

Hôpital du Valais  
Spital Wallis

# Carcinome hépato-cellulaire et traitement en radiologie

## Where are we today ?



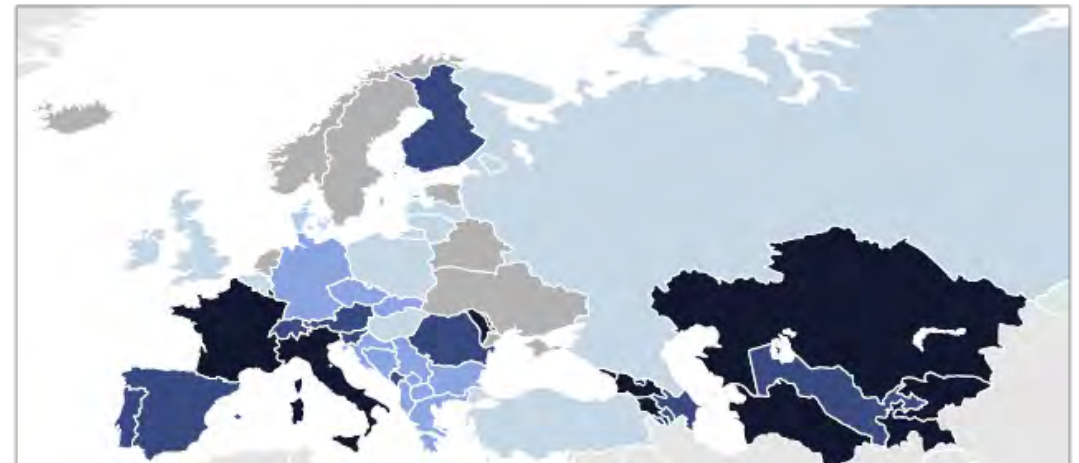
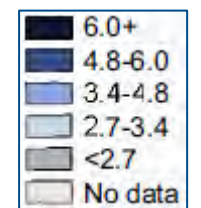
Christophe Constantin

6 décembre 2018

# Carcinome hépato-cellulaire

- ▶ 5ème cancer
- ▶ 2ème cause de décès par cancer (854'000 nouveaux cas, 810'000 décès/ans)
- ▶ 7% des cancers

Incidence par habitants 100,000



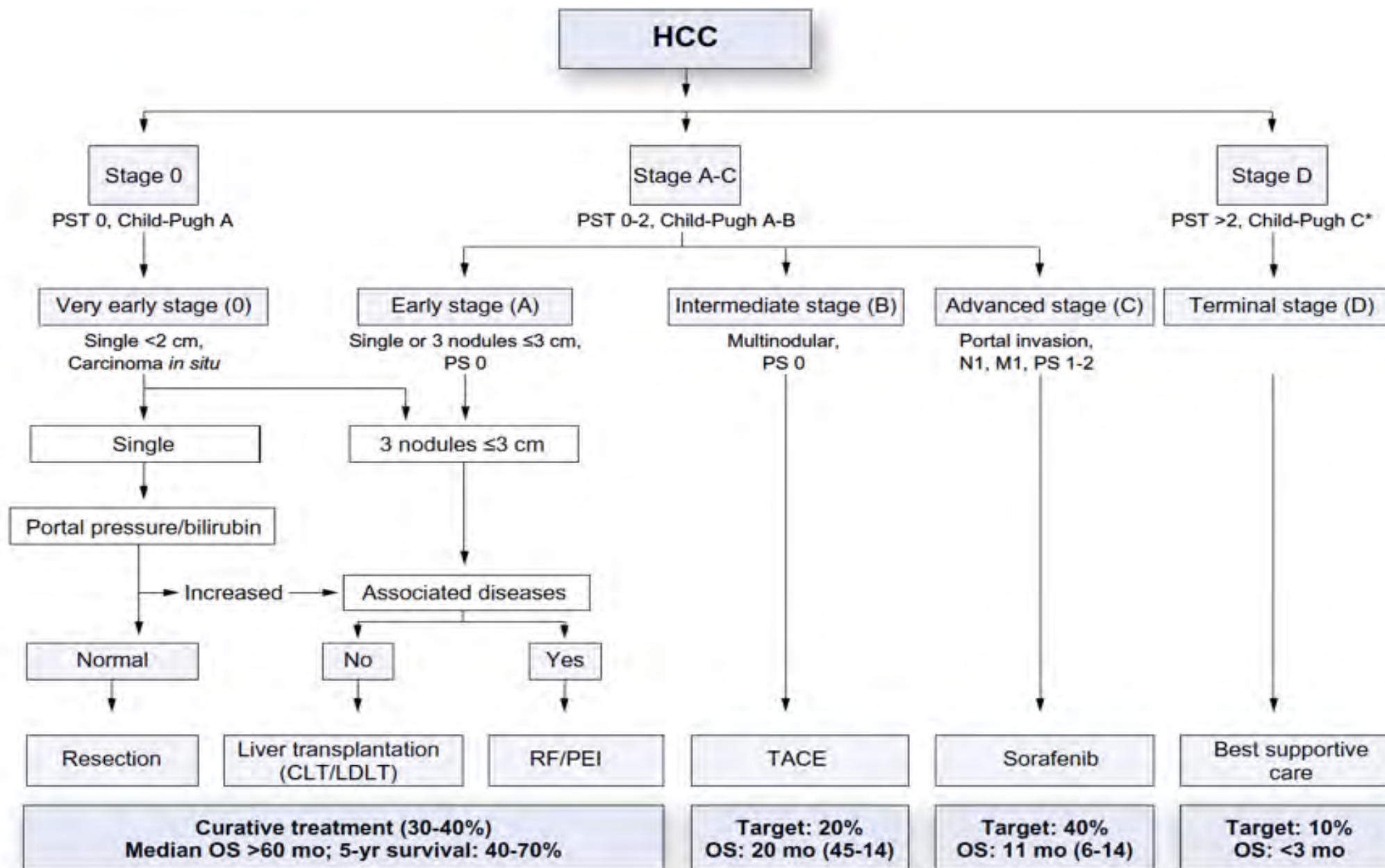
EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

# Carcinome hépato-cellulaire

- 90% étiologie identifiée :
  - HCV, HBV, alcool

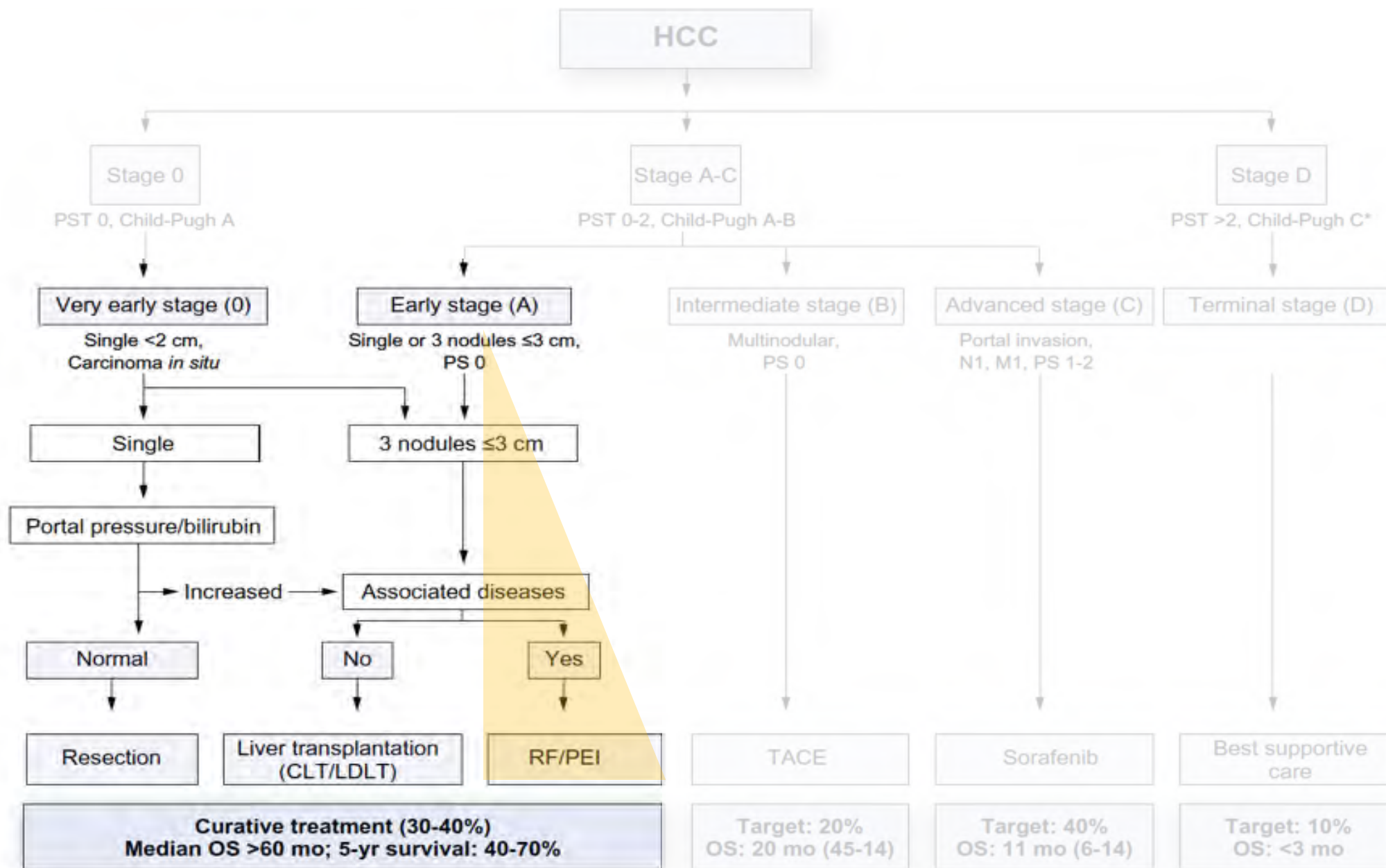
	Alcohol (%)	HBV (%)	HCV (%)	Others (%)
<b>Europe</b>				
Western	32	13	44	10
Central	46	15	29	10
Eastern	53	15	24	8
<b>North America</b>	37	9	31	23
<b>Andean Latin America</b>	23	45	12	20
<b>Asia</b>				
East Asia	32	41	9	18
Asia-Pacific	18	22	55	6
South-East Asia	31	26	22	21
<b>Africa</b>				
North Africa, Middle East	13	27	44	16
Southern (sub-Saharan)	40	29	20	11
Western (sub-Saharan)	29	45	11	15

\*Contribution of hepatitis B, C, alcohol and other causes on absolute liver cancer deaths, both sexes, globally and by region 2015. Data refer to all primary liver cancers (HCC, intrahepatic CCA and liver cancer of mixed differentiation)  
 1. Akinyemiju T, et al. JAMA Oncol 2017;3:1683–91;  
 EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019



# Traitement du CHC





# Traitement du CHC : RF

Percutaneous Radiofrequency Ablation for Hepatocellular Carcinoma

An An

Ryosuke Shuichir Takuma Shuntaro Shinpei Yukihiko Tomonori Haruhiko Takao K Masao O

Department kyo, Tokyo

Radiofrequency Ablation of Hepatocellular Carcinoma: Long-term Results and Prognostic Factors in 235 Western Patients with Cirrhosis

Gisèle N’Kontchou Emmanuelle Coderc,<sup>3</sup> Eri

For the treatn some centers debate with re 5-year surviva 205/30) who diameter: 29 for resection a 222 patients recurrence. N related death. rence occur transplantaic and tumor-fr and 32%. The overall surviv and serum le associated wit and serum AF recurrence bu first-line treatr serum AFP lev

Radiofrequency Ablation of Hepatocellular Carcinoma as Bridge Therapy to Liver Transplantation: A 10-Year Intention-to-Treat Analysis

Min Woo Lee,<sup>1,2</sup> Steven S. Raman,<sup>1</sup> Nazanin H. Asvadi,<sup>1</sup> Surachate Siripongsakun,<sup>1,3</sup> Robert M. Hicks,<sup>1</sup> Akeanong Worakitisitatorn,<sup>1,3</sup> Justin McWilliams,<sup>1</sup> Myron J. Tong,<sup>4</sup> Richard S. Finn,<sup>5</sup> Vatche G. Agopian,<sup>1</sup> Ronald W. Busuttil,<sup>6</sup> and David S.K. Lu<sup>1</sup>

In a long-term (10-year) study of radiofrequency ablation (RFA) of hepatocellular carcinoma (HCC) patients listed for orthotopic liver transplantation (LT), we evaluated the impact of RFA on waiting tumor recurrence, and long-term intention-to-treat, disease-specific survival (DSS). From March 2000 to March 2010, RFA was performed as the initial stand-alone bridge therapy to LT for 121 patients (men/women ratio, 83:38; mean age, 60.0 years) with 156 *de novo* HCCs (mean size, 2.4 cm). Follow-up period from initial RFA ranged from 1.3 to 128.0 months (median, 42.9 months). We assessed the overall and tumor-specific waiting list dropout rates, post-LT tumor recurrence, and 10-year post-LT and intention-to-treat survival rates. Dropout from the waiting list due to tumor progression occurred in 7.4% of patients. HCC recurrence after LT occurred in 5.6% of patients. The post-LT overall survival (OS) rate at 5 and 10 years was 75.8% and 42.2%, respectively, and the recurrence-free survival (RFS) rate was 71.1% and 39.6%, respectively. Intention-to-treat OS, RFS, and DSS rates for the entire study population at 5 and 10 years were 63.5% and 41.2%, 60.8% and 37.7%, and 89.5% and 89.5%, respectively. **Conclusion:** RFA as a first-line stand-alone bridge therapy to LT achieves excellent long-term overall and tumor-specific survivals, with a low dropout rate from tumor progression despite long wait list times and a sustained low tumor recurrence rate upon post-LT follow-up of up to 10 years. (HEPATOLOGY 2017;65:1979-1990)

cy ablation an ocellular carci

ng<sup>1</sup>, Ping

hina; <sup>2</sup>Institu rch Center fc <sup>1</sup>Department

Systematic Review of Randomized Trials for Hepatocellular Carcinoma Treated with Percutaneous Ablation Therapies

