8th LIVER INTEREST GROUP Annual Meeting

Cape Town 2017

Liver resection for HCC

Jose Ramos

University of the Witwatersrand
Donald Gordon Medical Centre

The liver is almost unique in that treatment of the underlying malignancy is determined not only by the stage of the malignancy but also the state of the organ itself

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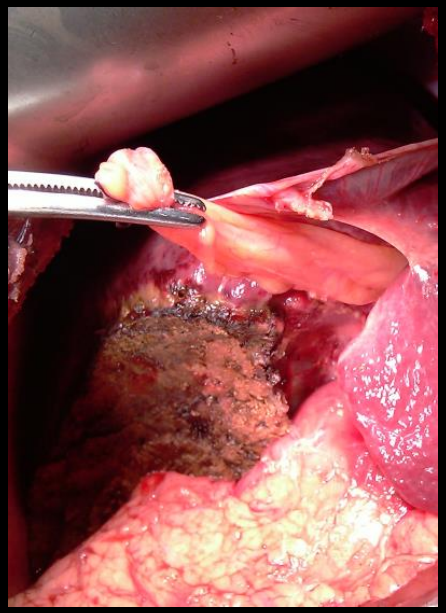
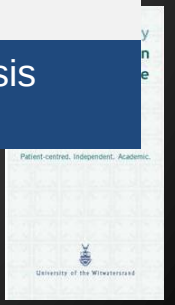
Treatment options in HCC are largely determined by the state of the liver



Staging Systems in HCC

Staging System	Hepatic Function	Alpha-fetoprotein	Performance Score	Tumor Staging
Okuda	Ascites, albumin, and bilirubin	No	No	Tumor > or < 50% of cross-sectional area of liver
TNM	No	No	No	Number of nodules, tumor size, presence of portal vein thrombosis, and presence of metastasis
CLIP	CTP	< 400 or ≥ 400 ng/mL	No	Number of nodules, tumor > or < 50% area of liver, and portal vein thrombosis
BCLC	CTP	No	Yes	Tumor size, number of nodules, and portal vein thrombosis
CUPI	Bilirubin, ascites, alkaline phosphatase	< 500 or ≥ 500 ng/mL	Presence of symptoms	TNM
JIS	CTP	No	No	TNM
GRETCH	Bilirubin, alkaline phosphatase	< 35 or ≥ 35 µg/L	Yes	Portal vein thrombosis

Marrero JA, et al. Hepatology. 2005;41:707-716.



HCC and state of liver

- Cirrhosis present in 80% - 85% of patients with HCC

[1] Sherman M. Semin Liver Dis 2005;25:143—54.
[2] Altekruse SF et al. J Clin Oncol 2009;27:1485—91.
[3] Borie F et al J Surg Oncol 2008;98:505—9.

- Absence of cirrhosis does not mean the liver is healthy
  - Fatty liver
  - Fibrosis

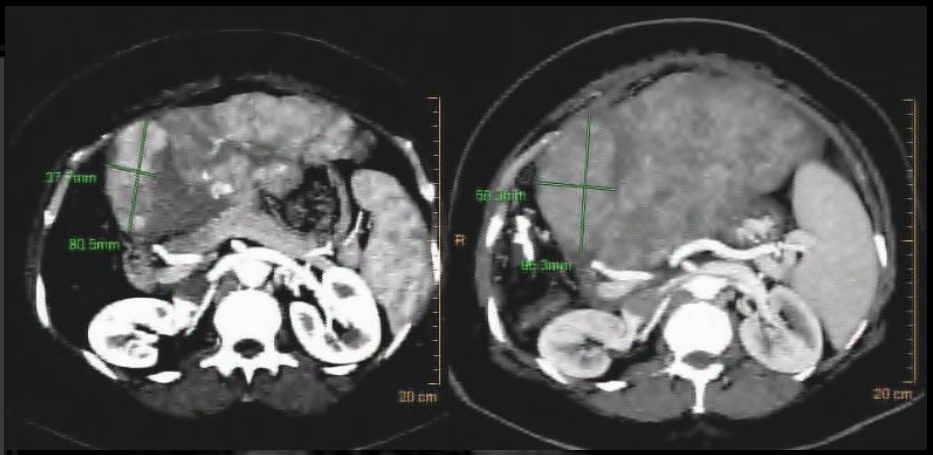
Not reported	8 (10)
Steatosis, *n* (%)	
Yes	42 (51)
No	40 (49)
Siderosis, *n* (%)	
Yes	24 (29)
No	30 (37)
Not reported	28 (34)

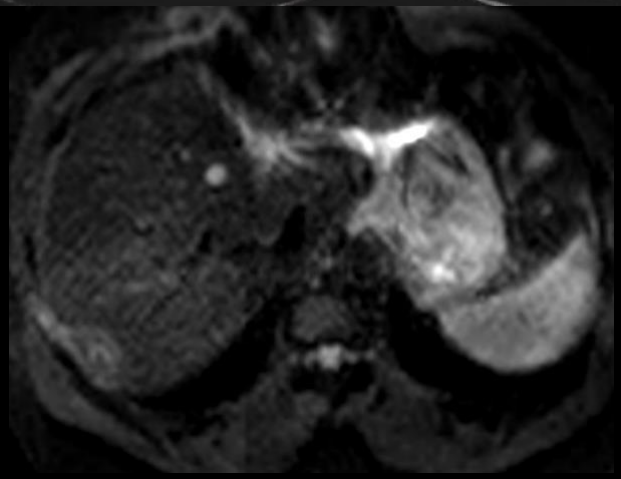
Fibrosis, *n* (%)	
0	23 (28)
1	24 (29)
2	26 (32)
3	9 (11)
Inflammation, *n* (%)	
0	7 (9)
1	47 (57)
2	18 (22)
3	2 (2)

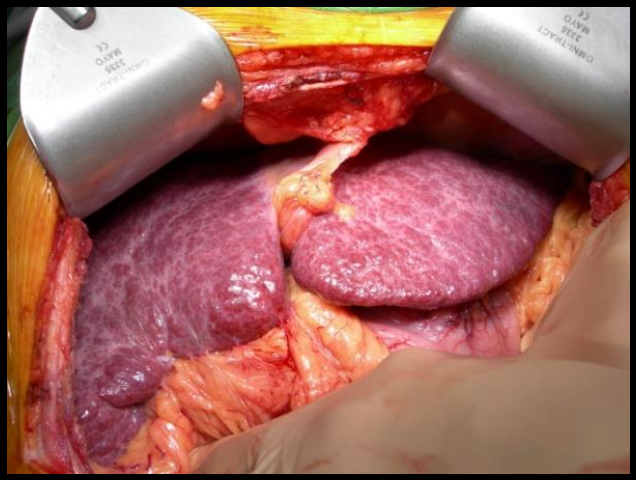
- Normal / healthy liver in 12% - 15%

Determinants of outcome in HCC

- Progression of HCC
- New HCC
- Progression of cirrhosis







Survival of unresected HCC according to BCLC classification (Italy)

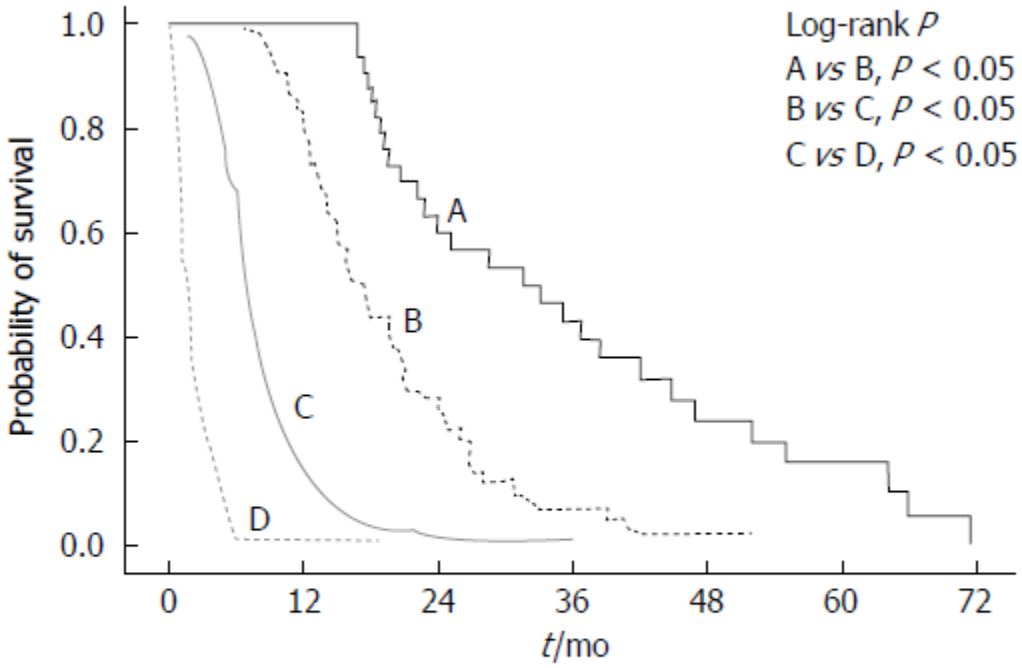


Figure 1 Kaplan-Meier analysis of 320 untreated hepatocellular carcinoma patients. Survival according to Barcelona Clinic Liver Cancer classification.

