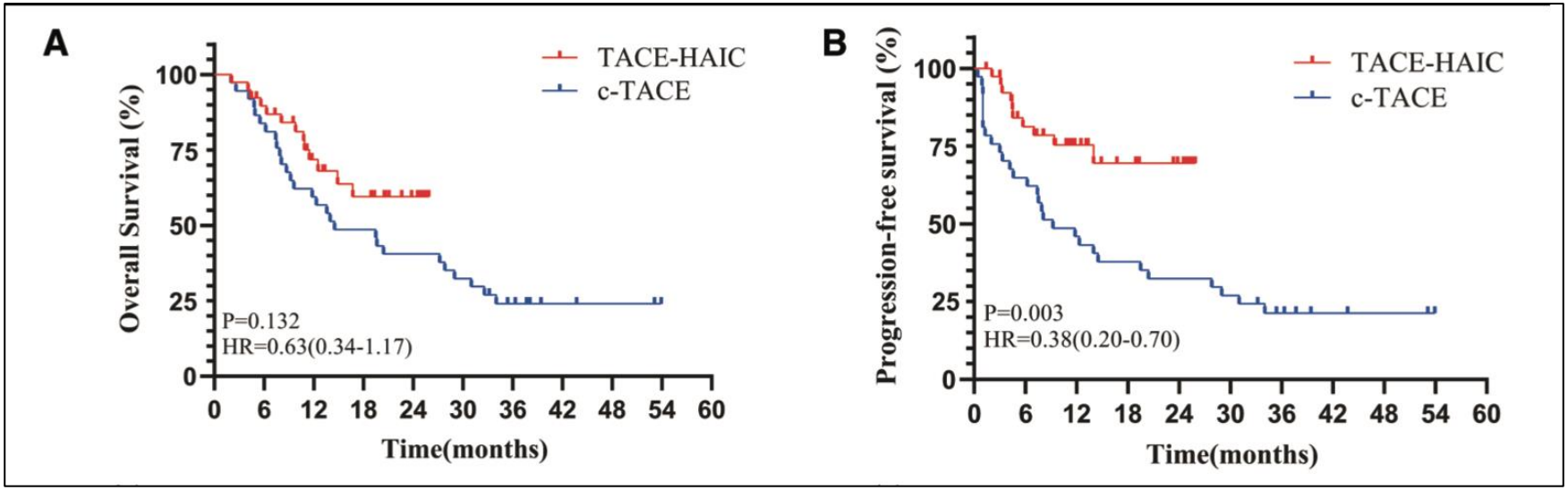
Conversion to Resectability Using Transarterial Chemoembolization Combined With Hepatic Arterial Infusion Chemotherapy for Initially Unresectable Hepatocellular Carcinoma

TACE+HAIC



Ann Surg 2021

Conversion to Resectability Using Transarterial Chemoembolization Combined With Hepatic Arterial Infusion Chemotherapy for Initially Unresectable Hepatocellular Carcinoma

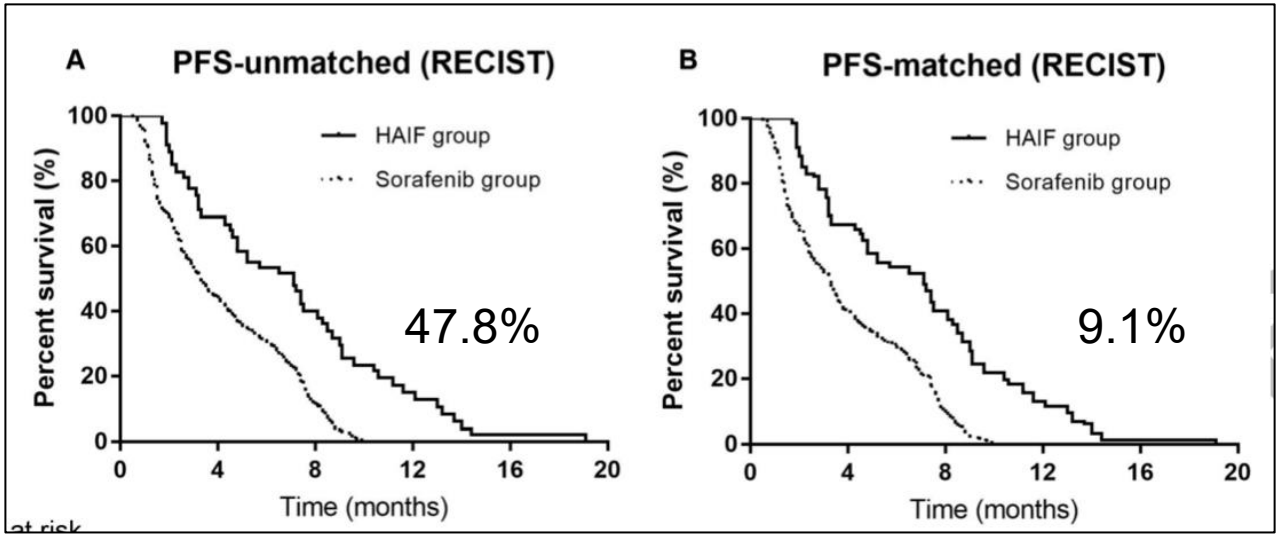


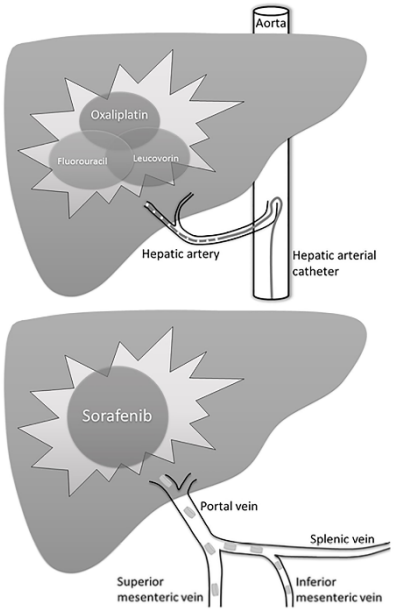
Conversion to Surgery rate		
TACE + HAIC	48.8%	
TACE	9.5%	*p<0.001*

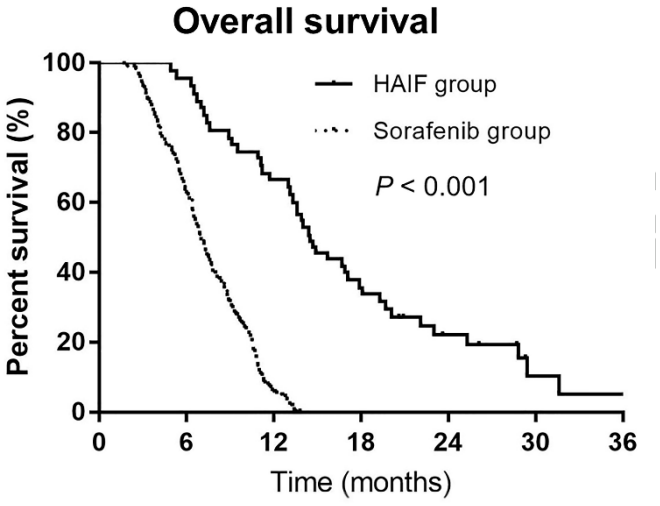
Multiple TACE treatments → Liver Damage!!!
NO TACE in PVT