Yun Ku Cho,<sup>1</sup> Jae Kyun Kim,<sup>1</sup> Mi Young Kim,<sup>1</sup> Hyunchul Rhim,<sup>2</sup> and Joon Koo Han<sup>3</sup>

According to the American Association for the Study of Liver Diseases guidelines, percutaneous ethanol injection (PEI) is a safe and highly effective treatment for small hepatocellular carcinomas (HCC) and should be the standard against which any new therapy is compared. The primary purpose of this study was to identify survival benefit of any percutaneous ablation therapy as compared with PEI in the treatment of patients with unresectable HCC. The secondary endpoints were initial tumor response, local tumor progression, and complications. Randomized controlled trials that compared percutaneous ablative therapies with PEI were included. MEDLINE, the Cochrane Library, CANCELIT, and manual search from 1978 to July 2008 were used. To control the potential heterogeneity, the random effects model of DerSimonian and Laird was used for a meta-analysis. Egger’s test was performed to test a potential publication bias. We identified seven randomized controlled trials (RCTs), but only four RCTs including 652 patients that compared radiofrequency ablation (RFA) with PEI met the inclusion criteria to perform a meta-analysis assessing 3-year survival. A meta-analysis of the four RCTs demonstrated a significant improvement in 3-year survival favoring RFA over PEI (odds ratio 0.477, 95% confidence interval 0.340-0.670;  $P < 0.001$ ). Heterogeneity among the four trials was not significant ( $Q = 4.586$ ;  $P = 0.205$ ). Egger’s test revealed that the publication bias was not significant ( $P = 0.647$ ). However, the number of patients included in the analysis was insufficient for a robust meta-analysis of initial tumor response. The definition of local tumor progression or major complication was not unified among the trials included in the meta-analysis. **Conclusion:** RFA demonstrated significantly improved 3-year survival status for patients with HCC, when compared to PEI. (HEPATOLOGY 2009;49:453-459.)

	0	5	10	15	20	25	30
	Time (mo)						
Patients at risk							
RES group	84	74	66	60	55	47	43
RFA group	84	71	62	52	47	36	34

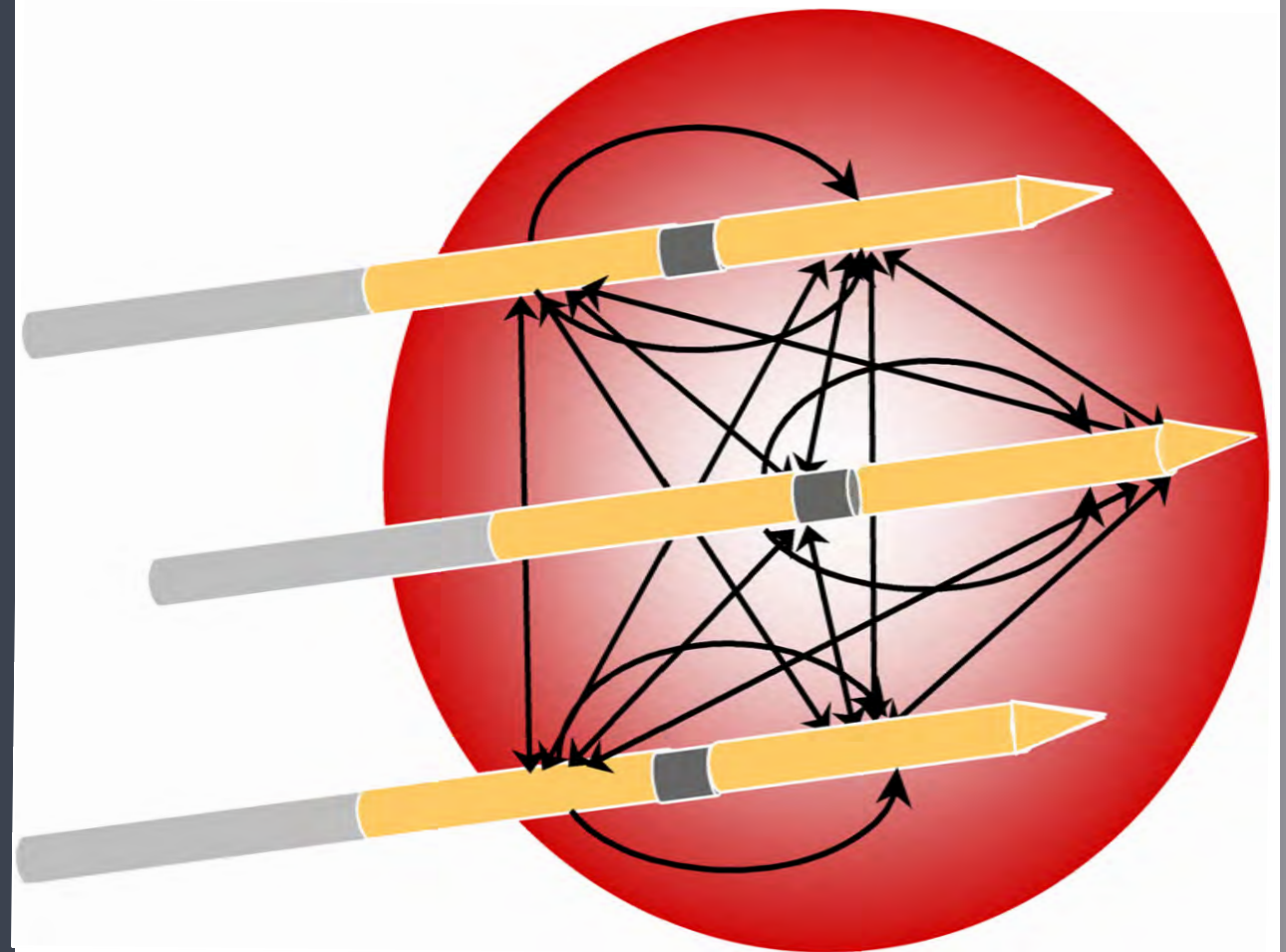
fig. 2. Survival analysis according to the treatment group. (A) Probability of survival in patients treated with surgical resection and in patients assigned to the radiofrequency ablation group (log-rank test,  $\chi^2 = 0.903$ ,  $p = 0.342$ ). (B) Probability of recurrence-free survival in patients treated with surgical resection and in patients assigned to the radiofrequency ablation group (log-rank test,  $\chi^2 = 2.389$ ,  $p = 0.122$ ).

Traitement du CHC : RF

# Traitement du CHC : RF

## Radiofréquence :

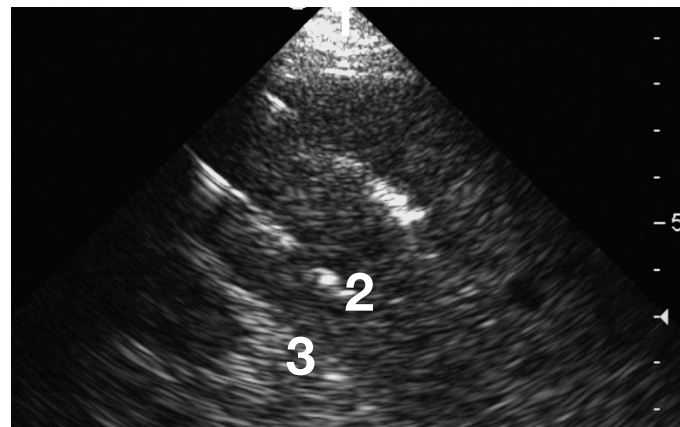
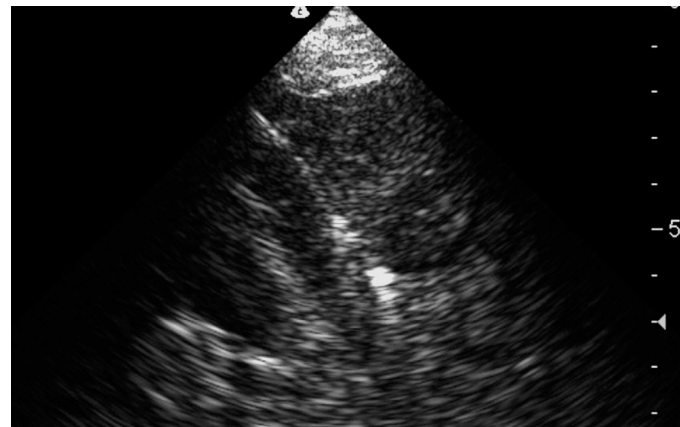
- ▶ But : échauffement par friction => nécrose par coagulation (50-60 C)
- ▶ Hospitalisation (24-48 h)
- ▶ Prophylaxie antibiotique (Rocéphine)
- ▶ Anesthésie générale
- ▶ Guidage US, CT, scopique



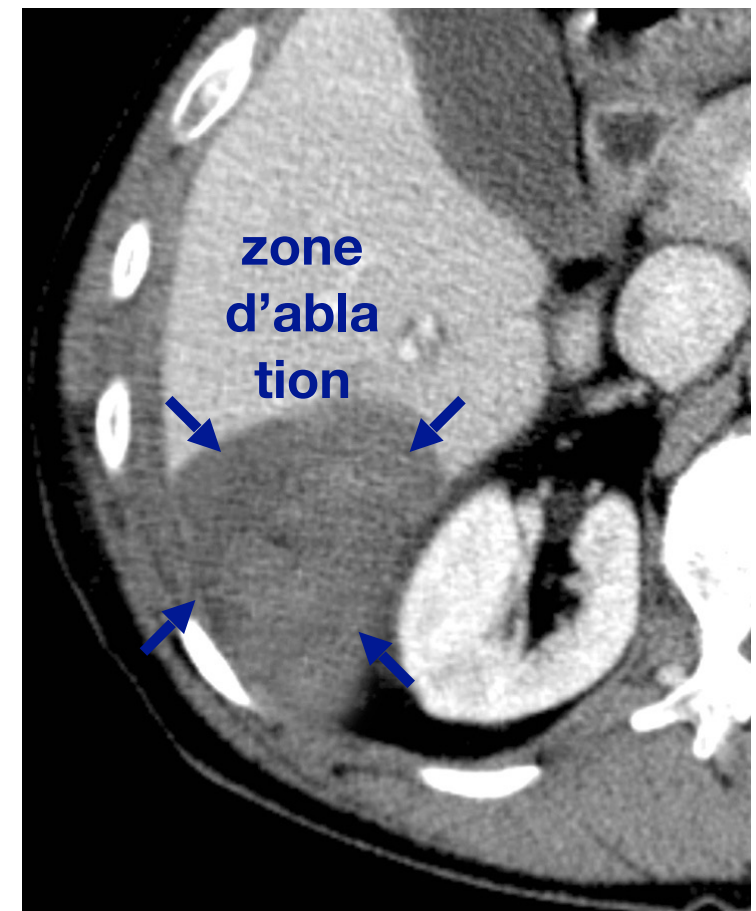




CHC du segment 6

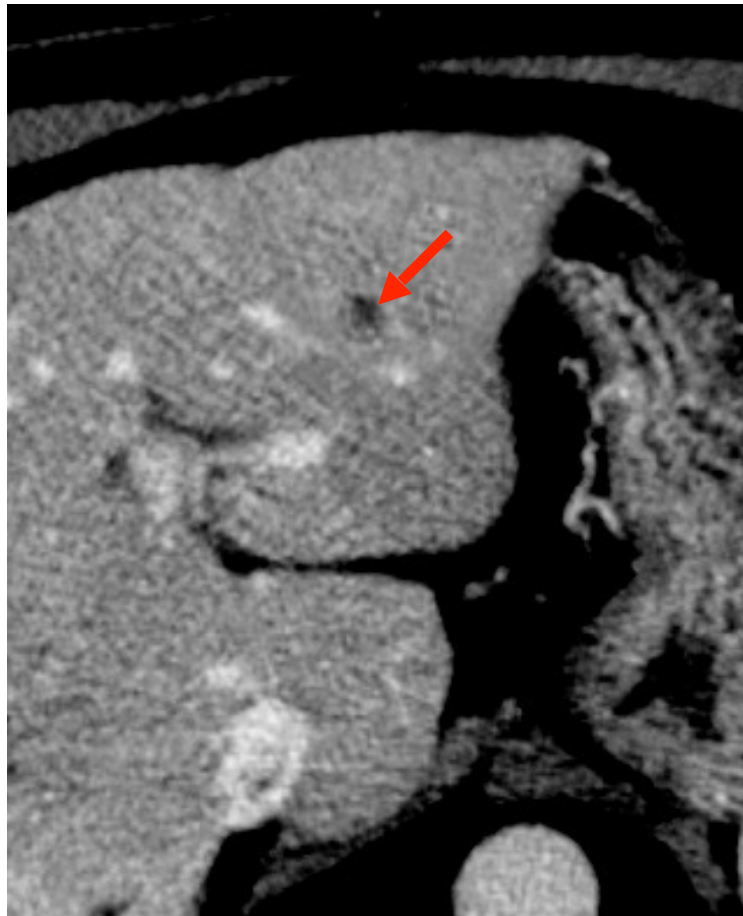


3 électrodes RF  
sous US



contrôle post-RF (24 h)