World J Hepatol 2012 September 27; 4(9): 256-261

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Curative options in HCC

- Surgical resection
  - Can only address the malignancy
  - Limited by the state of the liver, extent of malignancy
  - Failure due to recurrence of HCC or liver failure
- Transplantation
  - Can address both the diseased liver as well as the malignancy
  - Failure due to recurrence of HCC
  - May not be available to many HCC patients

Both options only applicable to a limited number of patients

Liver Transplantation for HCC: Milan Criteria (Stage 1 and 2)

Single tumor, not > 5 cm Up to 3 tumors, none > 3 cm

Table 1

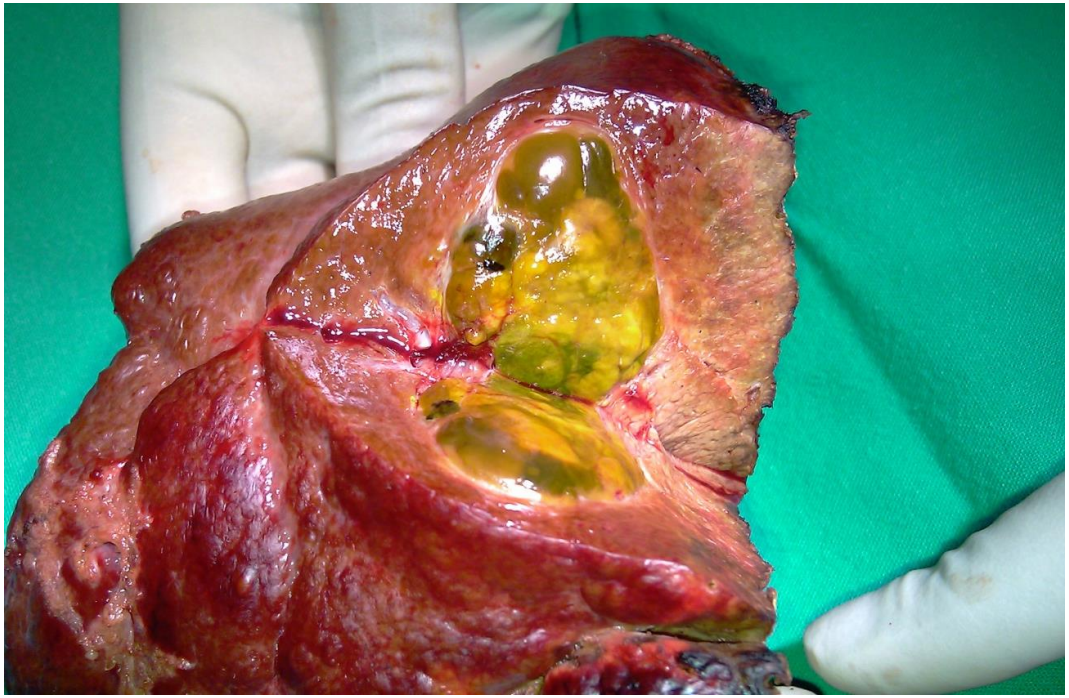
Liver Transplantation Criteria

Milan's Criteria[7]	UCSF Criteria[8]	Silva et al[9]
Single tumor ≤ 5 cm	Single tumor ≤ 6.5 cm	
Or up to 3 tumors ≤ 3 cm	Or up to 3 tumors ≤ 4.5 cm, and total sum is ≤ 8 cm	Up to 3 tumors ≤ 5 cm, and total sum is ≤ 10 cm
All Three Criteria Lists		
No vascular invasion		
No regional nodal/distant metastasis		

UCSF = University of California of San Fransisco.

- 5-yr survival with transplantation: ~ 70%
- 5-yr recurrent rates: < 15%

Mazzaferro V, et al. N Engl J Med. 1996;334:693-699.
Llovet JM. J Gastroenterol Hepatol. 2002;17(suppl 3):S428-S433.



Liver resection for HCC

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How much liver can be safely resected?

- No cirrhosis 60% – 70%
- Childs A 40% - 50%
- Childs B 20% - 30%
- Childs C Not resectable

Surgery not an option for majority of patients presenting with HCC

Extent of cirrhosis in screening program

Table 2. Epidemiologic and Clinical Features of the 112 Patients at the Time of Diagnosis of Hepatocellular Carcinoma

Patient features	Number
Males	88 (79%)
Mean age, yr (range)	61 (42–79)
More than 53 years of age	95 (85%)
Child–Pugh class	
A	78 (69%)
B	30 (27%)
C	4 (3%)
AFP, ng/mL	
≤ 20	43 (38%)
21–400	42 (38%)
>400	27 (24%)
Single tumor node	
at US	60 (54%)
after staging	46 (41%)
CLIP score	
0	29 (26%)
1	45 (40%)
2	27 (24%)
3	9 (8%)
4	2 (2%)

Table 5. Epidemiologic and Clinical Features of Cancer Patients Identified During the 3 Quinquennia of Surveillance

	Surveillance period			
Patient features	1987–1991	1992–1996	1997–2001	*P* value
Child–Pugh class				
A	29 (56%)[a]	30 (81%)[b]	19 (83%)[c]	a vs. b 0.014; a vs. c 0.036
B	19 (36%)	7 (19%)	4 (17%)	
C	4 (8%)	0	0	

GASTROENTEROLOGY 2004;126:1005–1014

Extent of cirrhosis in HCC patients at presentation

- Middle-East

Hepat Mon. 2013;13(5):e7612

CPT[a] Class, No. (%)	
A	101 (29.5)
B	152 (44.4)
C	89 (26.0)

- Europe

Child-pugh classes	
A	105 (33)
B	142 (44)
C	73 (23)

- Unresectable

World J Hepatol 2012 September 27; 4(9): 256-261

Child-pugh classes	
A	105 (33)
B	142 (44)
C	73 (23)

Extent of cirrhosis in HCC patients undergoing surgery

- Paris (Surg vs Tx)

Annals of Surgery • Volume 256, Number 6, December 2012

Child Pugh Class		
A	80 (87.9%)	19 (18.8%)
B	10 (11%)	45 (44.6%)
C	1 (1.1%)	37 (36.6%)

- New York (Surg vs TACE)

Ann Surg Oncol (2013) 20:2881–2886

Childs–Pugh class		
A	39 (100 %)	29 (88 %)
B	0 (0 %)	4 (12 %)
NA	1	

Long-term survival after resection HCC

- 8450 patients resected
- 1516 5-year survivors
- 520 10-year survivors

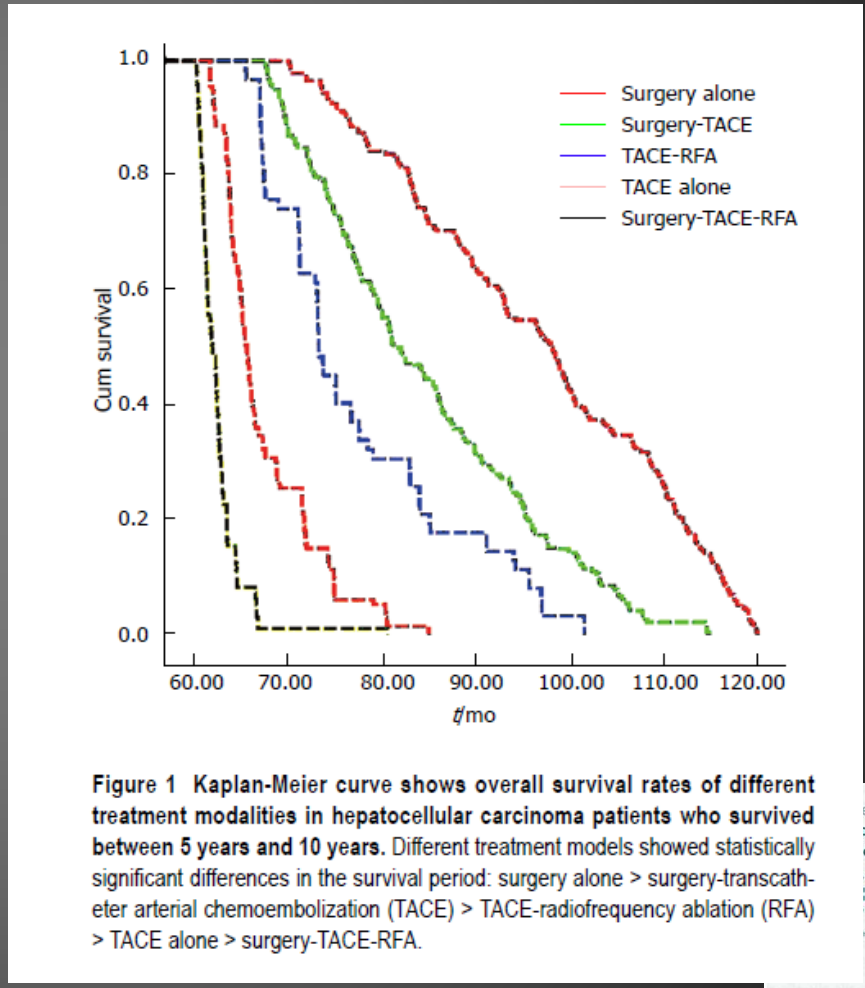

Figure 1 Kaplan-Meier curve shows overall survival rates of different treatment modalities in hepatocellular carcinoma patients who survived between 5 years and 10 years. Different treatment models showed statistically significant differences in the survival period: surgery alone > surgery-transcatheter arterial chemoembolization (TACE) > TACE-radiofrequency ablation (RFA) > TACE alone > surgery-TACE-RFA.