Ann Surg 2021

Title: Hepatic Arterial Infusion of Oxaliplatin plus Fluorouracil/Leucovorin versus Sorafenib for Advanced Hepatocellular Carcinoma



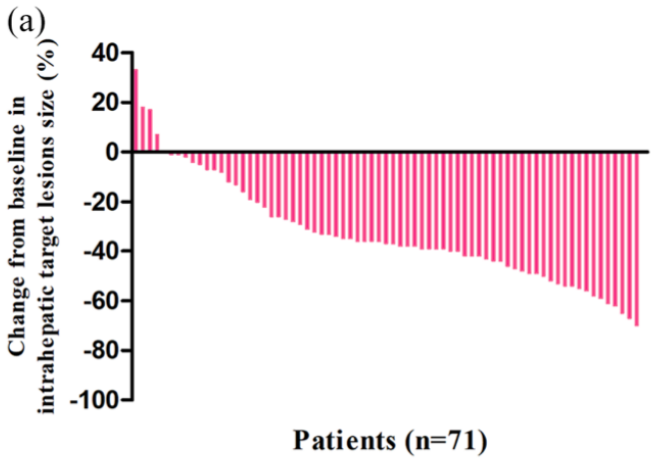


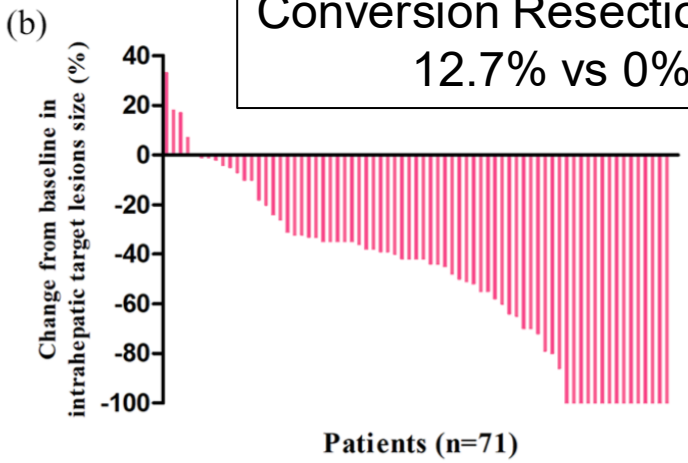


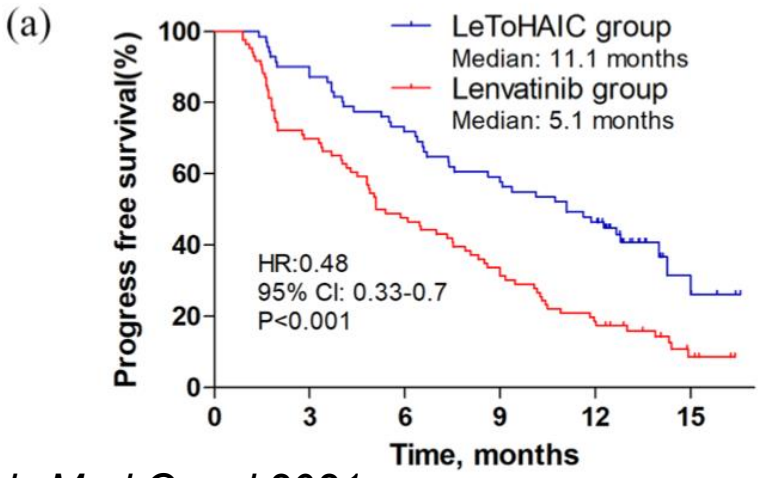
J Hepatol 2022

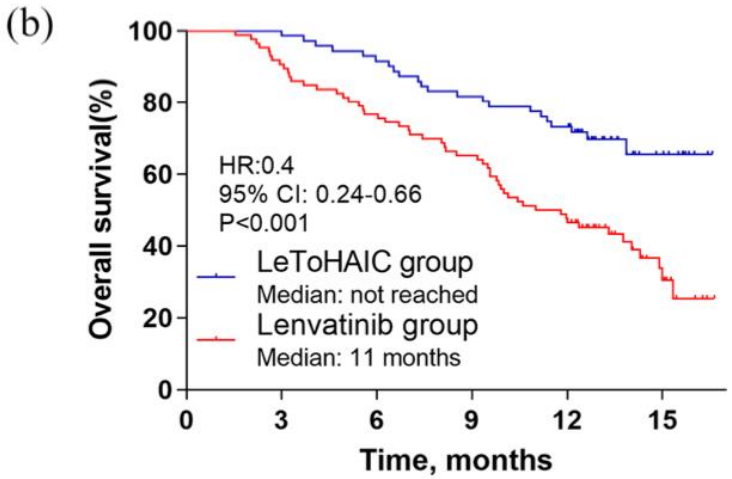
Lenvatinib, toripalimab, plus hepatic arterial infusion chemotherapy *versus* lenvatinib alone for advanced hepatocellular carcinoma