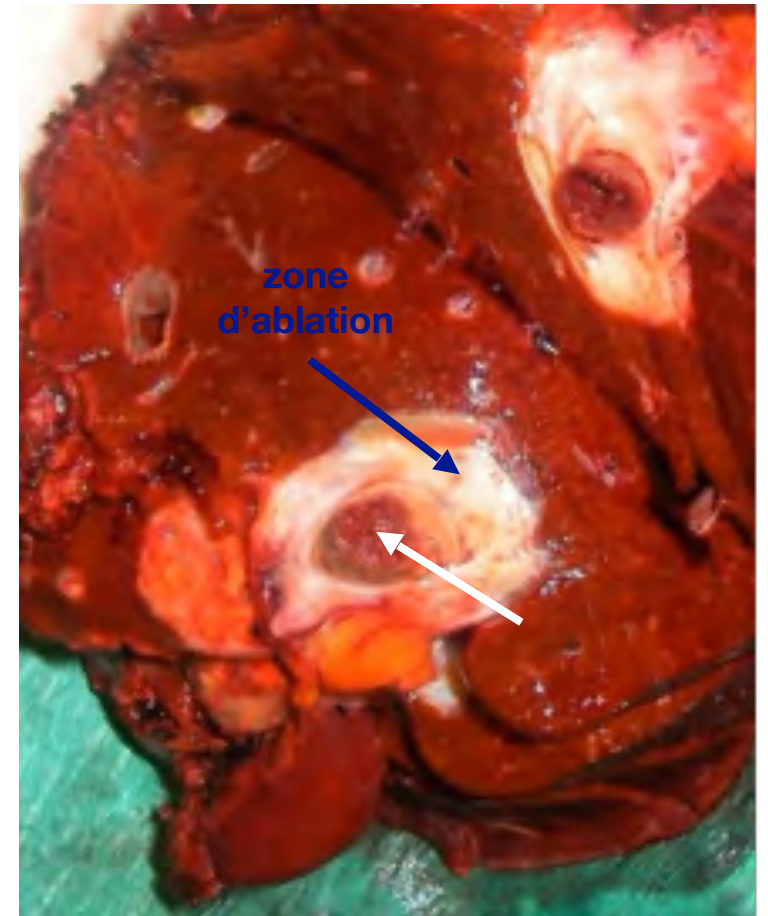
# Traitement du CHC : RF



petit nodule de CHC



post-RF sous US

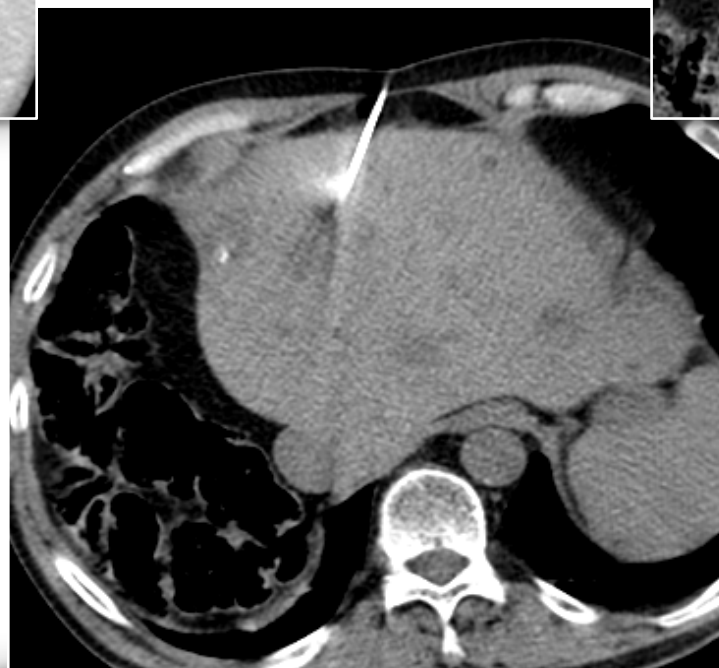


post-transplantation (2 mois)

# Traitement du CHC : RF

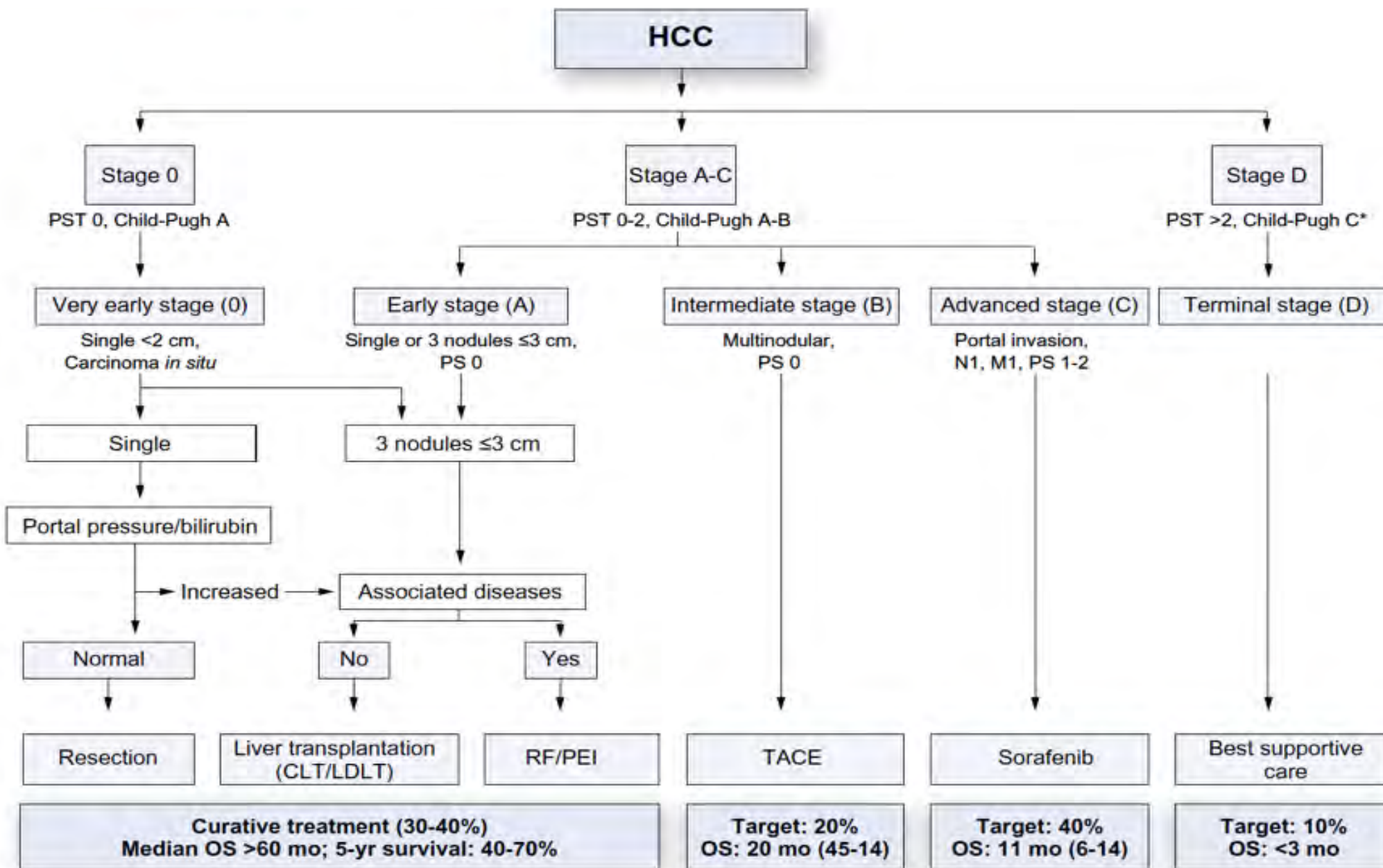


Récidive post  
hépatectomie

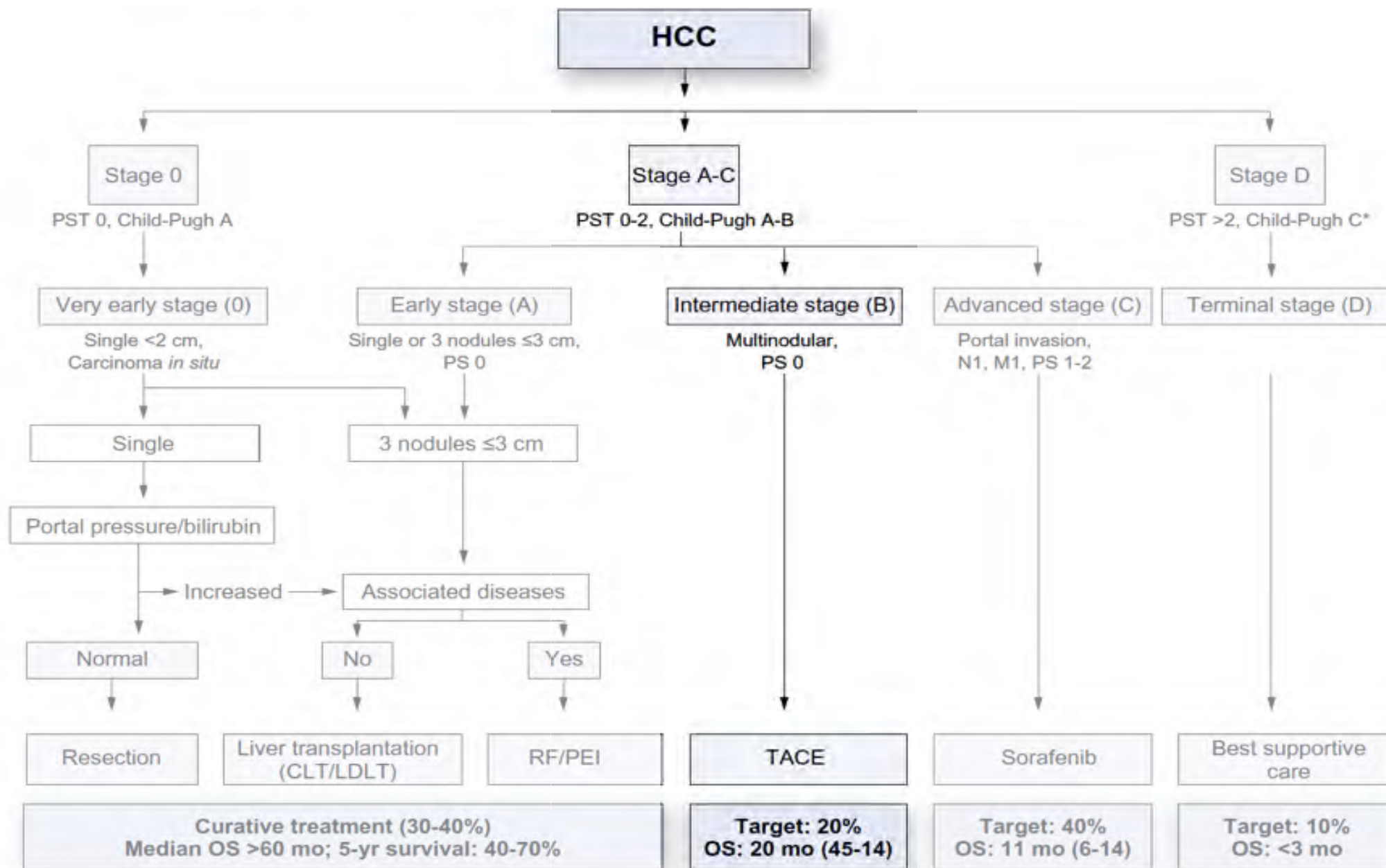


Traitement du CHC : RF





# Traitement du CHC

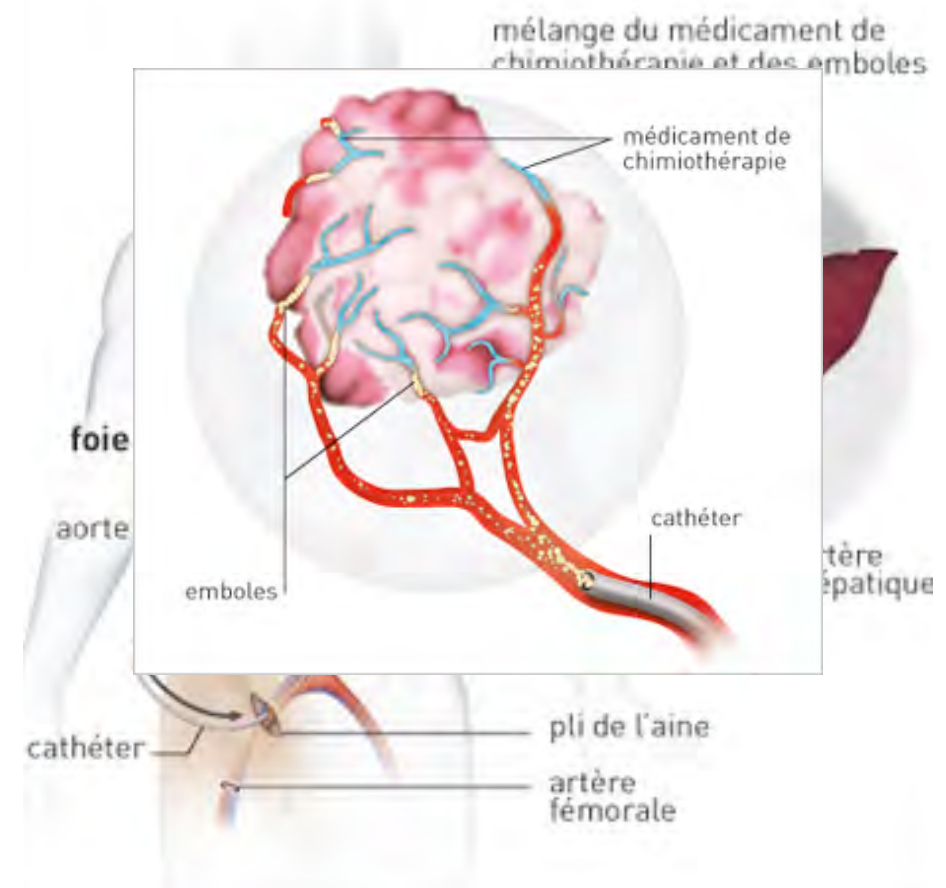


# Traitement du CHC : TACE

# Traitement du CHC : TACE

## Chimioembolisation :

- ▶ Hospitalisation (24-48 h)
- ▶ Prophylaxie antibiotique (Rocéphine)
- ▶ Sédation-analgésie
- ▶ Guidage scopique