World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i23.3649

World J Gastroenterol 2013 June 21; 19(23): 3649-3657
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
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BRIEF ARTICLE

Hepatocellular carcinoma: Clinical study of long-term survival and choice of treatment modalities

Ke-Tong Wu, Cun-Chuan Wang, Li-Gong Lu, Wei-Dong Zhang, Fu-Jun Zhang, Feng Shi, Chuan-Xing Li

World J Gastroenterol 2013 June 21; 19(23): 3649-3657

Surgical Resection

TABLE 2. Results of resection for hepatocellular carcinoma

Author	N	Operative mortality (%)	Survival 1 year	Survival 3 years	Survival 5 years
Okuda, 1985[7]	153	30	30	15	12
Japan Liver Survey, 1994*[39]	468	—	76	55	45
	3500	—	76	52	36
Bismuth, 1993, 1995[40,41]	68	3	74	52	40
	60	10	80	52	—
Fong, 1999[42]	54	3.7	83	58	42
	100	5	77	47	37
Grazi, 2001[43]					
Before 1992	107	9.3	—	53	32
After 1992	157	1.3	—	72	49
Poon, 2002[44]					
Milan Criteria	135	4	90	76	70
Esnaola, 2003[45]					
USA	169	5.3			31
France	187	6.4			31
Japan	230	3.5			41
Cha, 2003[46]					
Milan Criteria	36	2.8	85	74	69
Ouside Milan	144	5	70	44	31
Wu, 2005[47]	105	1	86	70	55
Nuzzo, 2007[48]	113	3			44
					24 (10 years)
Katz, 2009[49]	192	4.6	75	56	41
					23 (10 years)
Nathan, 2009 SEER[50]	788				39

*Multi-institutional series.

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Resection vs Transplantation

TABLE 3. Recent Studies Comparing Long-Term Outcome of Patients with HCC Treated Primarily With Resection (and salvage transplantation) or Primary Liver Transplantation

First Author	Year	Primary Therapy	Sample Size	5-year OS Rate	5-year DFS Rate	Study Period	ITT Analysis
Lee[85]	2010	Transplantation	78	68%	75%*	1997–2007	Yes
		Resection	130	52%	50%		
Facciuto[84#]	2009	Transplantation	119	62%	—	1997–2007	Yes
		Resection	60	61%	—		
Del Gaudio[83]	2008	Transplantation	147	58%	54%	1996–2005	Yes
		Resection	80	66%	41%		
Shah[82]	2007	Transplantation	140	64%	78%*	1995–2005	Yes
		Resection	121	56%	60%		
Poon[81]	2007	Transplantation	85	44%	—	1995–2004	Yes
		Resection	228	60%	—		
Margarit[80]	2005	Transplantation	36	50%	64%*	1988–2002	Yes
		Resection	37	78%	39%		
Bigourdan[79]	2003	Transplantation	17	71%	80%*	1991–1999	Yes
		Resection	20	36%	40%*		
Adam[79]	2003	Transplantation	195	61%*	58%*	1984–2000	Yes
		Resection	98	50%	18%		
Belghiti[77]	2003	Transplantation	70	—	59%	1991–2001	No
		Resection	18	—	61%		
Figueras[78]	2000	Transplantation	85	60%	60%*	1990–1999	Yes
		Resection	35	51%	31%		

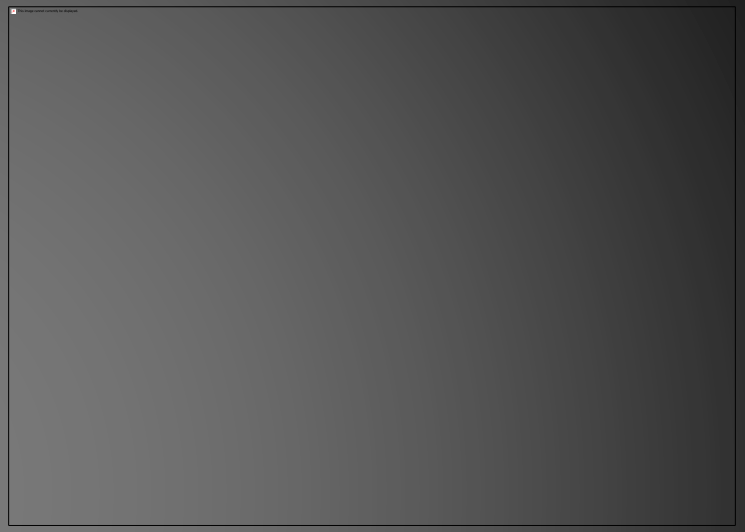
*Significant difference as reported in the original study; #4-year survival rates are reported for patient meeting the Milan criteria.
DFS indicates disease-free survival; ITT, Intention-to-treat analysis; OS, overall survival.

Resection of large HCC in non-cirrhotic liver

- Includes fibrolamellar HCC
- Hep B&C negative
- Younger patients
- Usually confined to liver
- Diagnosis often only confirmed after resection
- Worthwhile candidates for resection

Verhoef C et al Dig Surg 2004;21:380-386

Lang H et al Br J Surg 2005;192:198-202



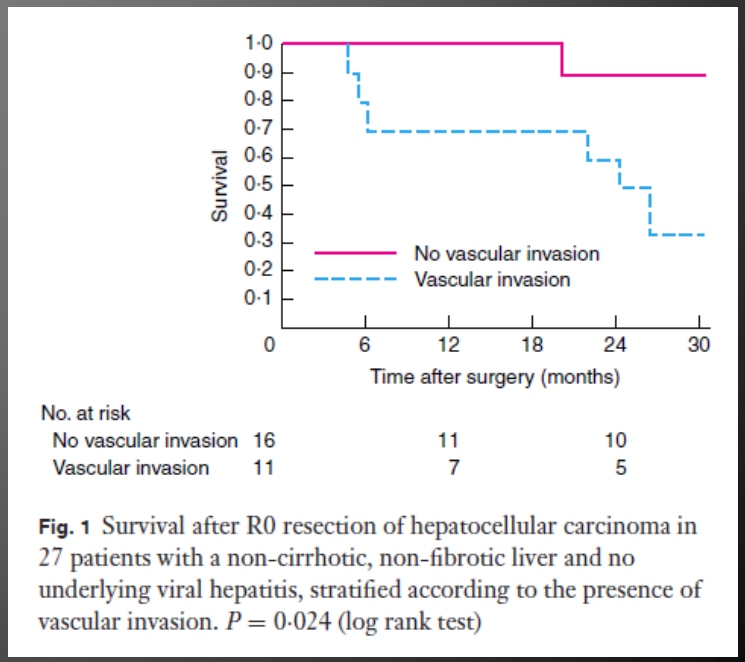


Fig. 1 Survival after R0 resection of hepatocellular carcinoma in 27 patients with a non-cirrhotic, non-fibrotic liver and no underlying viral hepatitis, stratified according to the presence of vascular invasion. $P = 0{\cdot}024$ (log rank test)

Survival after resection in non-cirrhotic HCC

Table 1 prognostic factors for hepatocellular cancer in non-cirrhotic liver.