Conversion Resection Rate
12.7% vs 0%





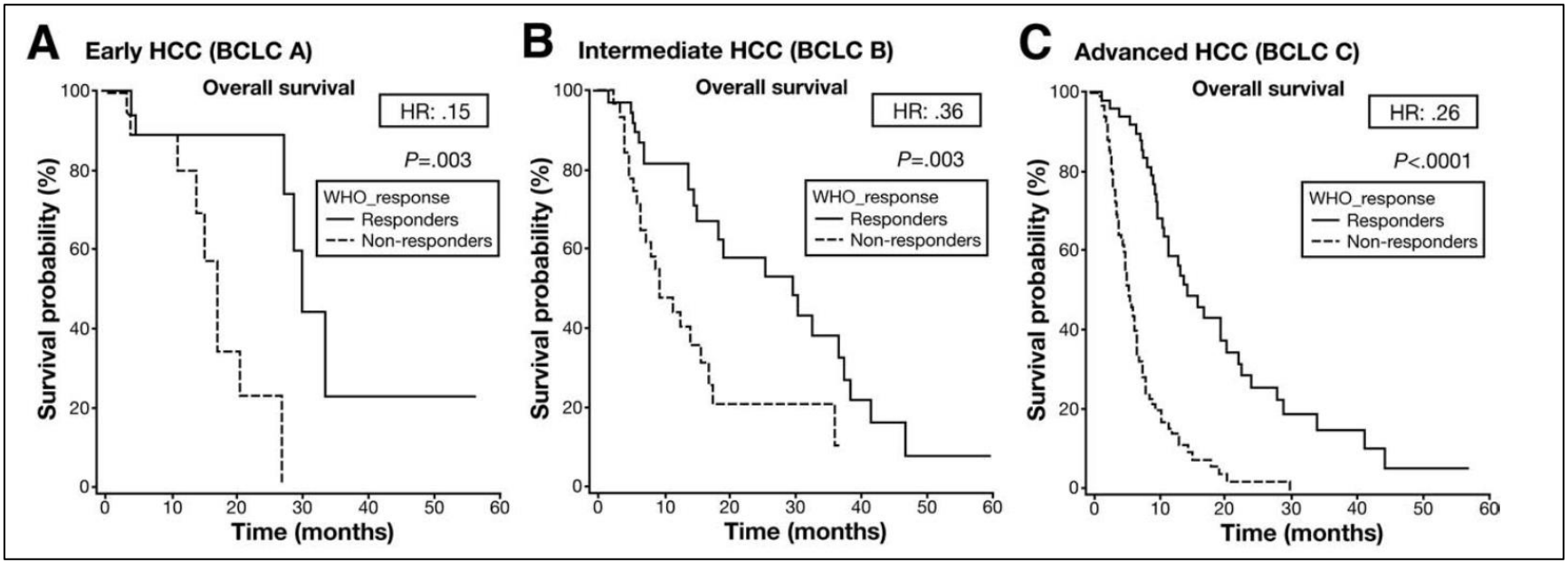




Ther Adv Med Oncol 2021

Radioembolization for Hepatocellular Carcinoma Using Yttrium-90 Microspheres: A Comprehensive Report of Long-term Outcomes

RIAD SALEM,[*,‡,§] ROBERT J. LEWANDOWSKI,[*] MARY F. MULCAHY,[‡] AHSUN RIAZ,[*] ROBERT K. RYU,[*] SAAD IBRAHIM,[*] BASSEL ATASSI,[*] TALIA BAKER,[§] VANESSA GATES,[*] FRANK H. MILLER,[*] KENT T. SATO,[*] ED WANG,[§] RAMONA GUPTA,[*] AL B. BENSON,[‡] STEVEN B. NEWMAN,[‡] REED A. OMARY,[*] MICHAEL ABECASSIS,[‡] and LAURA KULIK[‖]



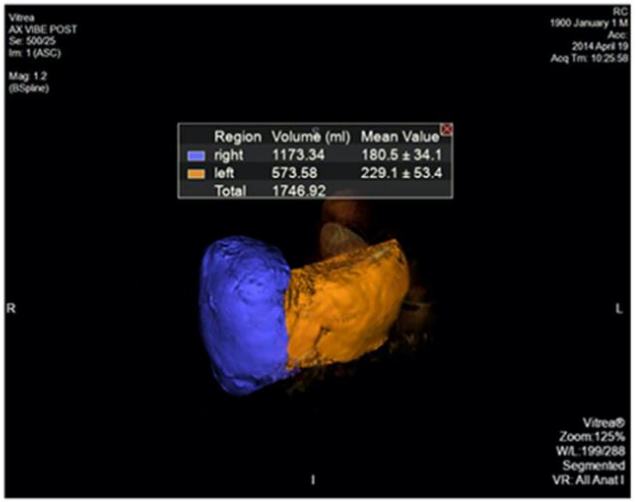
PR	10%	40%	25%

J Gastroenterol 2010

Conversion to resection post radioembolization in patients with HCC: recommendations from a multidisciplinary working group

a.

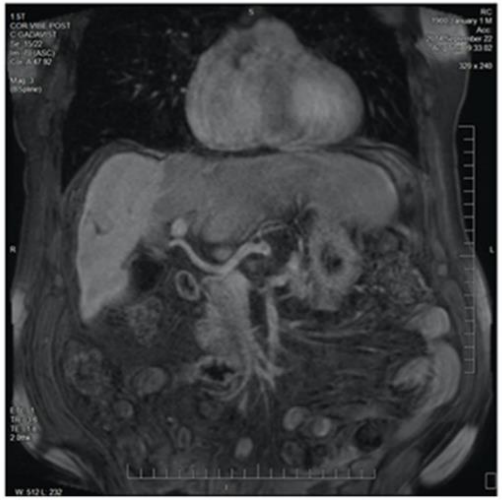
b.



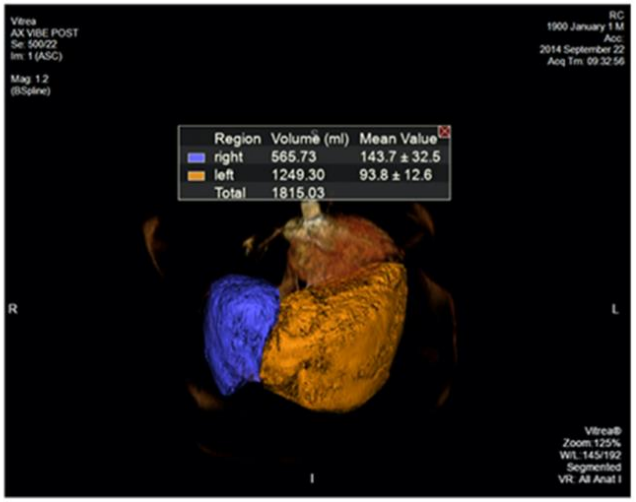
56 yr male
Class A cirrhosis
HCC 3cm
Seg 6-7

Pre-TARE
R Lobectomy
FLR<40%

c.



d.



Post-TARE
R Lobectomy
FLR 69%

HPB 2022

Radiation Lobectomy

a.

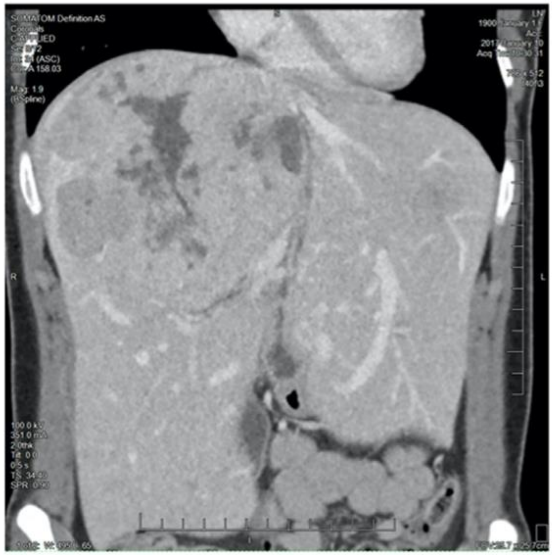
b.

33yr female
No cirrhosis

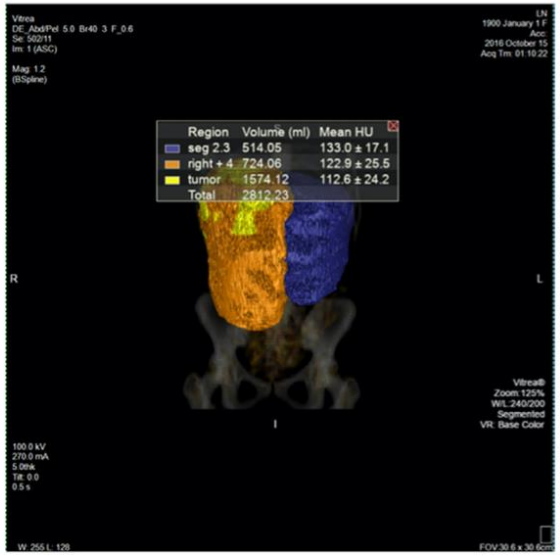
HCC 27cm

Pre-TARE <13%

c.



d.