# Traitement du CHC : TACE

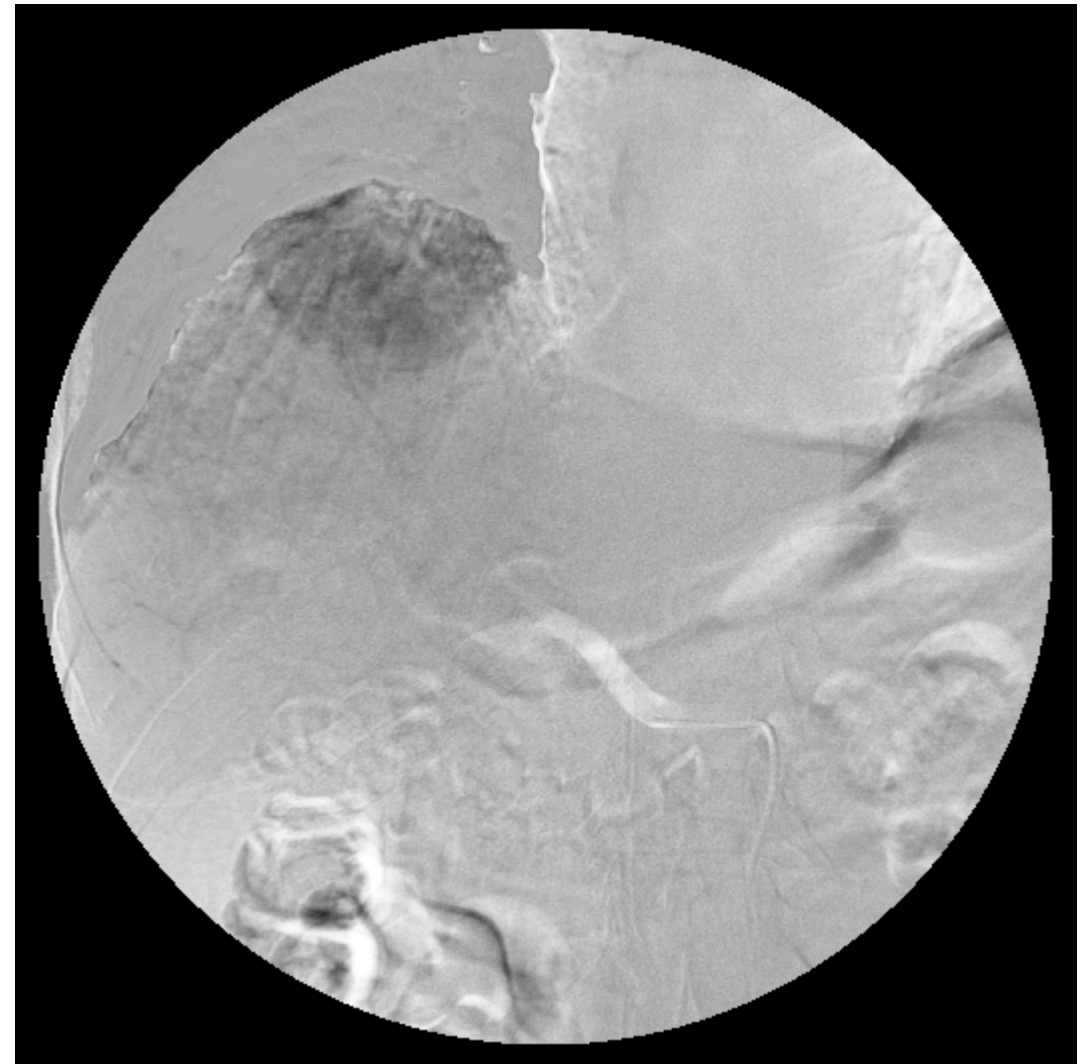
## Chimioembolisation :

- ▶ Tumeur hypervascularisée
- ▶ Injection intra-artérielle d'une émulsion agent cytostatique et de lipiodol
- ▶ +/- embolisation avec des particules





- ▶ Homme 83 ans
- ▶ Cirrhose OH child A
- ▶ Volumineux CHC segment VIII (6.3 cm)
- ▶ BEG



## Traitement du CHC : TACE

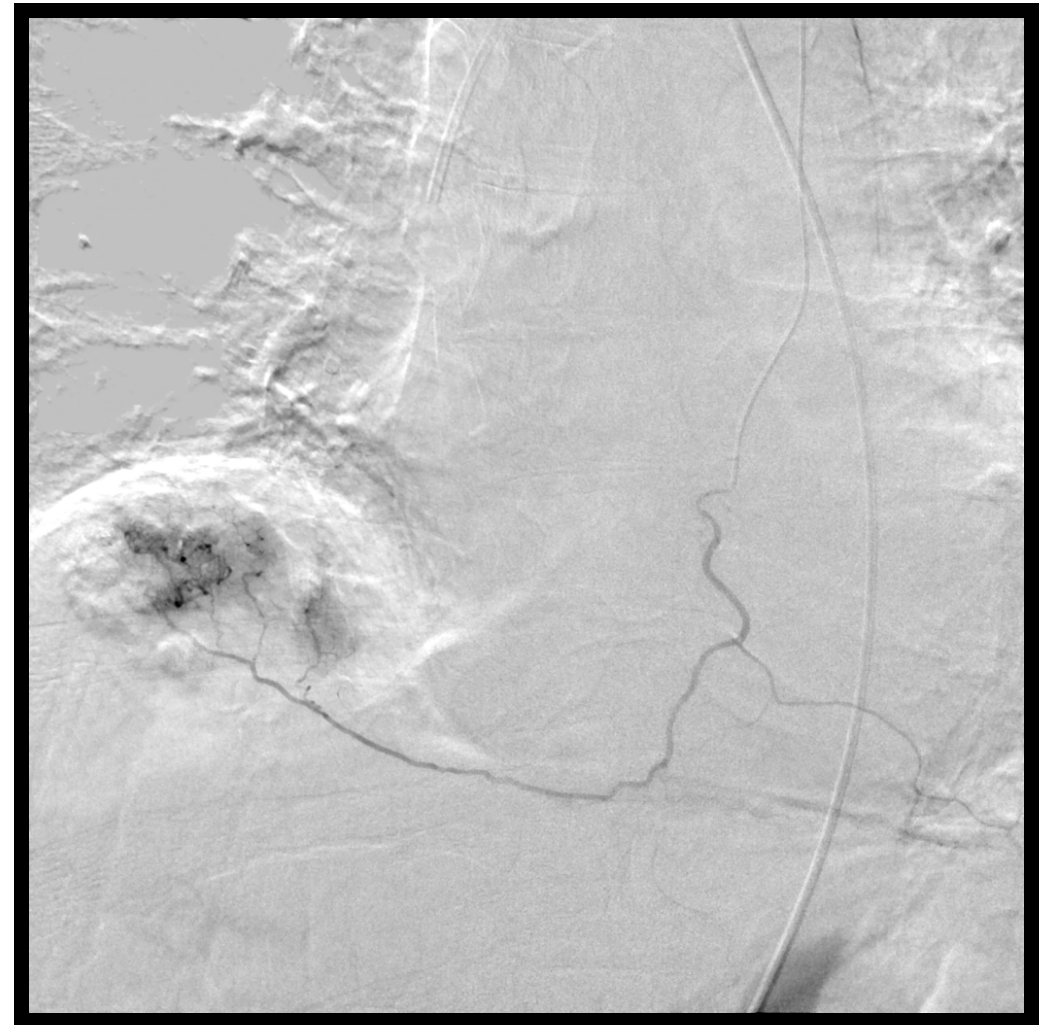
- ▶ Homme 83 ans
- ▶ Cirrhose OH child A
- ▶ Volumineux CHC segment VII (6.3 cm)
- ▶ BEG
- ▶ CT contrôle à 3 mois



## Traitement du CHC : TACE



- ▶ Homme 83 ans
- ▶ Cirrhose OH child A
- ▶ Volumineux CHC segment VII (6.3 cm)
- ▶ BEG
- ▶ CT contrôle à 3 mois



# Traitement du CHC : TACE

- ▶ Homme 83 ans
- ▶ Cirrhose OH child A
- ▶ Volumineux CHC segment VII (6.3 cm)
- ▶ BEG
- ▶ Décès > 3 ans plus tard

## Traitement du CHC : TACE

# Traitement du CHC

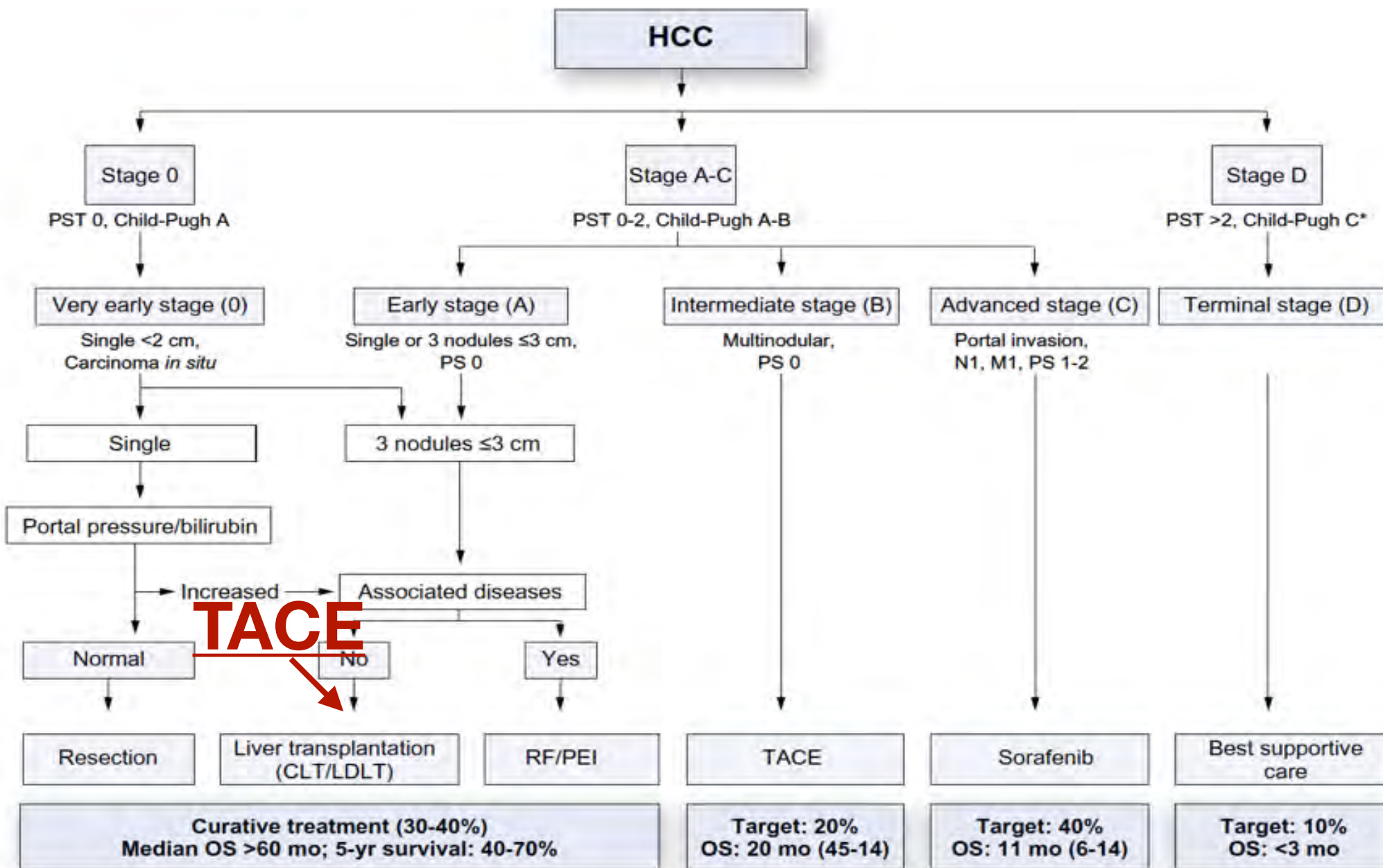


## Unresectable HCC in cirrhosis: randomised, controlled trial (112 pts) (Child- Pugh class A ou B)

	survival	
	1 year	2 years
TACE	82%	63%
Embolisation only	75%	50%
Control	63%	27%

*Chemoembolisation vs. control:  $p= 0.009$*

Llovet et al: Lancet 2002; 359:1734



# Traitement du CHC : TACE

**TABLE 4. Relevant Studies Reporting Neoadjuvant Treatment Before LT and Their Outcomes**

Study	Neoadjuvant Treatment	No. of Patients	Waiting Time, Months	Disease-Specific Dropout Rate, %	Post-LT HCC Recurrence, %	Post-LT Survival, %	Intention-to-Treat Survival, %
Fontana et al. <sup>(12)</sup>	RFA	23	Mean, 7.9	NA	13	OS, 85 (3 years)	NA
Mazzaferro et al. <sup>(5)</sup>	RFA	50	Median, 9.5	0	3.3	OS, 83 (3 years)	NA
Lu et al. <sup>(11)</sup>	RFA	52	Mean, 12.7	5.8	0	OS, 76 (3 years)	OS, 74 (3 years)
Millonig et al. <sup>(22)</sup>	TACE	116	Median, 9	8.6	14.2	NA	OS, 70.3 (5 years) <sup>†</sup>
Cherqui <sup>(31)</sup>	Resection	18*	NA	NA	NA	OS, 70 (5 years)	OS, 72 (5 years); RFS, 44 (5 years)
Cucchetti et al. <sup>(21)</sup>	Mixed	315	Median, 10	16.5	10.2	OS, 74.3 (5 years)	NA
Current study	RFA	121	Mean, 10.2	7.4	5.6	OS, 79.7 (3 years), 75.8 (5 years), 71.3 (8 years), 42.2 (10 years), RFS, 78.3 (3 years), 71.1 (5 years), 66.9 (8 years), 39.6 (10 years)	OS, 67.2 (3 years), 63.5 (5 years), 60.0 (8 years), 41.2 (10 years), RFS, 65.4 (3 years), 60.8 (5 years), 54.8 (8 years), 37.7 (10 years)

NA, not applicable.