1er author (references)	Number of patients	Dates of study	Overall 5 Year survival (%)	Factors of poor prognosis
Bege et al. [15]	116	1987–2005	40.0	R1 resection Vascular involvement HBV infection
Dupont-Bierre et al. [16]	84	1998–2003	44.4	Multiple tumors Gross vascular involvement
Lang et al. [17]	83	1998–2005	30.0	UICC stage Vascular involvement Tumor grade
Laurent et al. [18]	108	1987–2005	29.0	Blood transfusion Absence of capsule Satellite nodules Resection margin < 1cm
Capussotti et al. [19]	47	1985–2002	30.9	Size > 10 cm Satellite nodules

HBV: hepatitis B virus; UICC: Union Internationale Contre le Cancer

Journal of Visceral Surgery (2011) 148, 3–11

Received: 18 April 2017 | First decision: 9 May 2017 | Accepted: 21 July 2017

DOI: 10.1111/apt.14261

WILEY AP&T Alimentary Pharmacology & Therapeutics

Temporal trends, clinical patterns and outcomes of NAFLD-related HCC in patients undergoing liver resection over a 20-year period

R. Pais[1,2] | L. Fartoux[1] | C. Goumard[3] | O. Scatton[3] | D. Wendum[4] | O. Rosmorduc[1] | V. Ratziu[1,2]

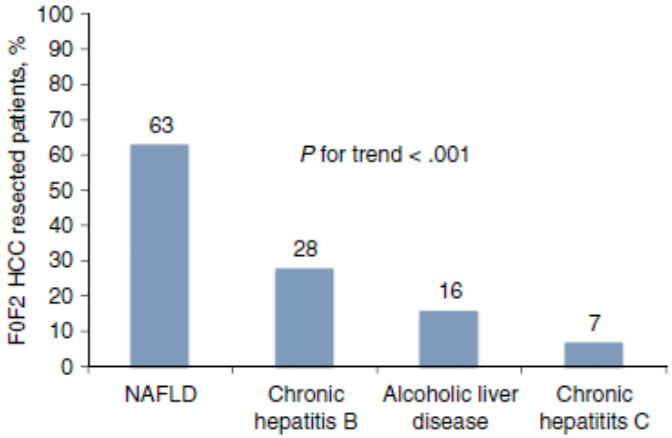
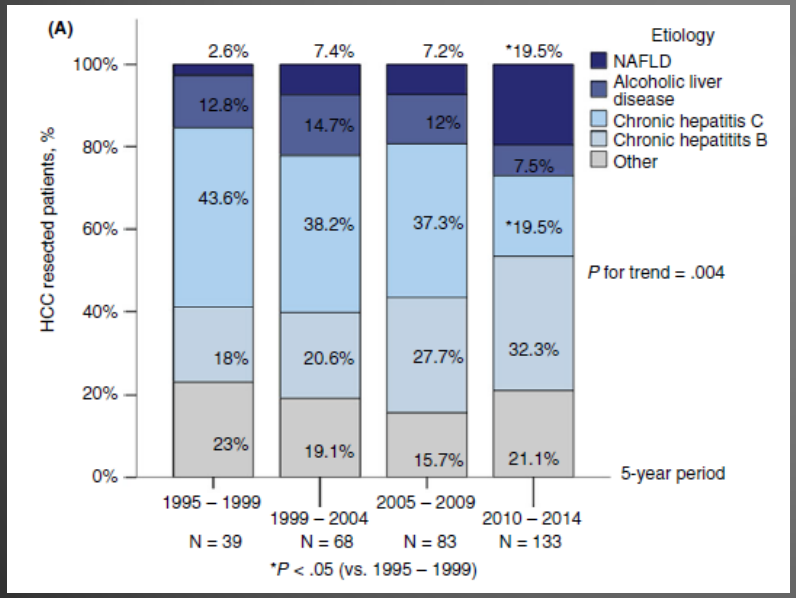


FIGURE 2 Proportion of HCC cases occurring in the absence of bridging fibrosis/cirrhosis according to the aetiology of chronic liver disease



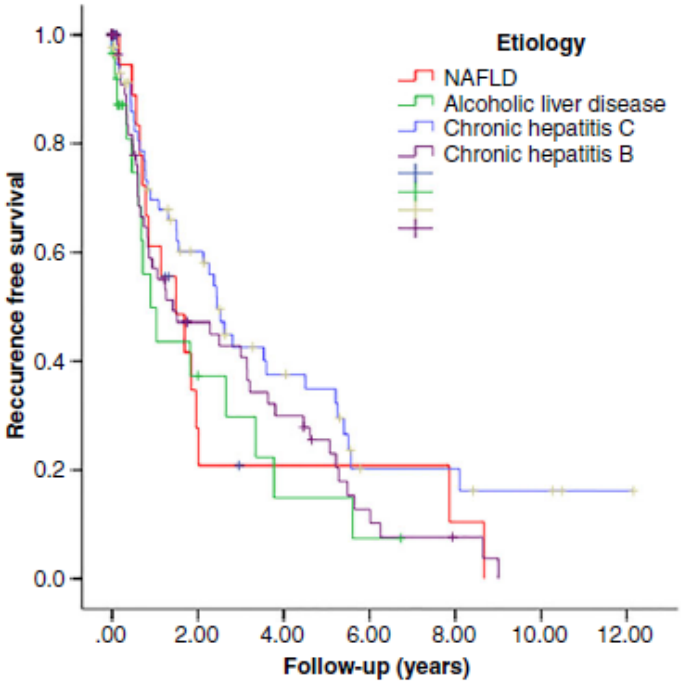
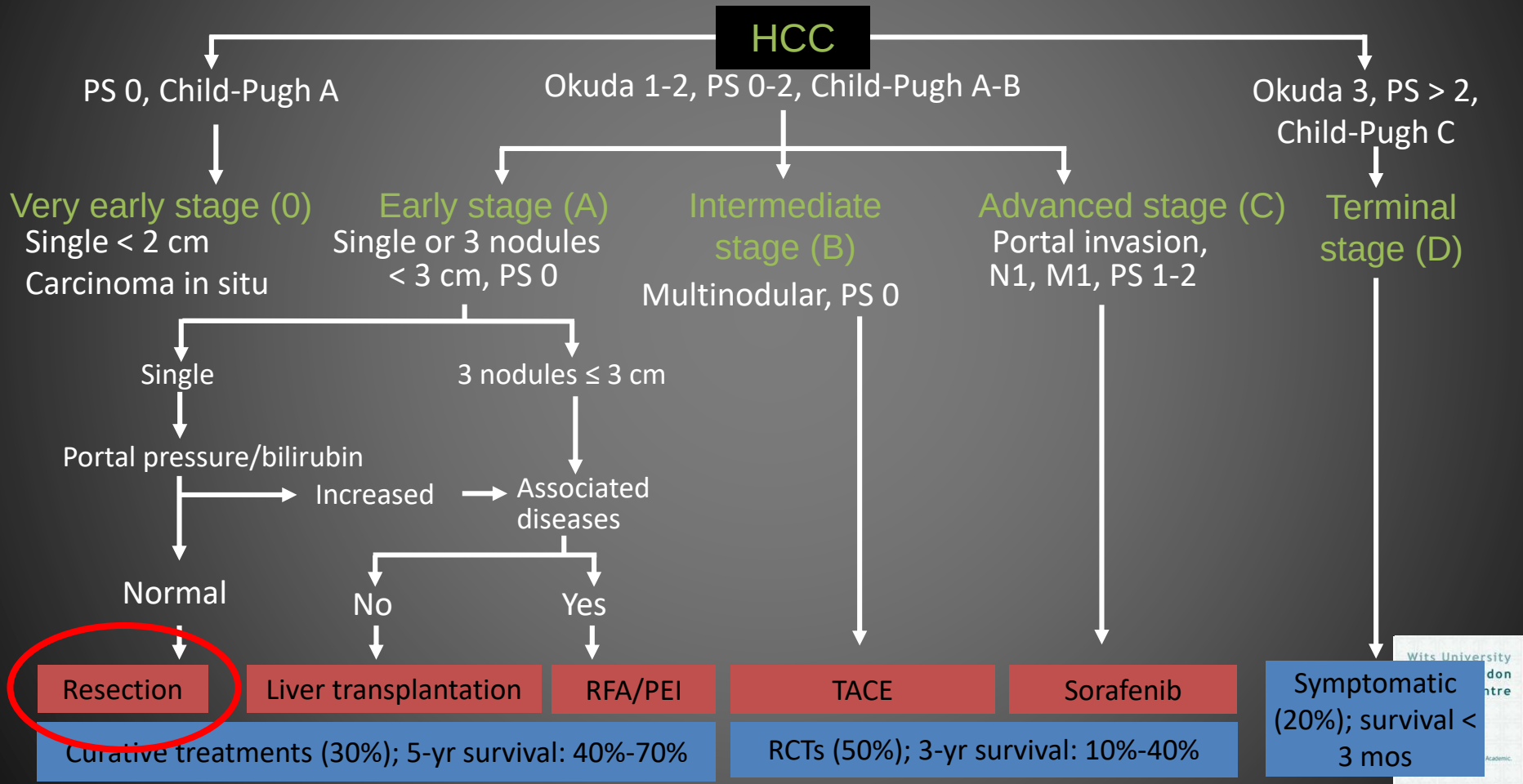