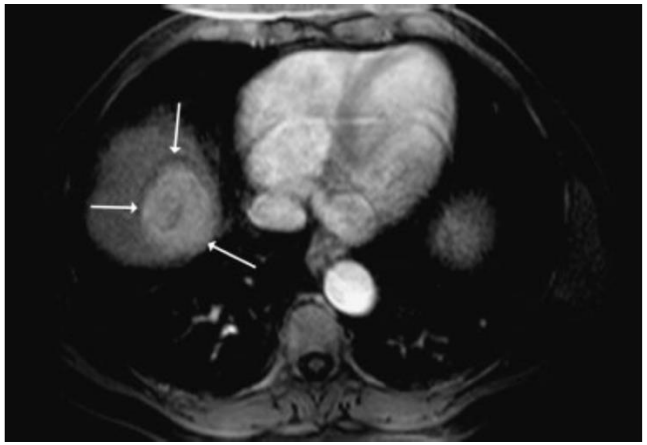
Post-TARE 27%

R Trisectionectomy

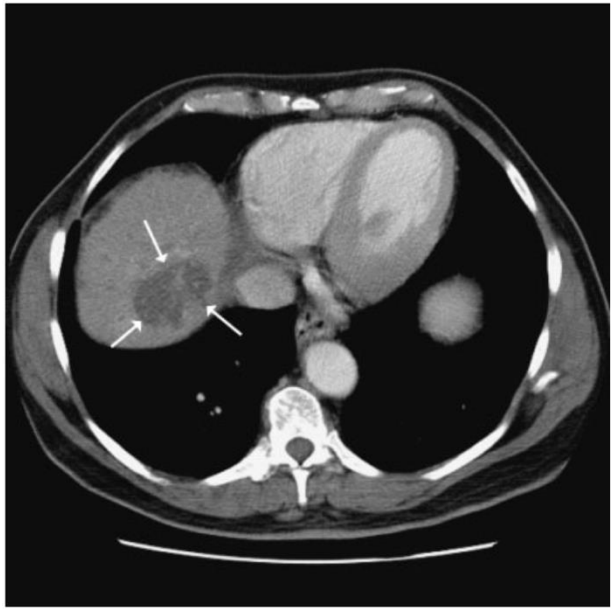
HPB 2022

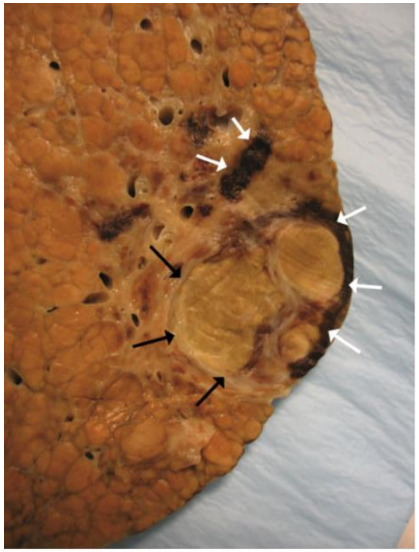
Yttrium-90 Microspheres (TheraSphere®) Treatment of Unresectable Hepatocellular Carcinoma: Downstaging to Resection, RFA and Bridge to Transplantation

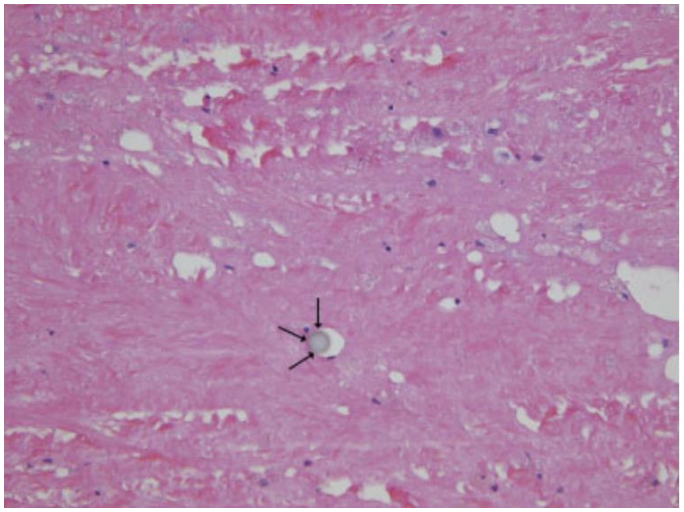
J Surg Oncol 2006



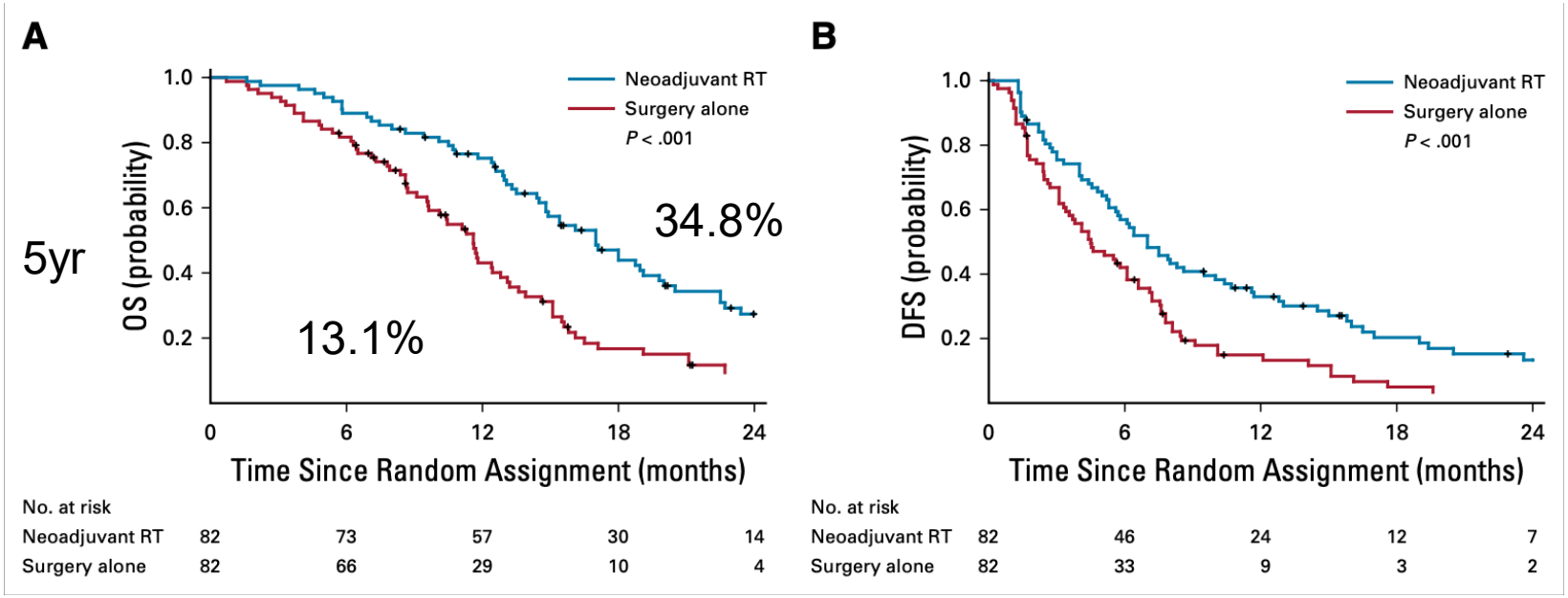
OS after TARE conversion resection	
1-yr	85%
2-yr	54%
3-yr	27%