\*Out of the entire study population (n = 67), only 18 patients underwent LT.

<sup>†</sup>Patients within Milan criteria at the time of listing.

# Traitement du CHC : TACE

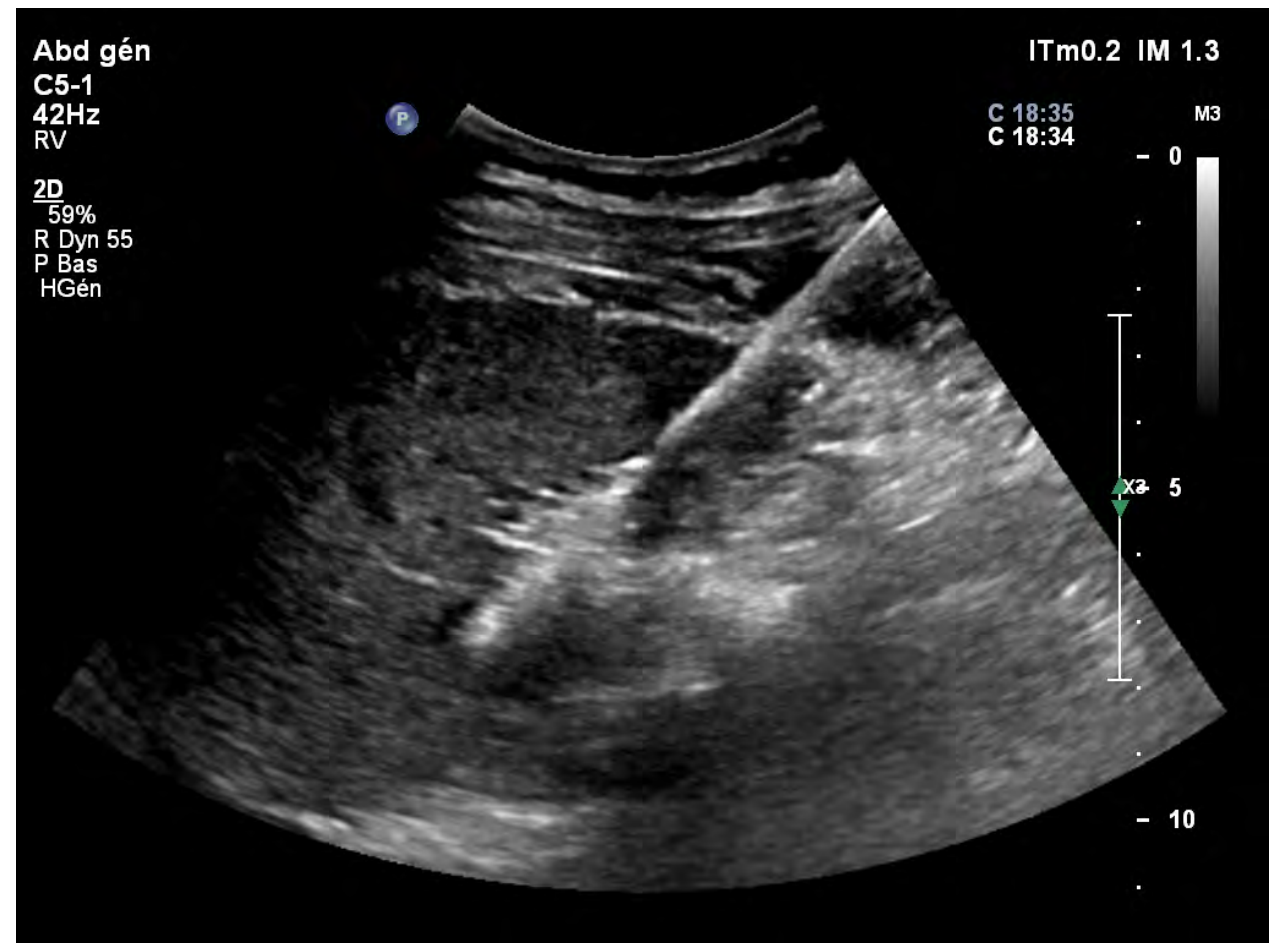
- ▶ Homme 43 ans
- ▶ Cirrhose HBV child A
- ▶ Apparition d'un nodule de 2.2 cm



# Traitement du CHC : TACE

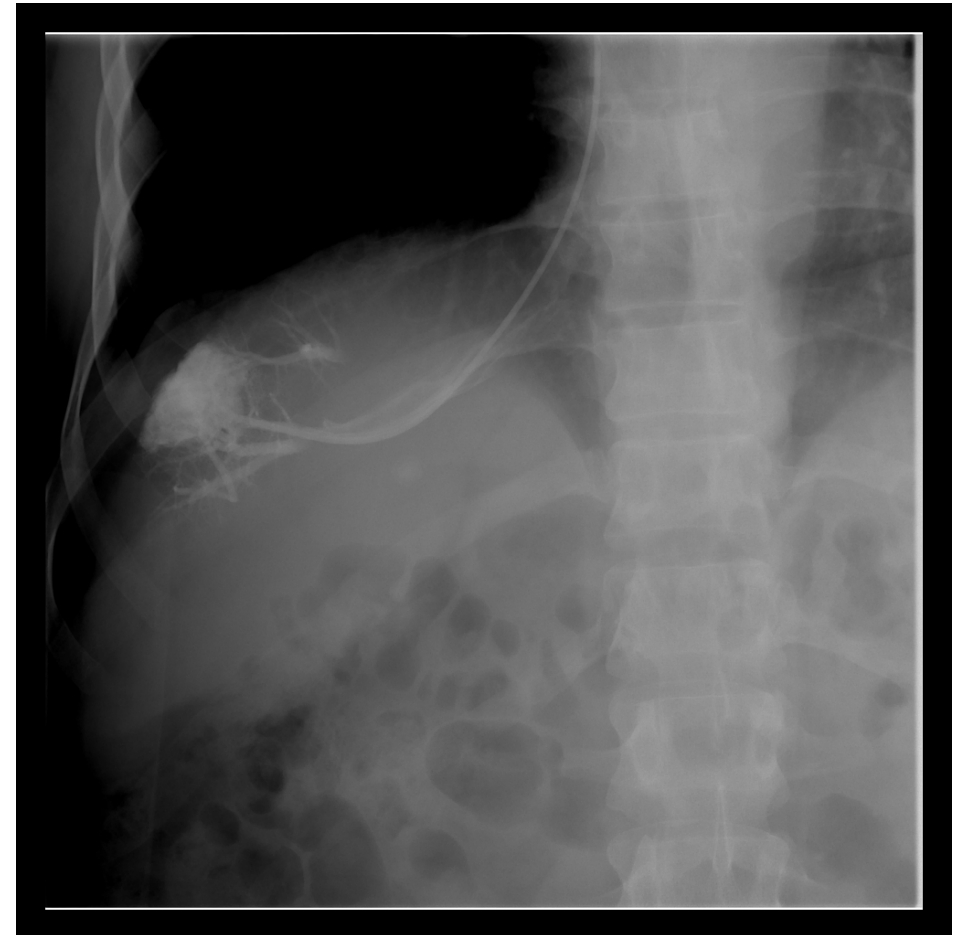


- ▶ Homme 43 ans
- ▶ Cirrhose HBV child A
- ▶ Apparition d'un nodule de 2.2 cm
- ▶ Biopsie : CHC



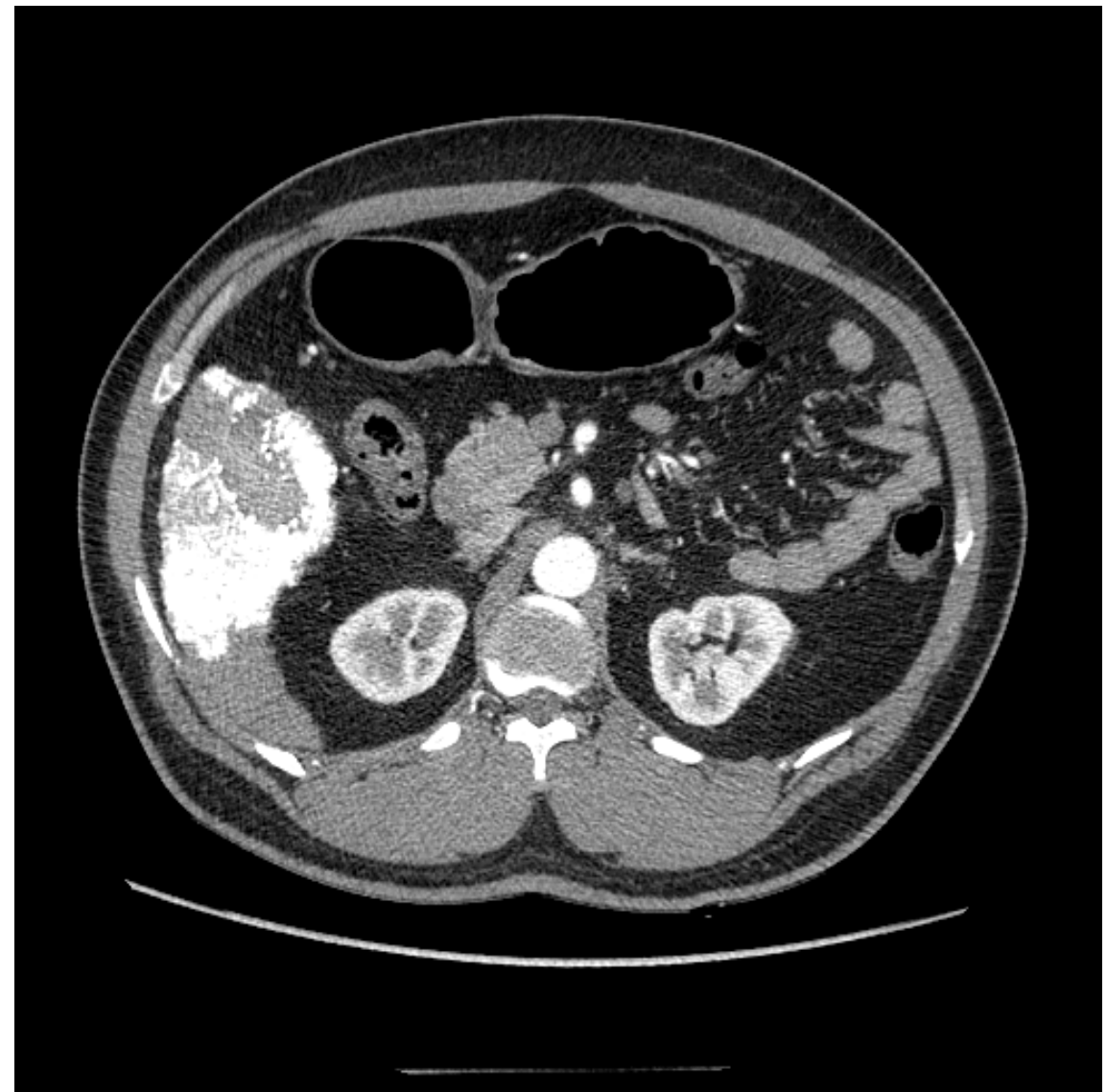
# Traitement du CHC : TACE

- ▶ Homme 43 ans
- ▶ Cirrhose HBV child A
- ▶ Apparition d'un nodule de 2.2 cm
- ▶ Biopsie transjugulaire : pas de gradient (4 mm Hg)