FIGURE 3 HCC-recurrence-free survival curves according to the aetiology of chronic liver disease

BCLC Staging and Treatment Strategy



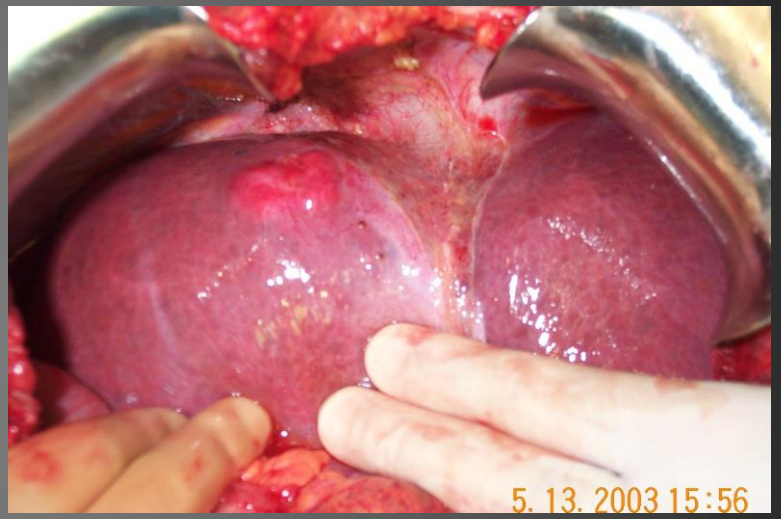
Llovet JM, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. Journal of the National Cancer Institute. 2008;100(10):698-711

Surgical resection only appropriate in CTP A and some B patients - BCLC Early Stage (A)

this applies to only 20% - 40% of patients with HCC

Is surgical resection possible?

- State of liver
- Stage of the disease
  - No extrahepatic metastases
  - Resectable disease
  - No major vessel invasion
- Remnant liver volume
- Better alternatives to resection?
  - MDT



How can we improve outcomes after resection of HCC?

- Improve surgical technique
  - Segmental resection
  - Combined resection and ablation
- Increase proportion of resectable cases (conversion)
  - PVE
  - TACE /TARE
- Improve diagnostic accuracy
  - Imaging

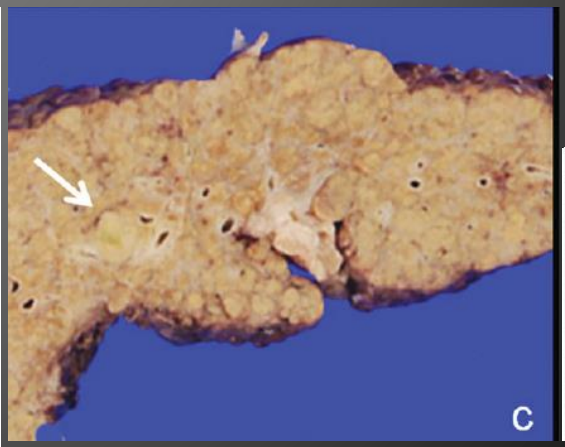
Despite best imaging with MRI ….

Detectability of Hepatocellular Carcinoma by Gadoxetate Disodium-Enhanced Hepatic MRI: Tumor-by-Tumor Analysis in Explant Livers

Yuko Nakamura, MD,[1*] Hirotaka Tashiro, MD,[2] Junko Nambu, MD,[2] Hideki Ohdan, MD,[2] Hideaki Kakizawa, MD,[1] Shuji Date, MD,[1] and Kazuo Awai, MD[1]

JOURNAL OF MAGNETIC RESONANCE IMAGING 37:684–691 (2013)

- Only 69% of HCCs were diagnosed on MRI
- Mean diameter of detected lesions 11.5mm
- Mean diameter of undiagnosed lesions 6.0mm



Role of Portal Vein Embolization in Hepatocellular Carcinoma Management and Its Effect on Recurrence: A Case-control Study

Rohan C. Siriwardana · Chung Mau Lo · See Ching Chan · Sheung Tat Fan

World J Surg (2012) 36:1640–1646

	Pre-PVE FRLV	Post-PVE FRLV
Non-resected	25%	29%
Resected	23%	34%

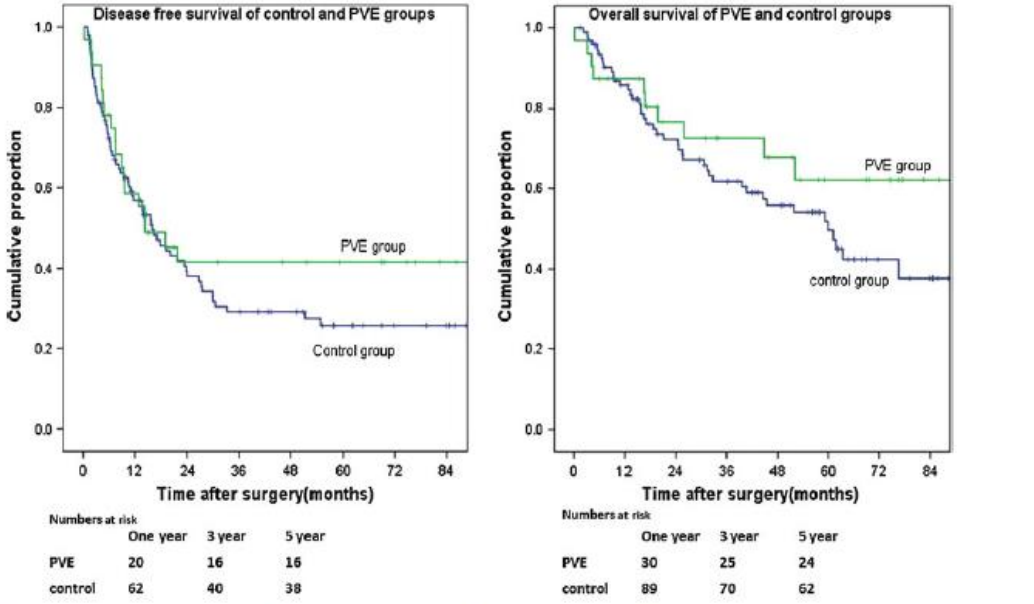


Fig. 2 Kaplan-Meier disease-free and overall survival curves of the PVE group ($n = 34$) and the control group ($n = 102$). Disease-free survival, PVE versus control: $p = 0.335$; overall survival, PVE versus control: $p = 0.221$ (log-rank test)

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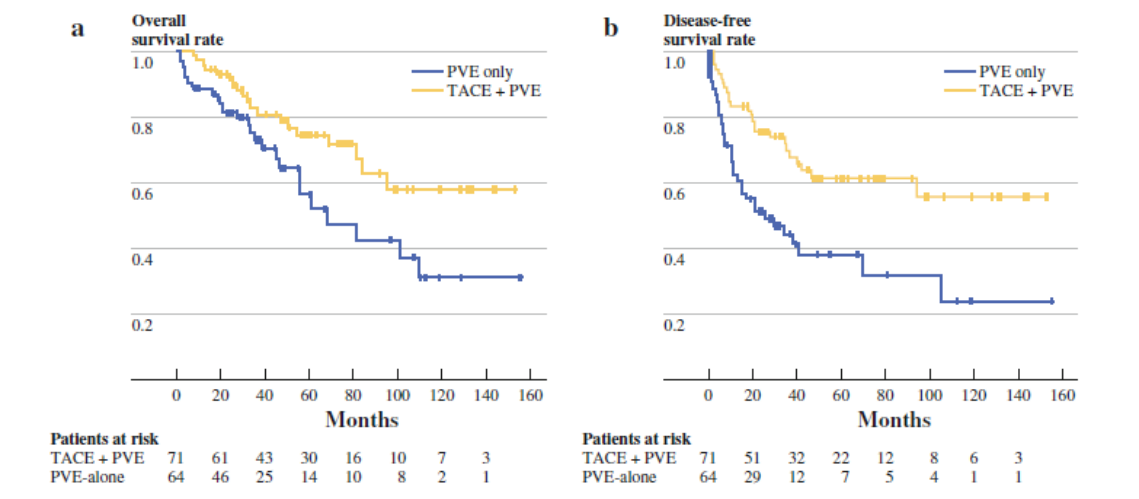
Sequential Transcatheter Arterial Chemoembolization and Portal Vein Embolization versus Portal Vein Embolization Only before Major Hepatectomy for Patients with Hepatocellular Carcinoma

Hyunkyung Yoo, MD[1], Jin Hyoung Kim, MD[1], Gi-Young Ko, MD[1], Kyoung Won Kim, MD[1], Dong Il Gwon, MD[1], Sung-Gyu Lee, MD[2], and Shin Hwang, MD[2]

Ann Surg Oncol (2011) 18:1251–1257

Results:

- Before PVE, the mean percentage of FLR volume to TELV in the TACE + PVE and the PVE-only groups was 34.1 ± 7.2% and 34.5 ± 7.6%, respectively.
- After PVE, the mean percentage of FLR volume in the TACE + PVE and PVE-only groups was 41.4 ± 7.3% and 40.3 ± 8.1%, respectively.
- The mean increase in percentage of FLR volume was statistically significantly (P = 0.035) higher in the TACE + PVE group (7.3 ± 3.6%) than in the PVE-only group (5.8 ± 4.5%).