Neoadjuvant Three-Dimensional Conformal Radiotherapy for Resectable Hepatocellular Carcinoma With Portal Vein Tumor Thrombus: A Randomized, Open-Label, Multicenter Controlled Study



Increased Liver Toxicity!!!

J Clin Oncol 2020

Surgical Resection After Down-Staging of Locally Advanced Hepatocellular Carcinoma by Localized Concurrent Chemoradiotherapy

243 pts

Unresectable HCC BCLC A-C

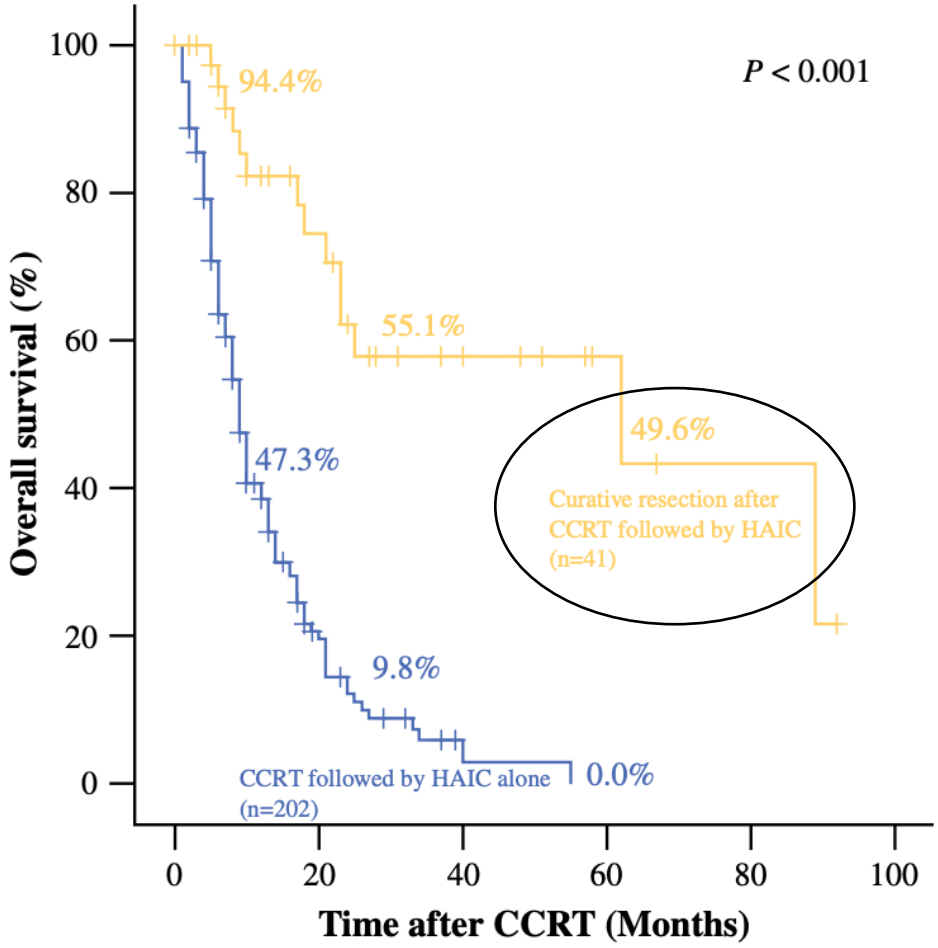
PVT

CCRT + HAIC

Hepatectomy 17%

Tumor Downstaging 78%

FLRV 47% ➡ 70% before surgery



Ann Surg Oncol 2014

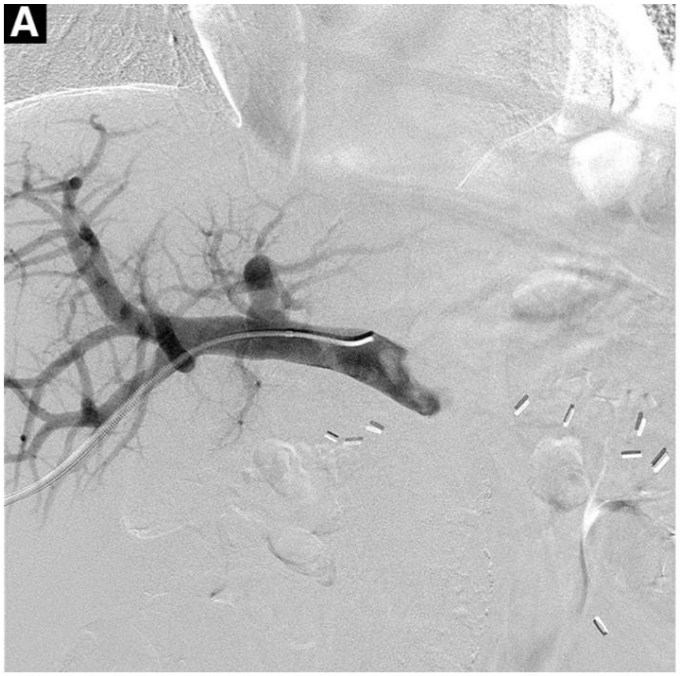
Portal Vein Embolization for Hepatocellular Carcinoma