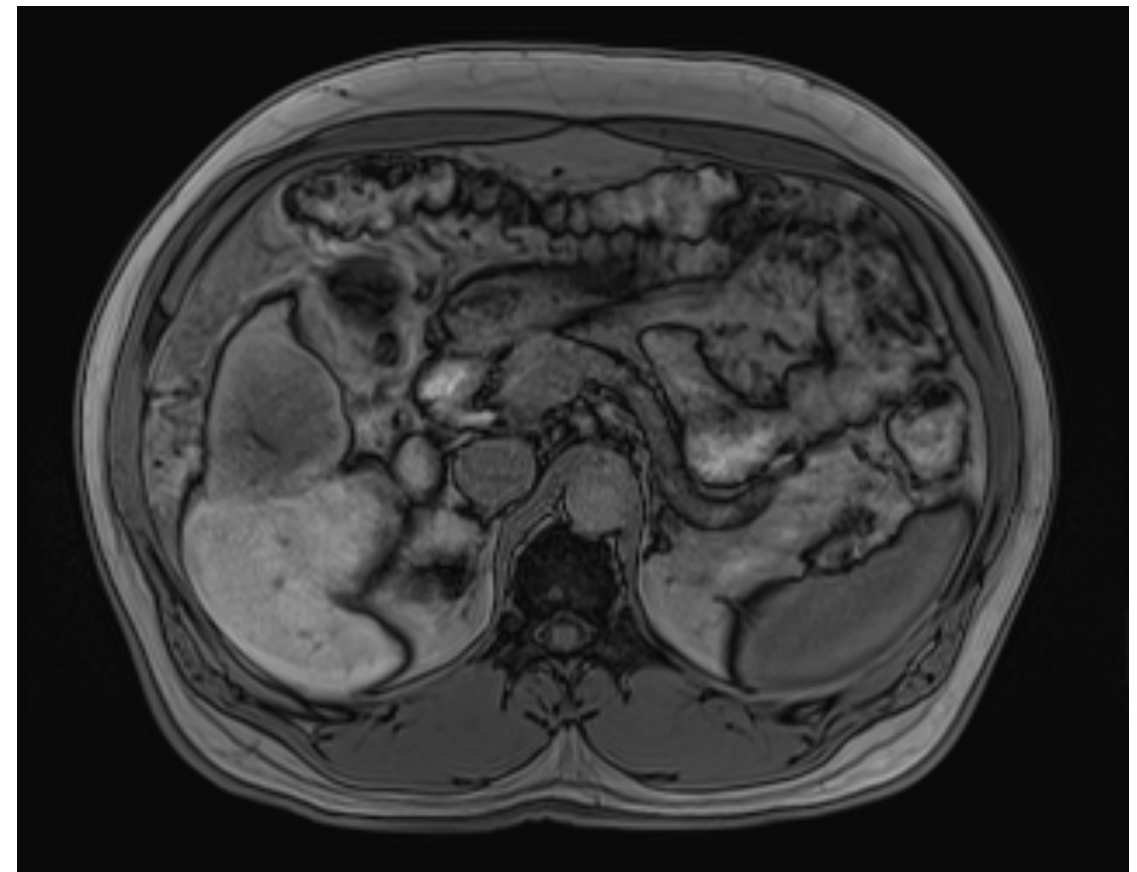
# Traitement du CHC : TACE

- ▶ Homme 43 ans
- ▶ Cirrhose HBV child A
- ▶ Apparition d'un nodule de 2.2 cm
- ▶ Stratégie : TACE et RF

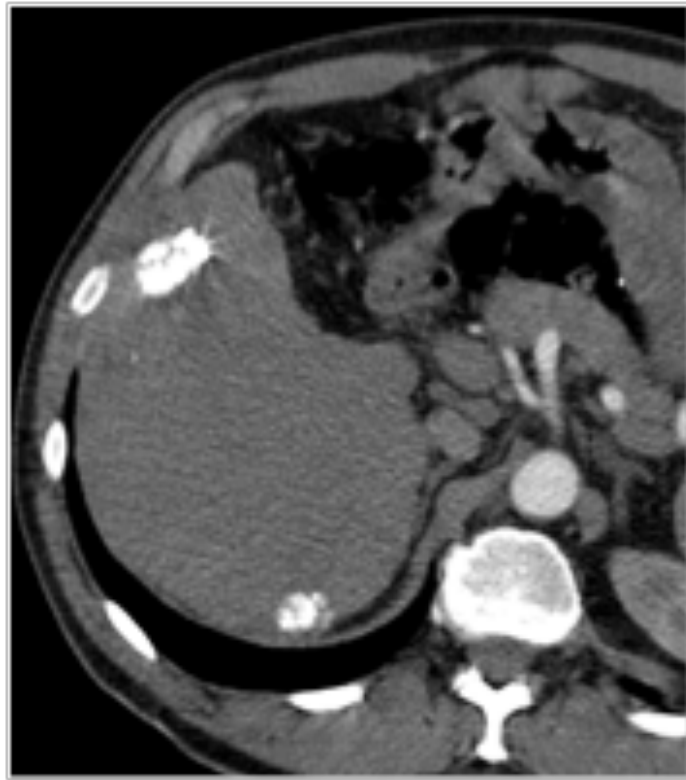


## Traitement du CHC : TACE

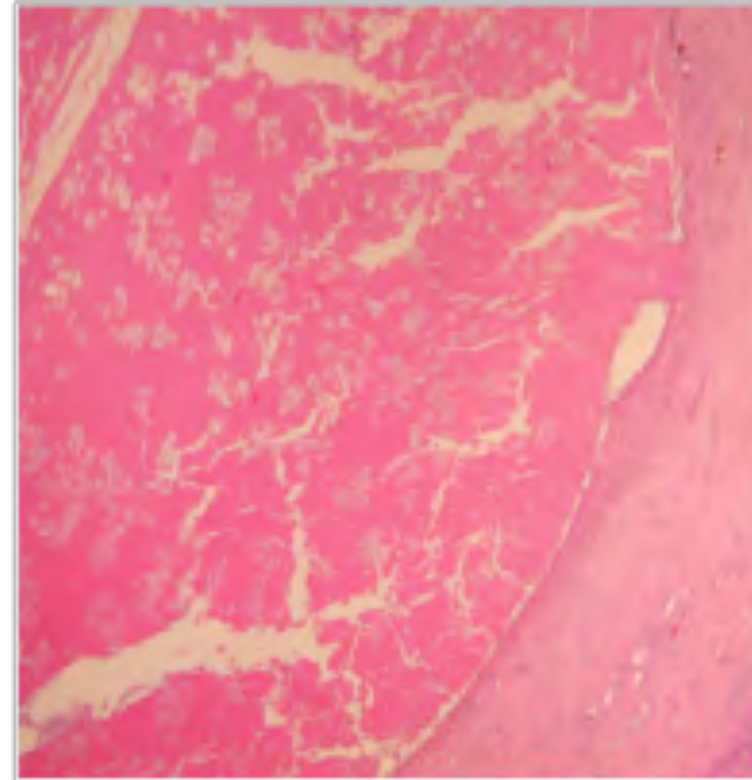
- ▶ Homme 43 ans
- ▶ Cirrhose HBV child A
- ▶ Apparition d'un nodule de 2.2 cm
- ▶ Contrôle IRM à 3 ans



# Traitement du CHC : TACE



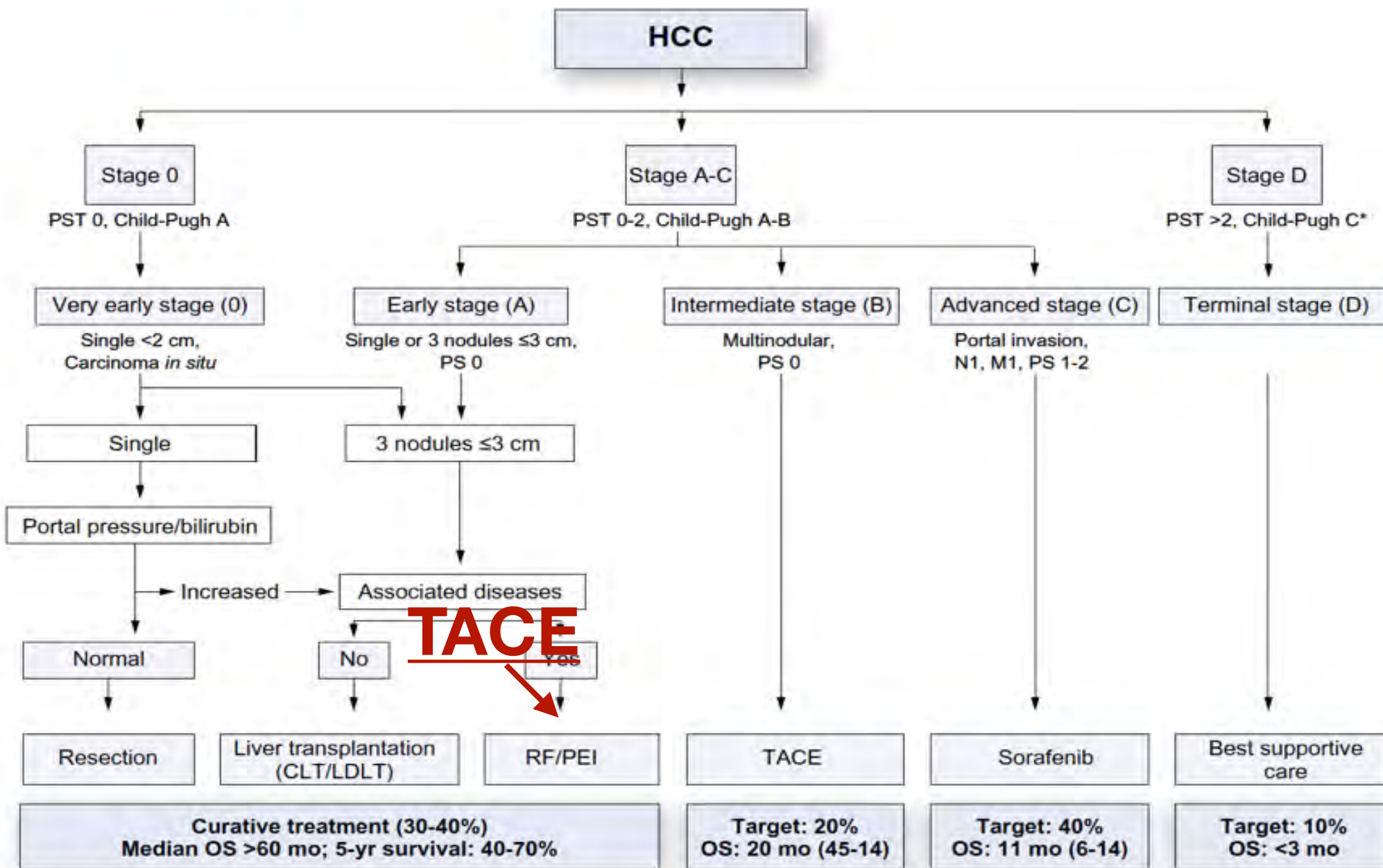
CT à 3 mois



nécrose complète des 2  
nodules à OLT à 3 mois

# Traitement du CHC : TACE





# Traitement du CHC : TACE



## CLINICAL STUDIES

### Transarterial chemoembolization in combination with percutaneous ablation therapy in unresectable hepatocellular carcinoma: a meta-analysis

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#### Keywords

chemoembolization – hepatocellular carcinoma – percutaneous ablation

#### Correspondence

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#### Abstract

**Background:** Recent evidence suggests that transcatheter arterial chemoembolization (TACE) combined with radiofrequency ablation (RFA) or a percutaneous ethanol injection (PEI) may have a synergistic effect in treating hepatocellular carcinoma (HCC). The aim of the current meta-analysis was to identify the survival benefits of TACE combined with percutaneous ablation (PA) therapy (RFA or PEI) for unresectable HCC compared with those of TACE or PA alone. **Methods:** Randomized-controlled trials (RCTs) published as full papers or abstracts were searched to assess the survival benefit or tumour recurrence for patients with unresectable HCC on electronic databases. The primary outcome was survival. The secondary outcomes were response to therapy and tumour recurrence. **Results:** Ten RCTs met the criteria to perform a meta-analysis including 595 participants. TACE combined with PA therapy, respectively improved, 1-, 2-, and 3-year overall survival compared with that of monotherapy [odds ratio (OR) 2.28, 95% confidence interval (CI) 1.14–4.57;  $P=0.020$ ], (OR = 4.53, 95% CI 2.62–7.82,  $P < 0.00001$ ) and (OR = 3.50, 95% CI 1.75–7.02,  $P=0.0004$ ). Sensitivity analysis demonstrated a significant benefit in 1-, 2- and 3-year overall survival of TACE plus PEI compared with that of TACE alone for patients with large HCC lesions, but not in TACE plus RFA vs RFA for patients with small HCCs. The pooled result of five RCTs showed that combination therapy decreased tumour recurrence compared with that of monotherapy (OR = 0.45, 95% CI 0.26–0.78,  $P=0.004$ ). **Conclusion:** TACE combined with PA therapy especially PEI improved the overall survival status for large HCCs.

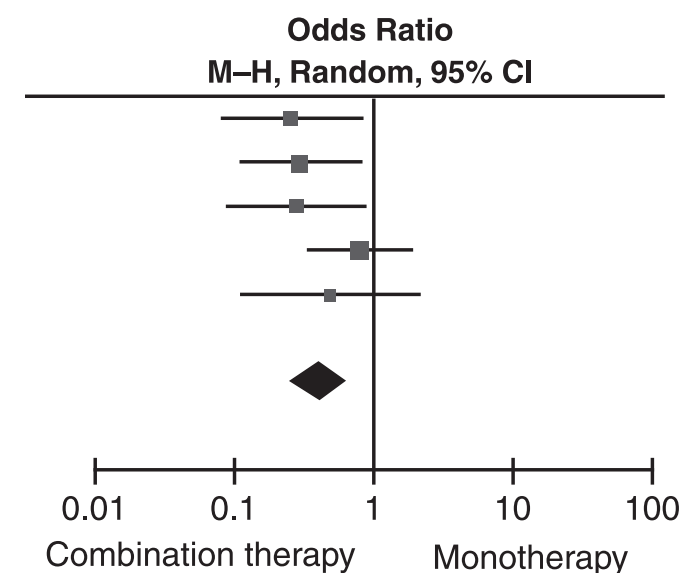


Fig. 4. Meta-analysis of the five randomized-controlled trials comparing the number of patient recurrence between combination therapy vs monotherapy for unresectable hepatocellular carcinoma patients.