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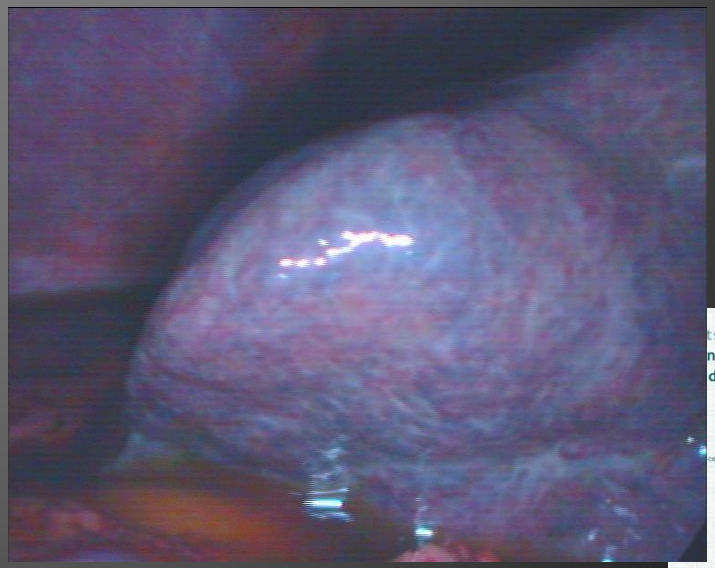
Can we improve outcome after surgical resection of HCC?

- Adjuvant chemotherapy
  - No benefit
- Adjuvant interferon or immunotherapy
  - Some data but not conclusive
- Adjuvant Sorafenib?



Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial

Jordi Bruix, Tadatoshi Takayama, Vincenzo Mazzaferro, Gar-Yang Chau, Jiamei Yang, Masatoshi Kudo, Jianqiang Cai, Ronnie T Poon, Kwang-Hyub Han, Won Young Tak, Han Chu Lee, Tianqiang Song, Sasan Roayaie, Luigi Bolondi, Kwan Sik Lee, Masatoshi Makuuchi, Fabricio Souza, Marie-Aude Le Berre, Gerold Meinhardt, Josep M Llovet*, on behalf of the STORM investigators*

www.thelancet.com/oncology **Vol 16 October 2015**

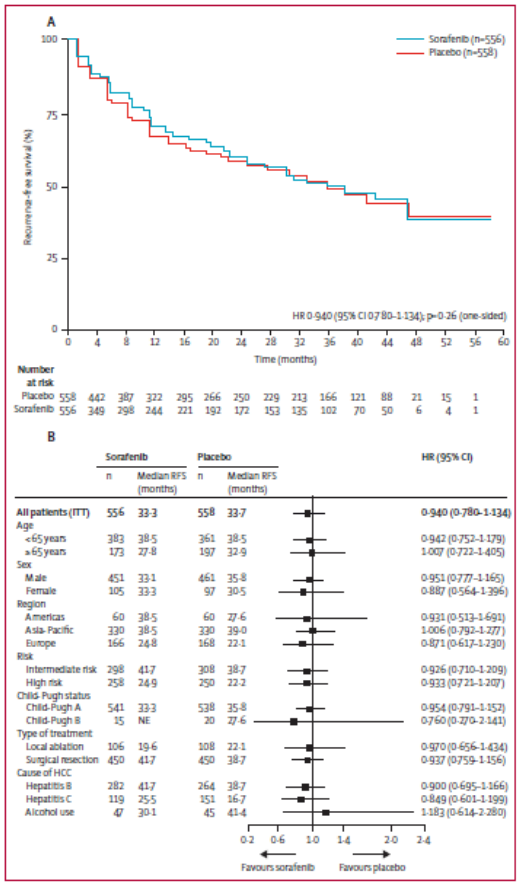


Figure 2: **Kaplan-Meier analysis of RFS based on independent assessment (A) and subgroup analysis of RFS by Cox regression based on independent assessment (B)**
RFS=recurrence-free survival. HR=hazard ratio. ITT=intention to treat. NE=not evaluable.

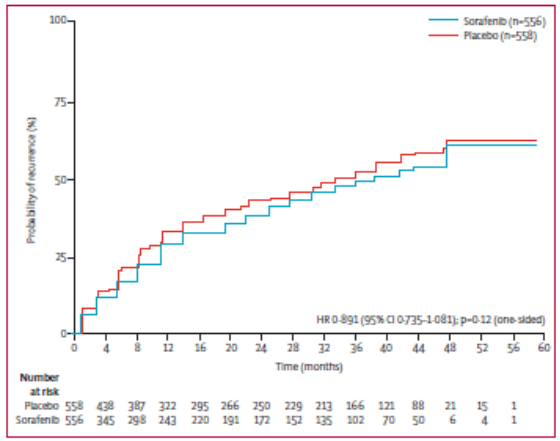


Figure 3: **Kaplan-Meier analysis of time to recurrence based on independent assessment**
HR=hazard ratio.

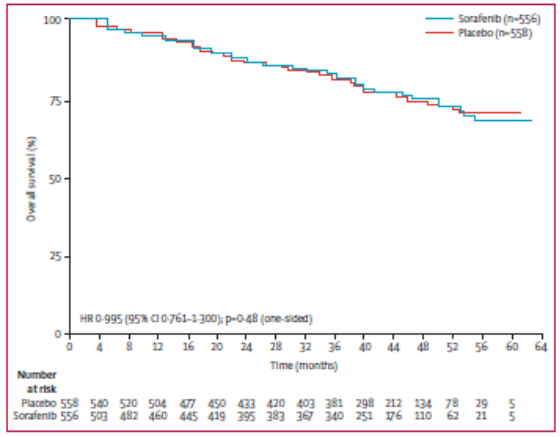


Figure 4: **Kaplan-Meier analysis of overall survival**
HR=hazard ratio.

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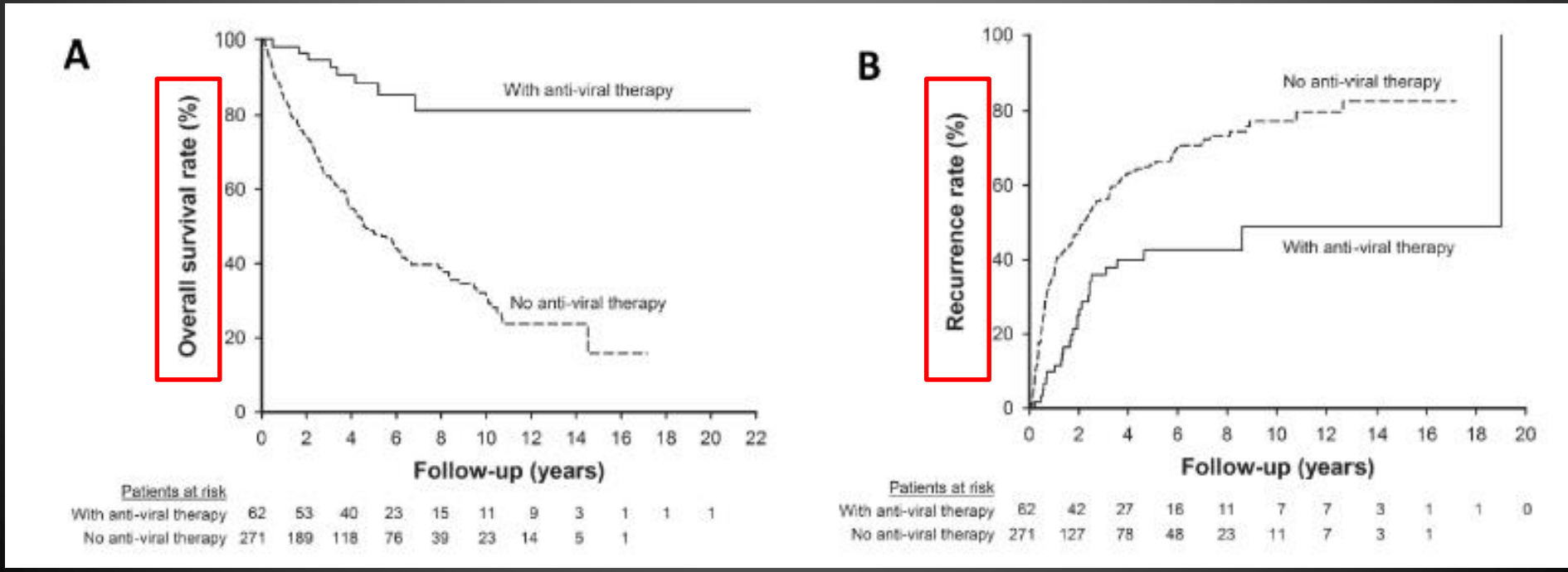
Can we improve outcome after surgical resection of HCC?