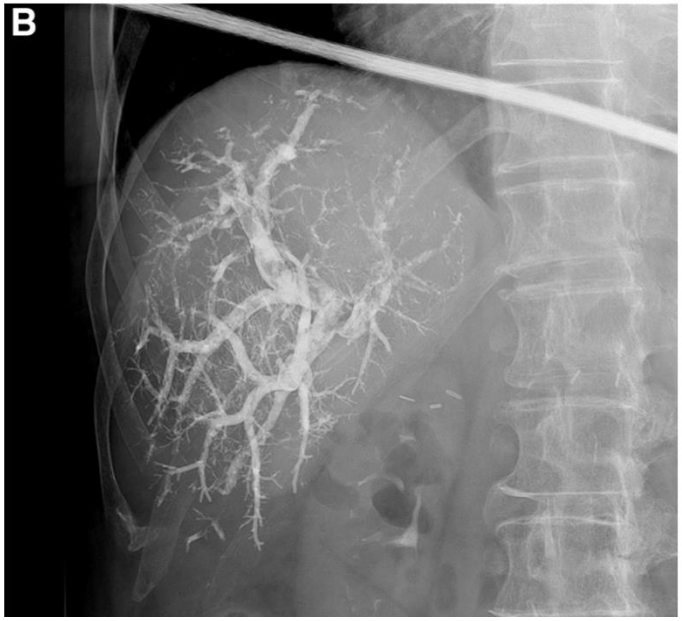
Junichi Shindoh Ching-Wei D. Tzeng Jean-Nicolas Vauthey

Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, USA

Criteria:

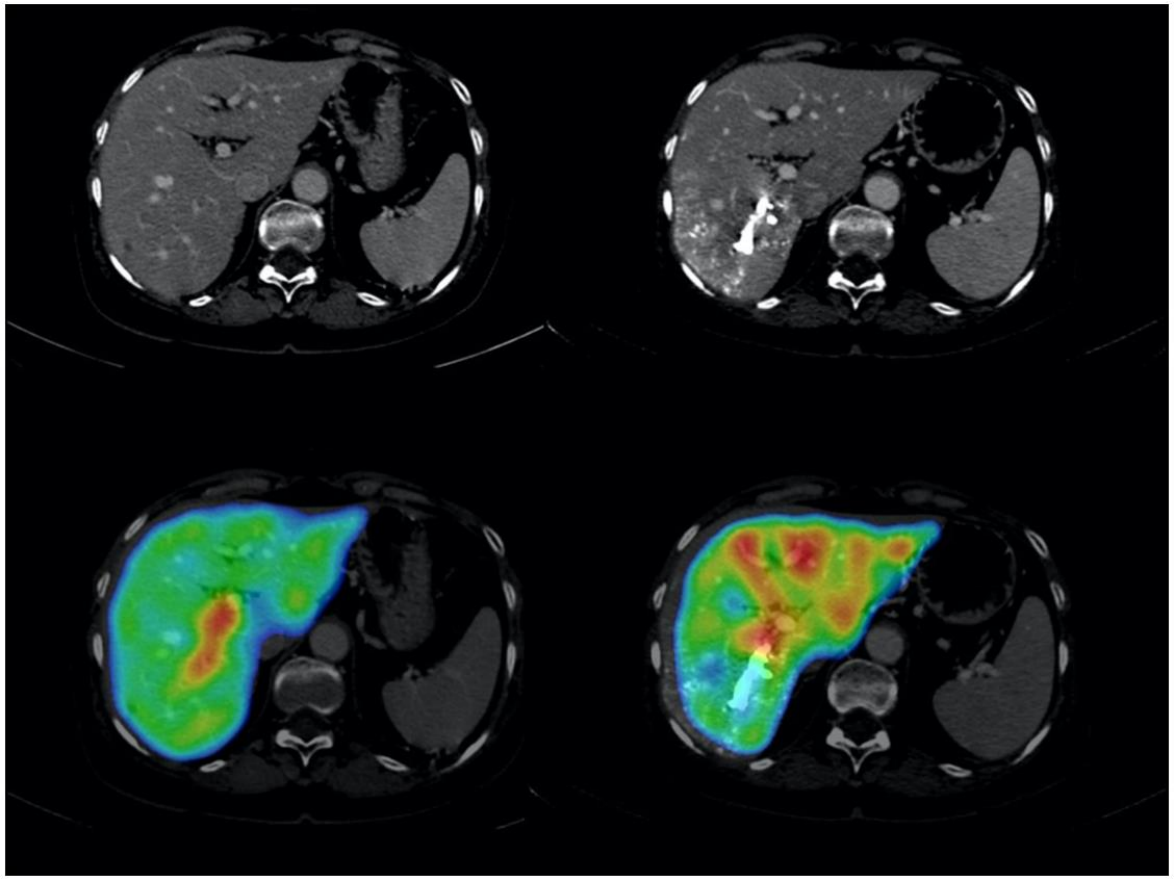
<65 years
Normal liver function Child-Pugh A, ICG-R15<10%
FLR/SLV < 30% (normal liver)
FLR/SLV < 40% (chronic liver damage)
ASA 0-1
No severe cirrhosis
No fatty liver disease
No severe portal hypertension
MELD<10





Liver Cancer 2012

Embolisation portale préopératoire : présent et futur



Increase FLRV: 5-20%

4 – 6 weeks

Downstaging 60-80%

Complications 10-20%

20% lose surgery

a. Insufficient growth
b. Tumor progress

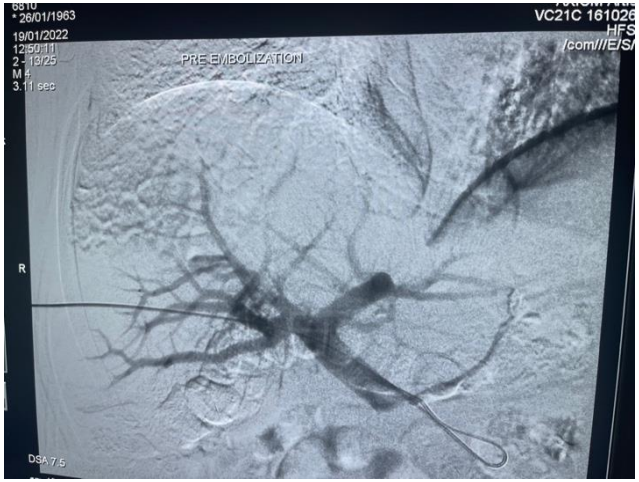
PVE + TACE

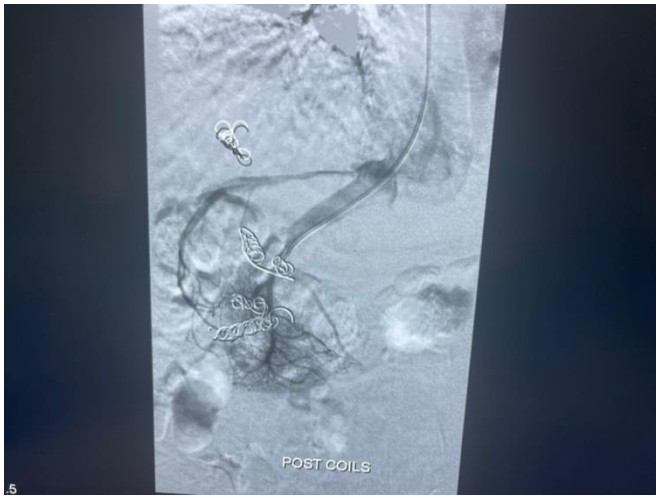
Bull Cancer 2017

Preoperative Sequential Portal and Hepatic Vein Embolization in Patients with Hepatobiliary Malignancy