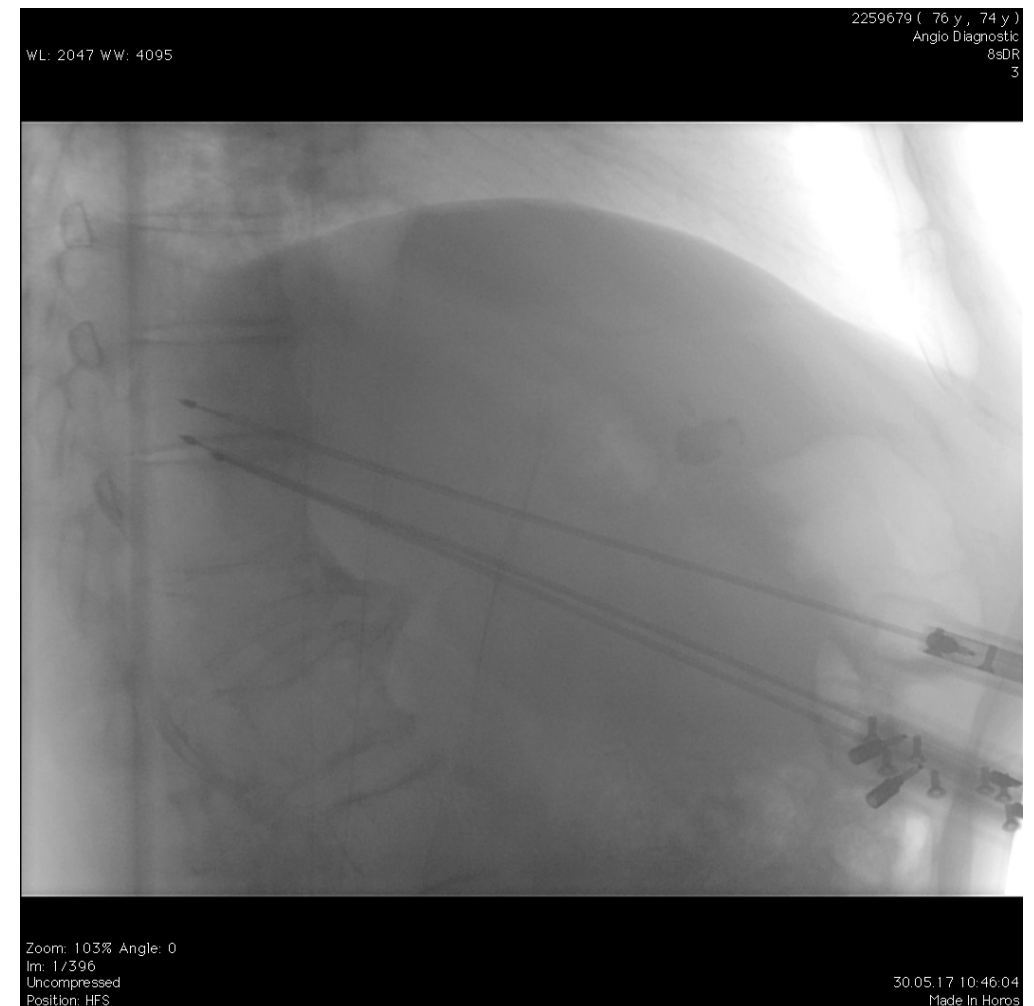
# Traitement du CHC : TACE

- ▶ Homme 69 ans
- ▶ BEG
- ▶ Cirrhose OH child A
- ▶ Suivi US à 6 mois :  
apparition de 2 nodules
- ▶ Gradient porto-systémique :  
6 mm Hg



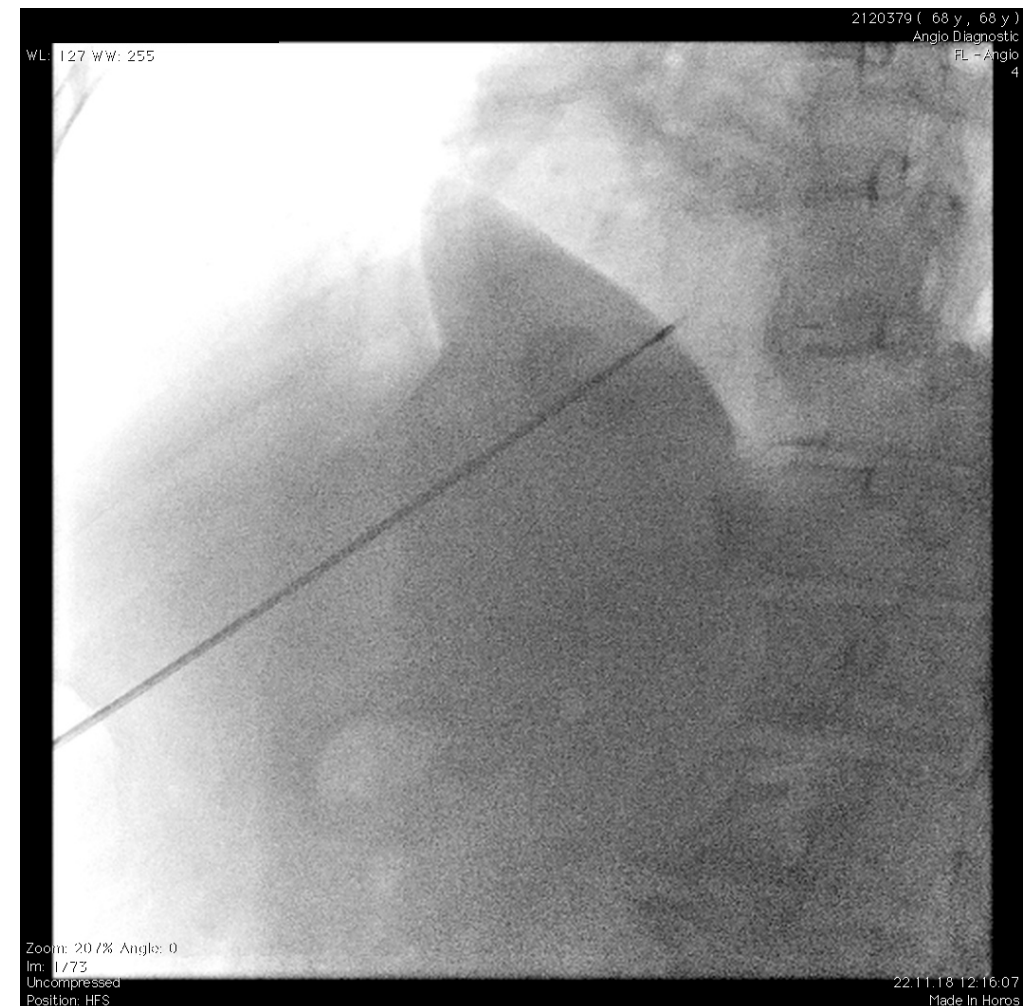
## Traitement du CHC : TACE

- ▶ Homme 69 ans
- ▶ Excellente réponse après 2 TACE
- ▶ Radiofréquence à 8 mois



# Traitement du CHC : TACE

- ▶ Homme 69 ans
- ▶ Excellente réponse après 2 TACE
- ▶ Radiofréquence à 8 mois



# Traitement du CHC : TACE

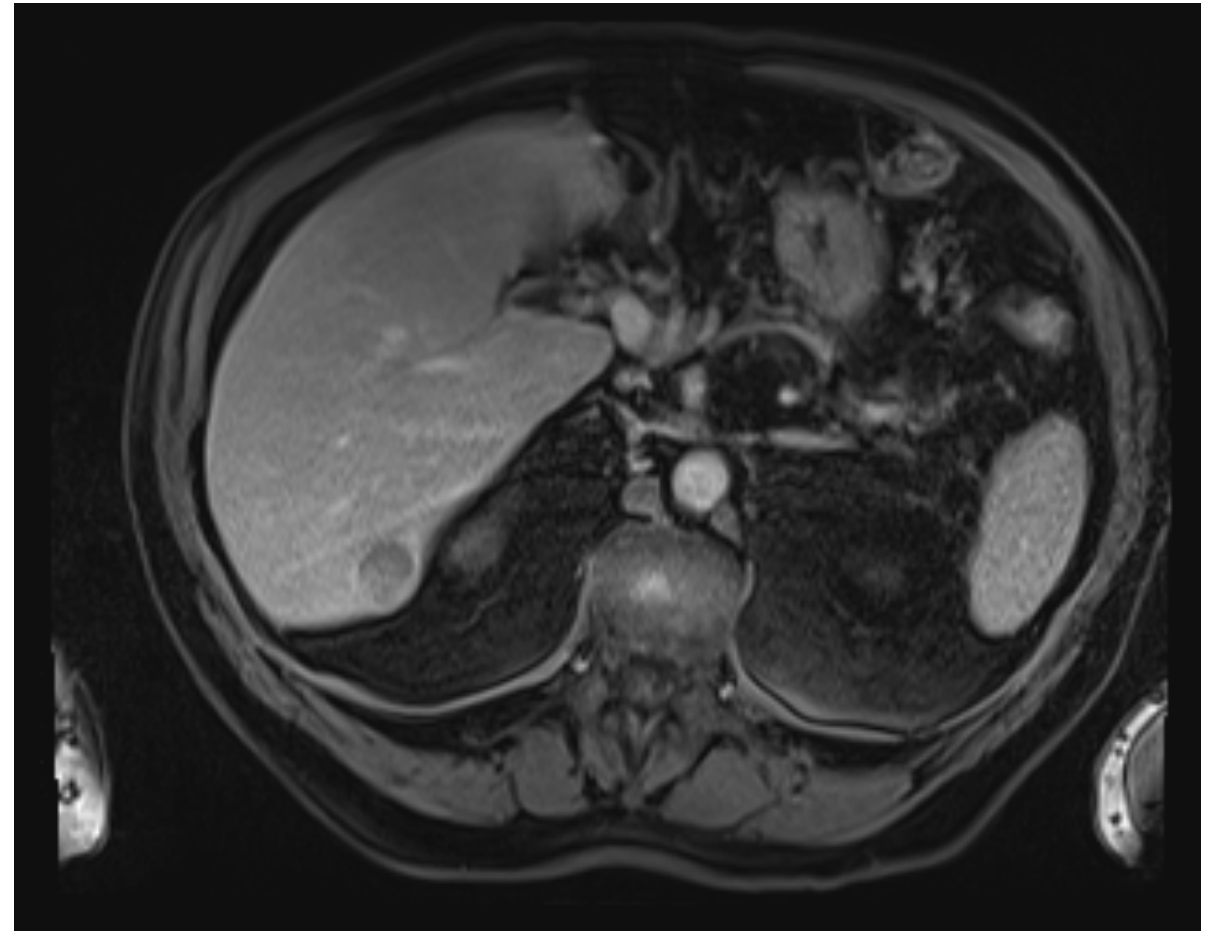


- ▶ Homme 69 ans
- ▶ Excellente réponse après 2 TACE
- ▶ Radiofréquence à 8 mois



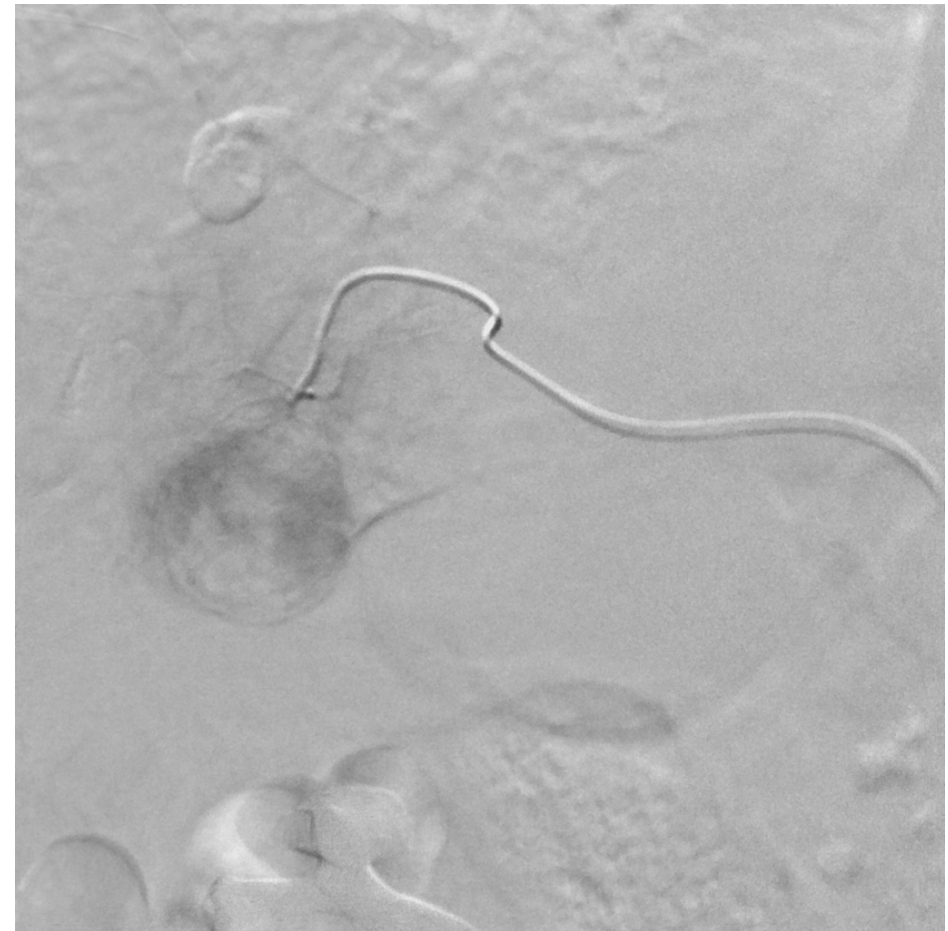
# Traitement du CHC : TACE

- ▶ Homme 75 ans
- ▶ Diabète
- ▶ Cirrhose OH child A
- ▶ Suivi IRM d'une lésion pancréas
- ▶ 5 lésions suspectes



# Traitement du CHC : TACE

- ▶ Homme 75 ans
- ▶ Diabète
- ▶ Cirrhose OH child A
- ▶ 1 séance de chimio-embolisation