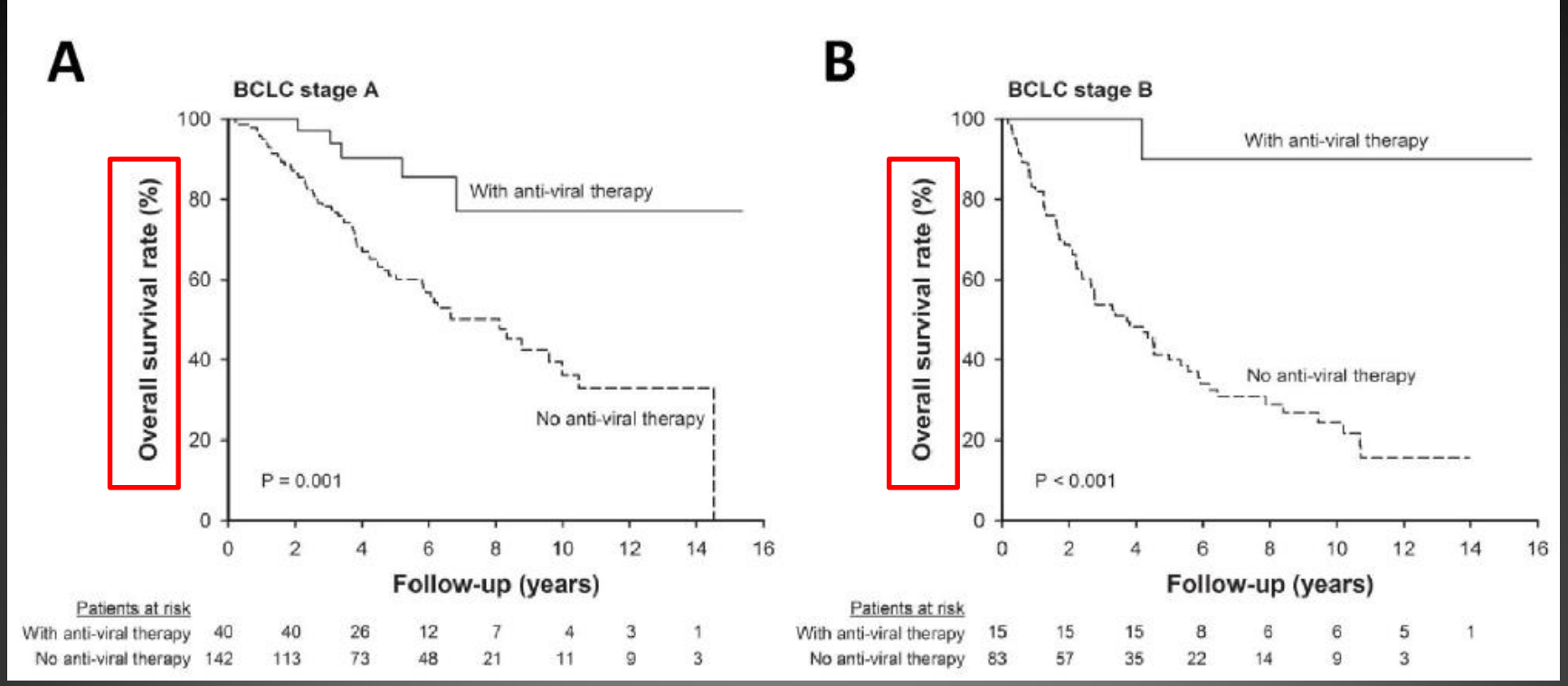
- Adjuvant chemotherapy
  - No benefit
- Adjuvant interferon or immunotherapy
  - Some data but not conclusive
- Adjuvant Sorafenib?
  - No benefit
- Antiviral therapy in Hep B and Hep C

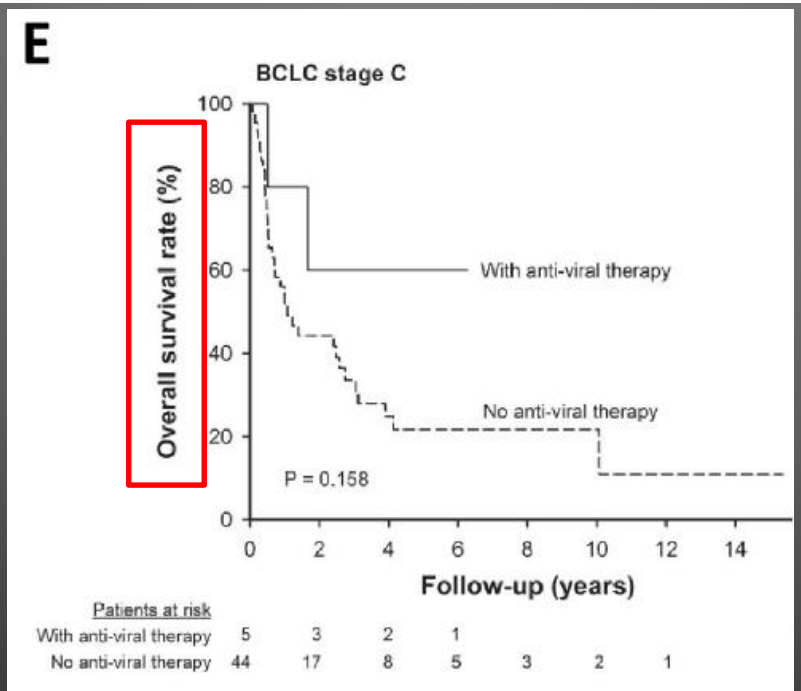
The Influence of Hepatitis B Viral Load and Pre-S Deletion Mutations on Post-Operative Recurrence of Hepatocellular Carcinoma and the Tertiary Preventive Effects by Anti-Viral Therapy

Chien-Wei Su[1,2,3], Yu-Wei Chiou[4], Yi-Hsuan Tsai[3], Ruei-Dun Teng[3], Gar-Yang Chau[2,5], Hao-Jan Lei[2,5], Hung-Hsu Hung[2,3,6], Teh-la Huo[1,7], Jaw-Ching Wu[3,4]*

PLOS ONE | June 2013 | Volume 8 | Issue 6 | e66457







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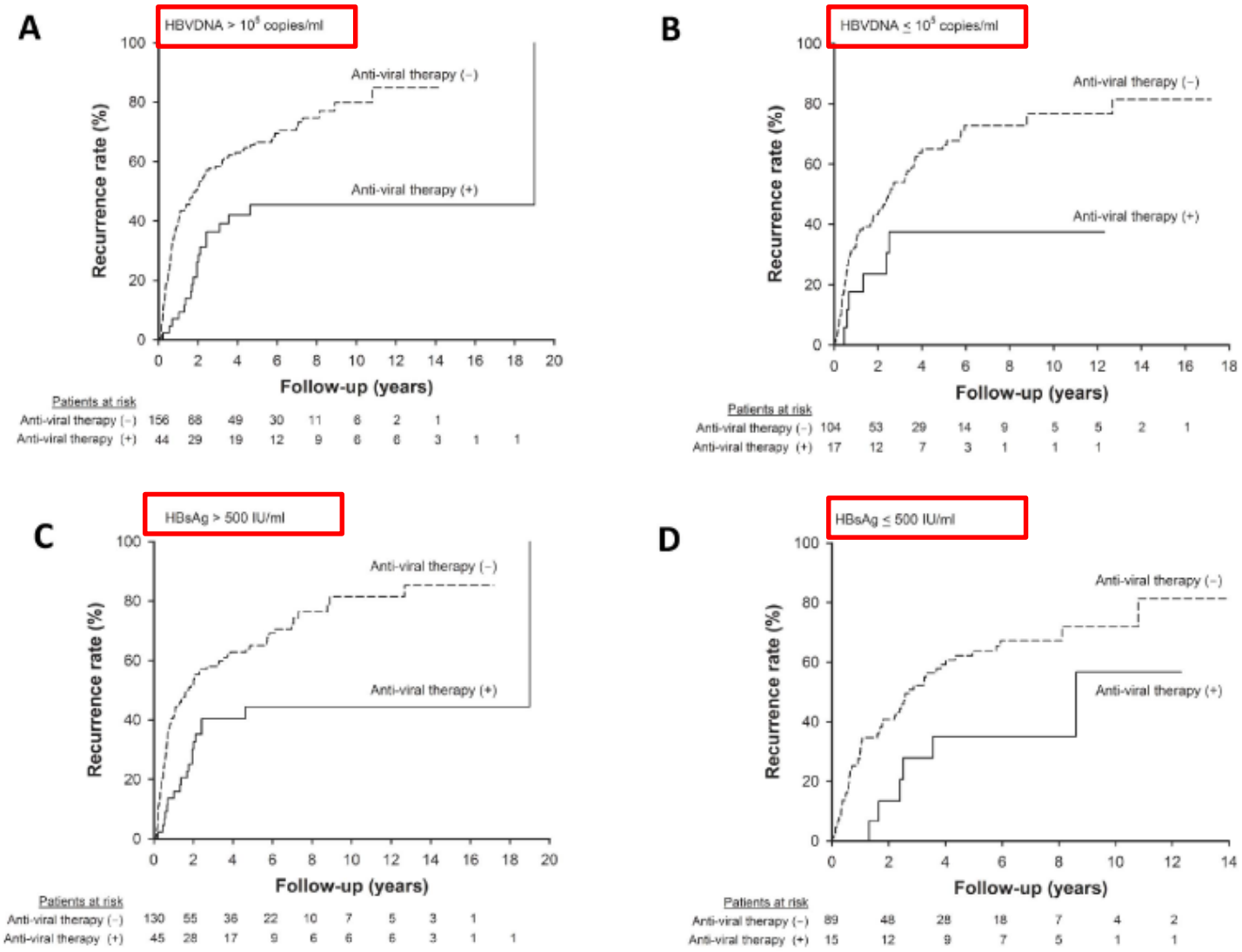