World J Surg 2015

Hepatic Venous Deprivation





ORIGINAL ARTICLE

ALPPS as a salvage procedure after insufficient future liver remnant hypertrophy following portal vein occlusion

Marcelo Enne[1], Erik Schadde[2,3], Bergthór Björnsson[4], Roberto Hernandez Alejandro[5], Klaus Steinbruck[6], Eduardo Viana[1], Ricardo Robles Campos[7], Massimo Malago[8], Pierre-Alain Clavien[9], Eduardo De Santibanes[10], Brice Gayet[11] & On Behalf of ALPPS Registry Group

Figure 1. CT revealing a large liver tumor involving segments 4,5,6,8 (volume of segments 2-3: 295 cmc, 13% of total liver volume) (13)

Figure 2. The intra-operative aspect

HPB 2017

ALPPS

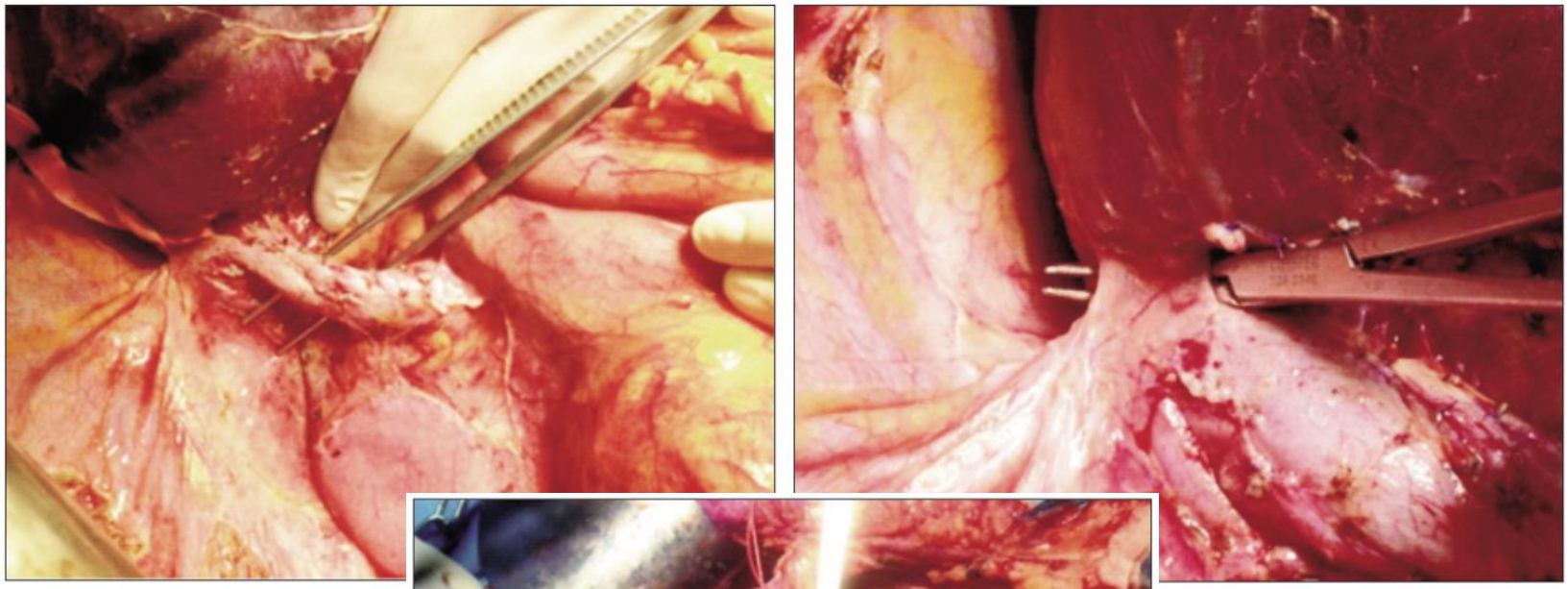


Figure 6. The dissection of of right hepatic vein

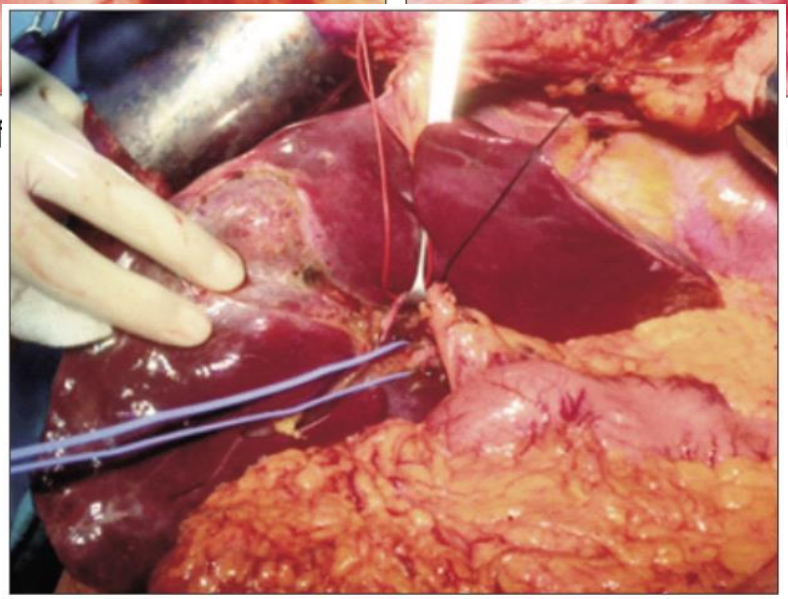
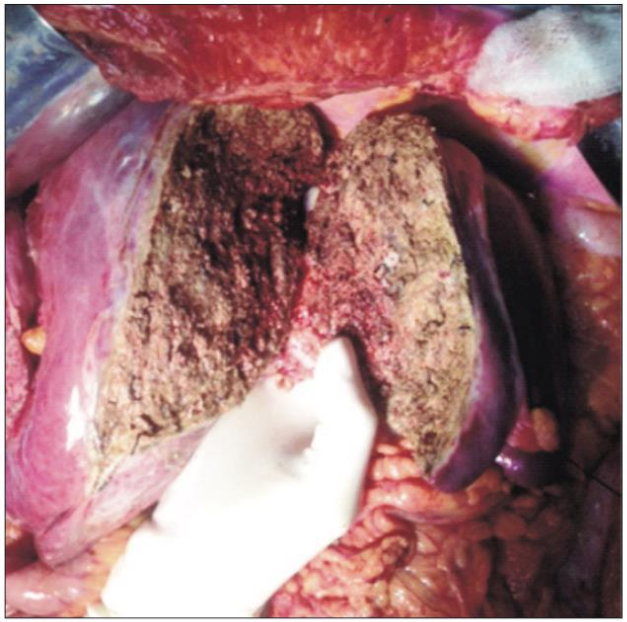


Figure 8. The dissection of right portal vein (13)