Figure 3. The impact of anti-viral therapy on post-operative recurrence stratified by viral factors. Patients who received anti-viral therapy after resection had significantly lower recurrence rate both in the setting of serum HBV DNA levels $>10^5$ copies/mL (**A**, $p<0.001$) and $\leq 10^5$ copies/mL (**B**, $p=0.038$). (**C**) Among patients with serum HBsAg >500 IU/mL, anti-viral therapy was associated with lower recurrence rate ($p=0.001$). (**D**) In patients with serum HBsAg ≤500 IU/mL, the recurrence rates were also lower in patients receiving antiviral therapy after resection surgery ($p=0.037$).

Conclusions: Ongoing HBV viral replication and pre-S deletion are crucial for determining post-operative tumor recurrence. Anti-viral therapy can help reduce recurrence and improve prognosis, especially for those with early stage HCC.

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Can we improve outcome after surgical resection of HCC?

- Adjuvant chemotherapy
  - No benefit
- Adjuvant interferon or immunotherapy
  - Some data but not conclusive
- Adjuvant Sorafenib?
  - No benefit
- Antiviral therapy in Hep B and Hep C
  - Good data in favour, recommended
- Salvage Transplantation
  - Best option

Liver Transplantation for High Risk Hepatocellular Carcinoma After Liver Resection: A Sequential or Salvage Approach?

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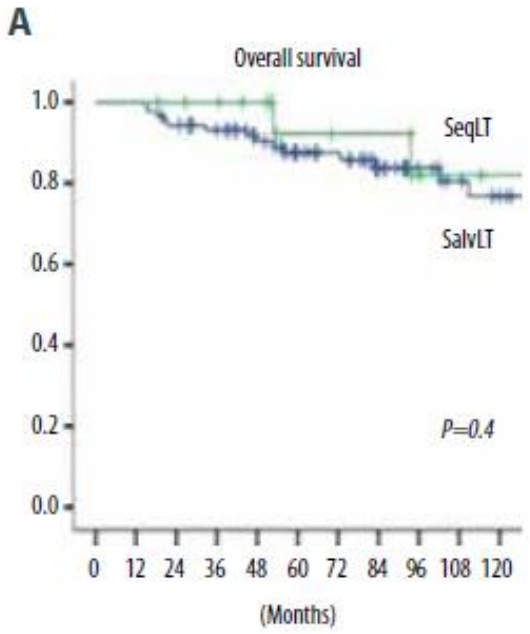

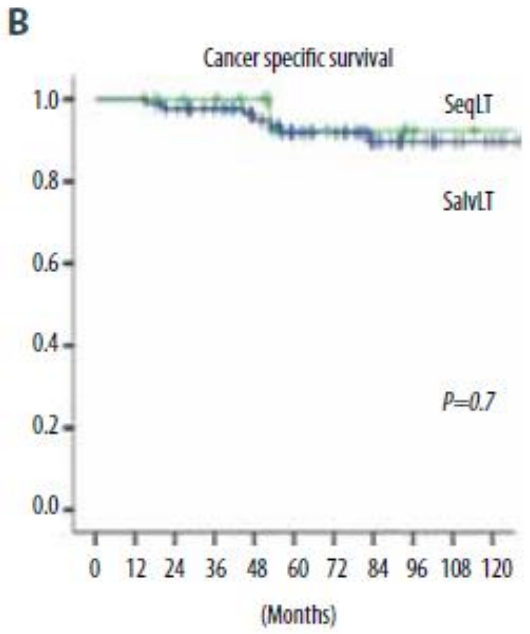

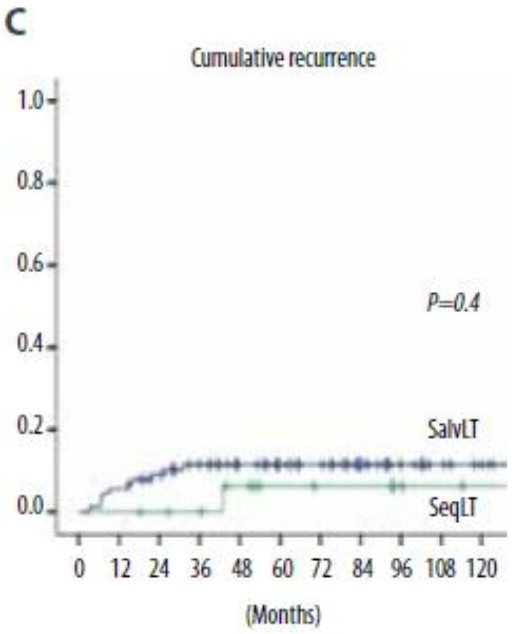

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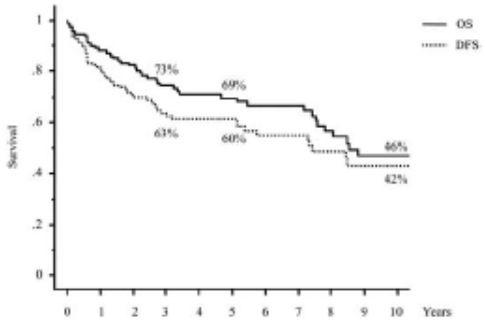
HEPATOLOGY

HEPATOLOGY, VOL. 00, NO. 00, 2017

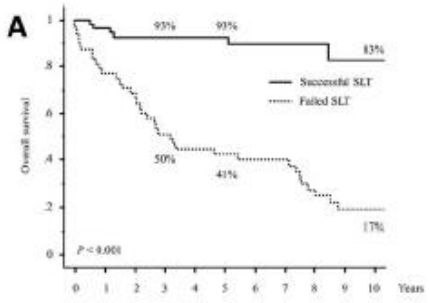
Curative Salvage Liver Transplantation in Patients With Cirrhosis and Hepatocellular Carcinoma: An Intention-to-Treat Analysis

Robbert J. de Haas,[1,2] Chetana Lim,[3] Prashant Bhangui,[4] Chady Salloum,[3] Philippe Compagnon,[3,5] Cyrille Feray,[5,6] Julien Calderaro,[7] Alain Luciani,[1,5*] and Daniel Azoulay[3,5*]



Patients at risk	Total	1 yr	2 yrs	3 yrs	5 yrs	10 yrs
OS	110	89	83	67	49	17
DFS	110	82	70	57	41	14

FIG. 2. OS and DFS after liver resection in the total study population (ITT analysis).



Patients at risk	Total	1 yr	2 yrs	3 yrs	5 yrs	10 yrs
Successful SLT	60	52	50	44	31	11
Failed SLT	48	35	31	22	18	6

Patients at risk	Total	1 yr	2 yrs	3 yrs	5 yrs	10 yrs
Successful SLT	60	52	50	44	31	11
Failed SLT	48	28	18	12	10	3

FIG. 3. (A) OS after liver resection according to successful or failed SLT strategy. (B) DFS after liver resection according to successful or failed SLT strategy.

Conclusions

- Surgical resection plays an important role in the management of HCC with curative intent
- It is possible to increase resection rates and outcomes with patient selection, improved staging and conversion therapy
- Transplantation offers better outcomes than surgical resection for HCC as it treats both the HCC as well as the diseased liver
- Only limited numbers of these patients can be considered for surgery or transplantation
- Treatment of the HBV and HCV infection beneficial