ALPPS



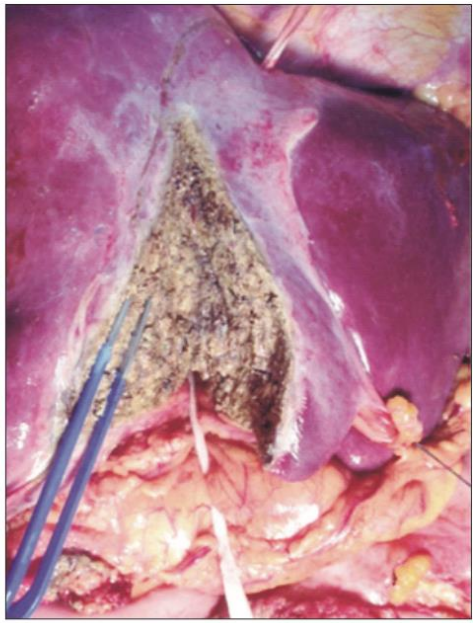
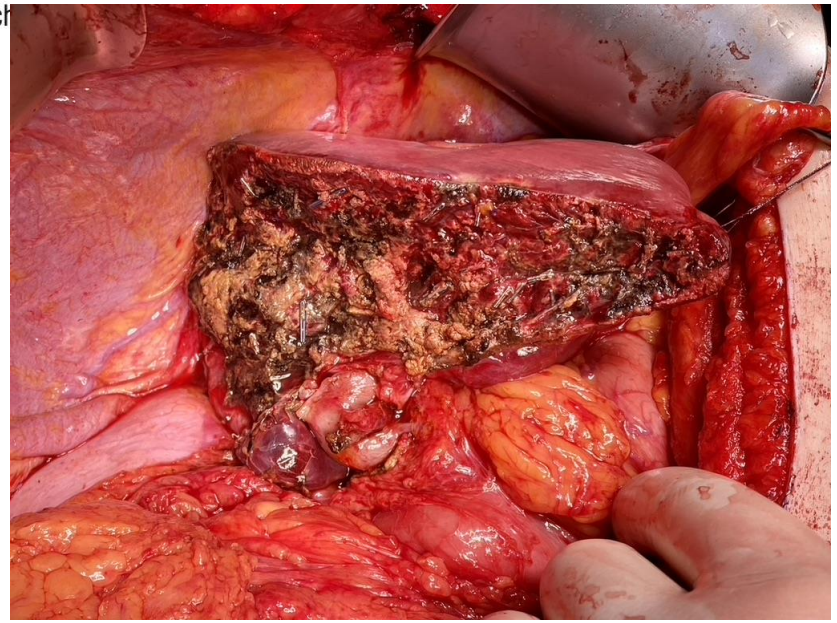


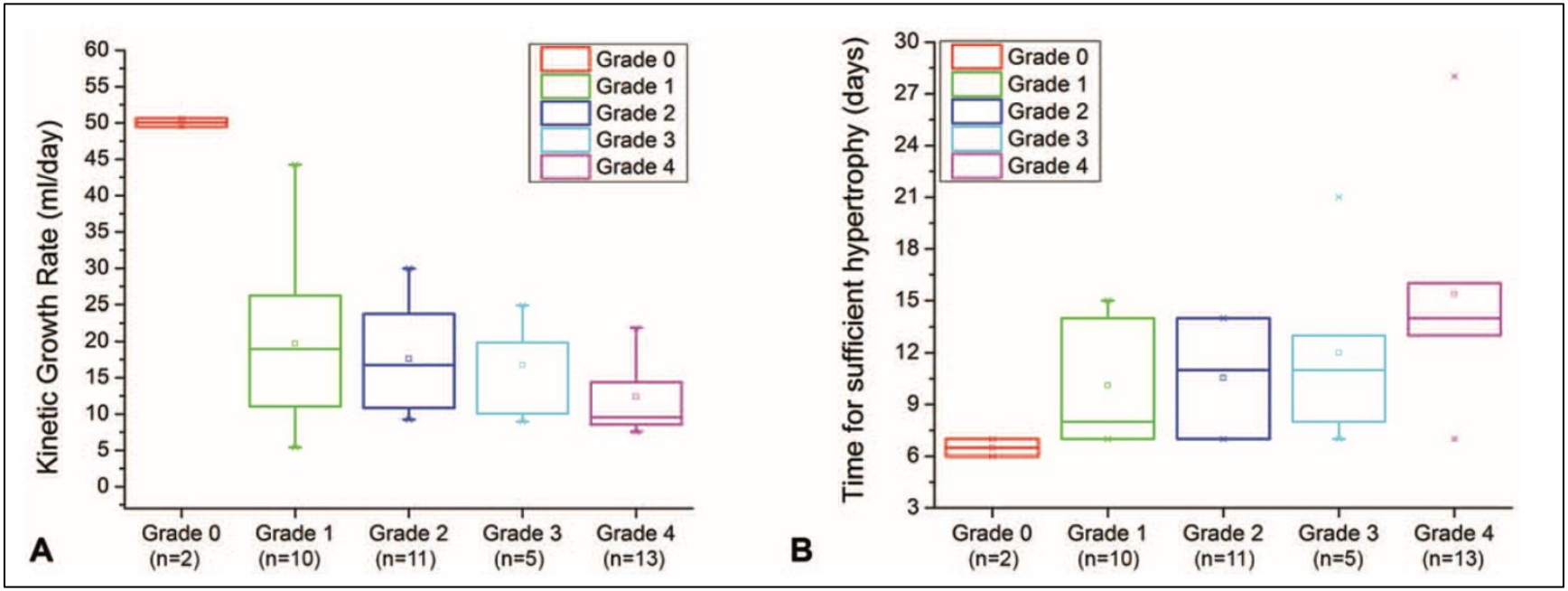
Figure 4. CT scan: final aspect after ALPPS



Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy for Unresectable Hepatitis B Virus-related Hepatocellular Carcinoma

A Single Center Study of 45 Patients

Ann Surg 2016



↑↑↑ FLRV: 47% - 192%

Time: 7 – 14 days

Conversion to Surgery Rate > 90%

Mortality up to 12%!!!

Chinese expert consensus on conversion therapy for hepatocellular carcinoma (2021 edition)

1. Resection is an important means to achieve long-term survival after successful conversion therapy…

2. OS after conversion and resection is related to the No of surviving tumor cells in the resected specimen (pCR, MPR 10%, SD 3-4mo)…

3. Eliminates potential residual tumor cells…

4. Reduces drug exposure and systemic tx adverse effects…

5. Provides guidance to adjuvant treatment through postop pathological examination…

6. Even in disappearing lesions…

7. CT, MRI, PET, mRECIST…

8. Needs to be supported by RCTs…

HepatoBiliary Surgery and Nutrition 2021

Conversion Therapy for HCC

"…Biology is King,

Selection of Cases is Queen,

Technical Details of Surgical Procedures are Princes and Princesses who frequently try to overthrow the powerful forces of the King and Queen,

Usually to no long-term avail, although with some temporary apparent victories…"

Dr. Blake Cady
1930 - 2023