## Traitement du CHC

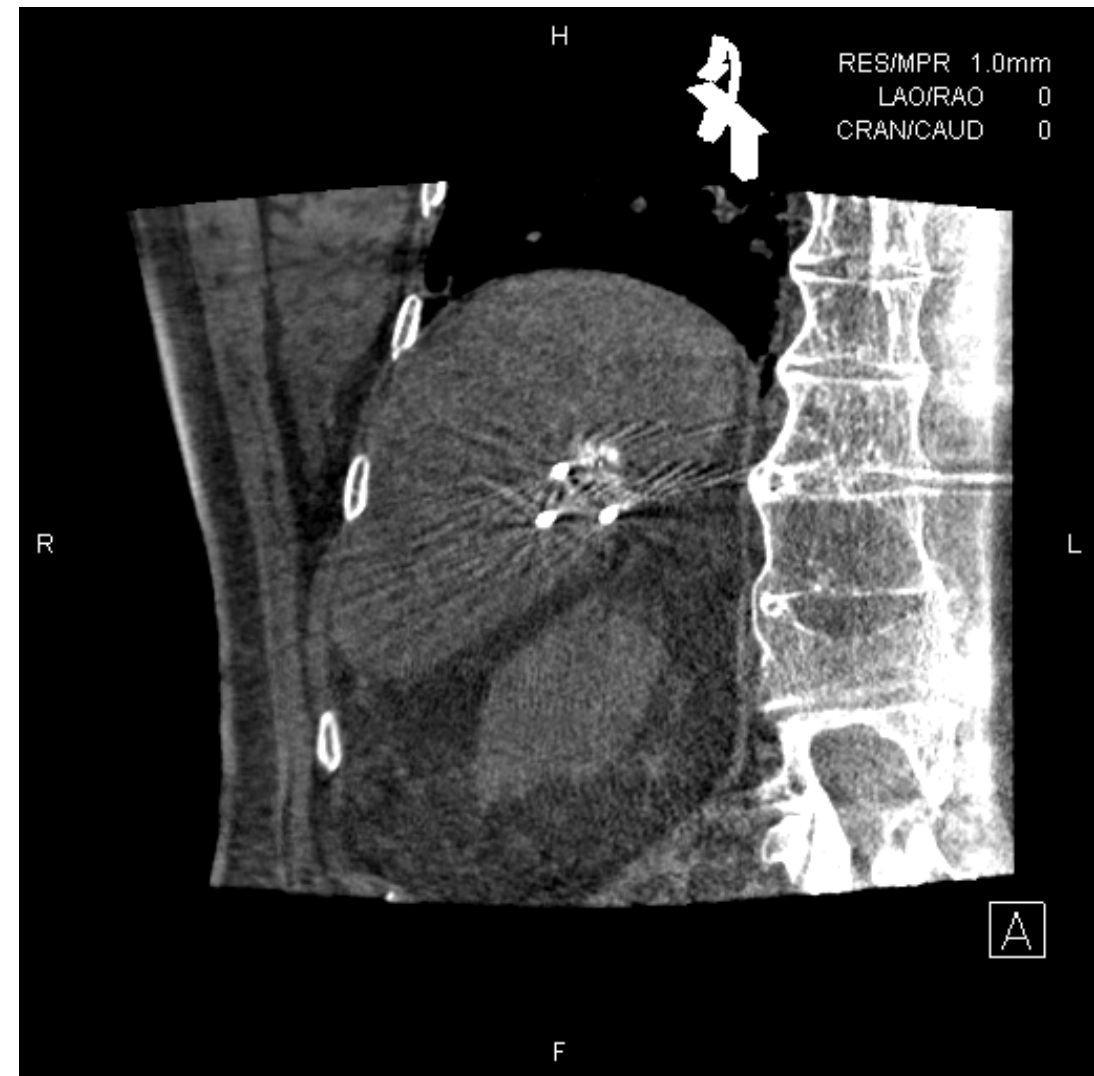
- ▶ Homme 75 ans
- ▶ Diabète
- ▶ Cirrhose OH child A
- ▶ Contrôle CT à 1 mois



# Traitement du CHC : TACE

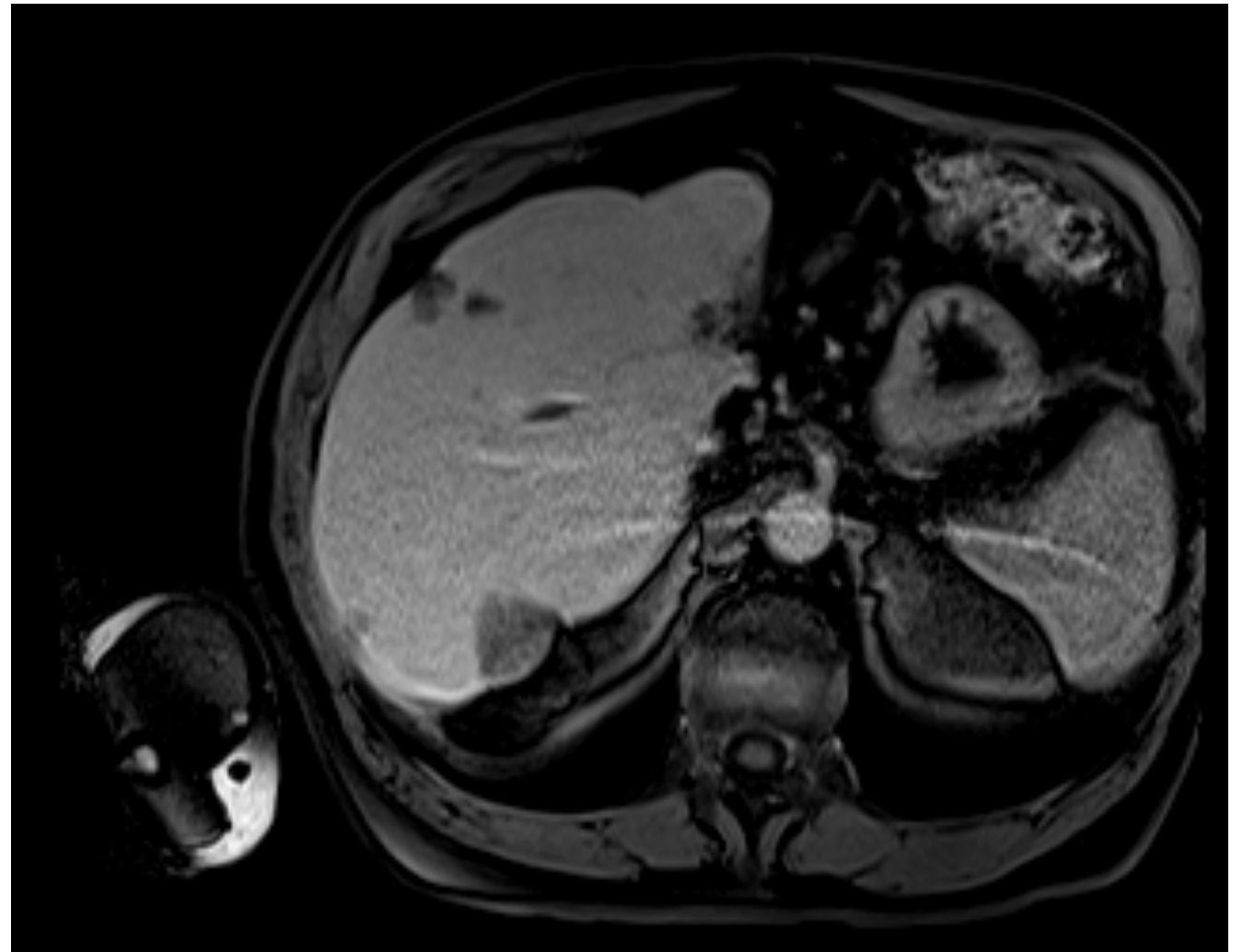


- ▶ Homme 75 ans
- ▶ Diabète
- ▶ Cirrhose OH child A
- ▶ Radiofréquence



## Traitement du CHC : TACE

- ▶ Homme 75 ans
- ▶ Diabète
- ▶ Cirrhose OH child A
- ▶ IRM à 16 mois



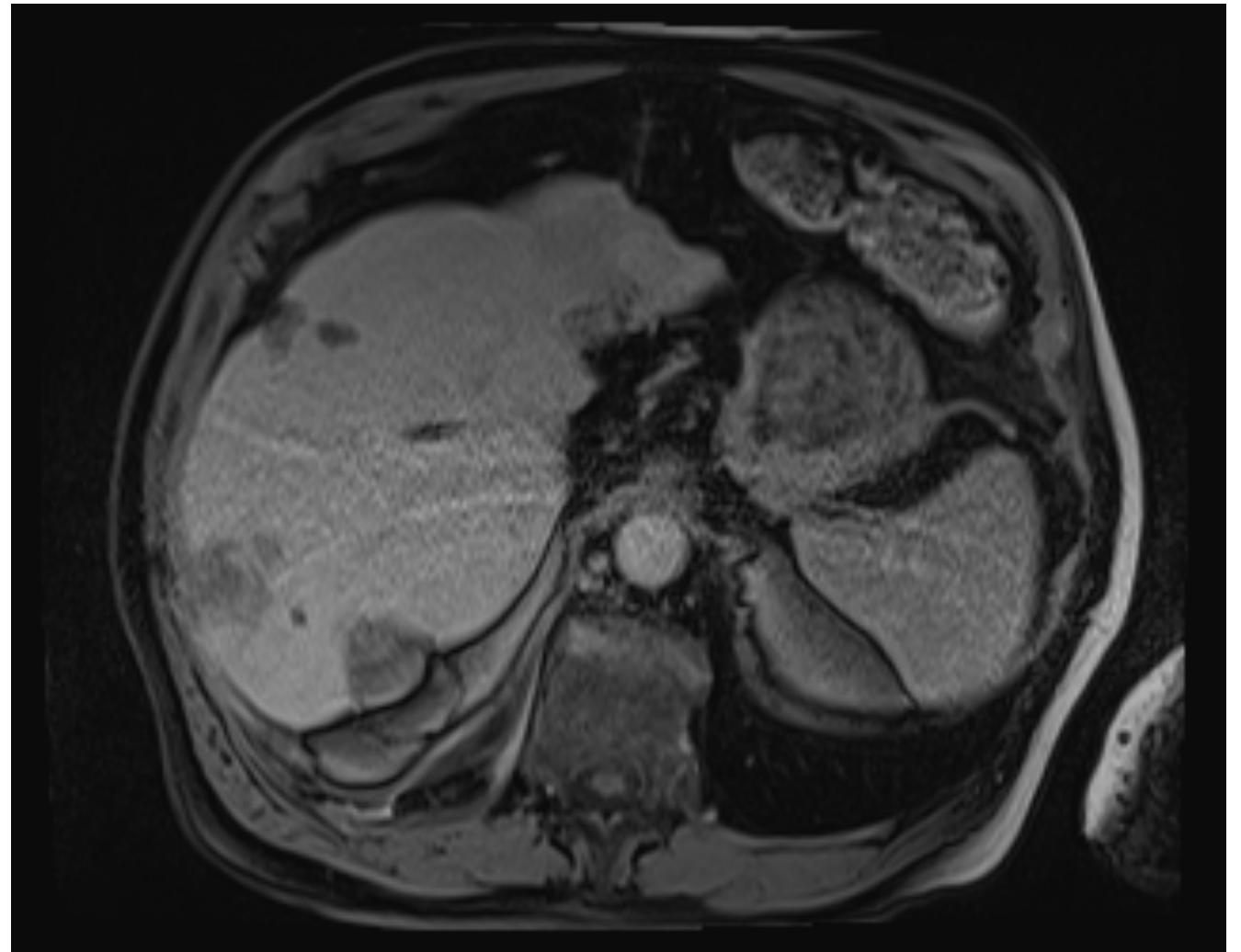
## Traitement du CHC : TACE

- ▶ Homme 75 ans
- ▶ Diabète
- ▶ Cirrhose OH child A
- ▶ Nouvel RF à 17 mois



## Traitement du CHC : TACE

- ▶ Homme 75 ans
- ▶ Diabète
- ▶ Cirrhose OH child A
- ▶ IRM à 18 mois

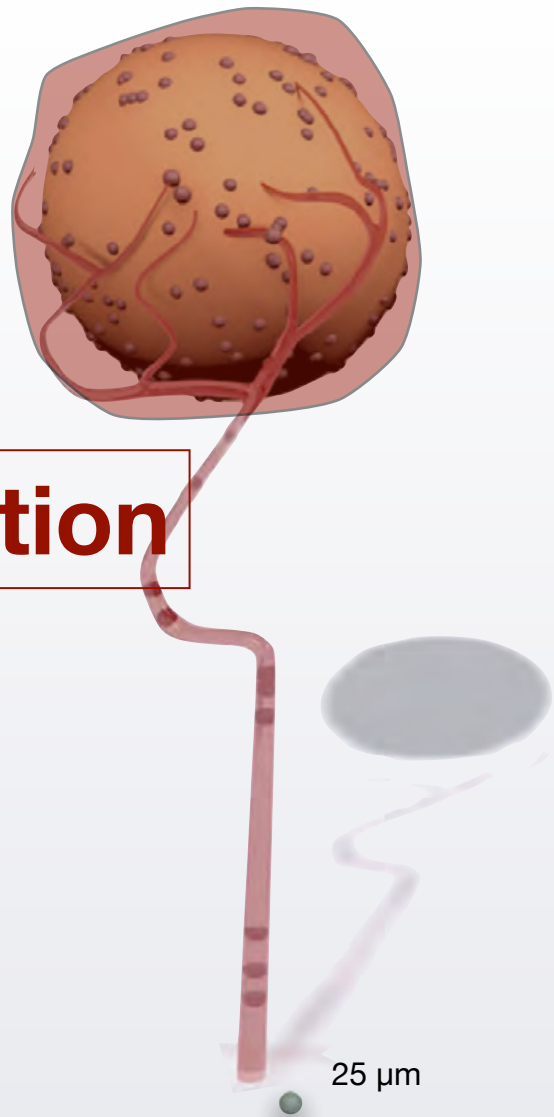


## Traitement du CHC : TACE



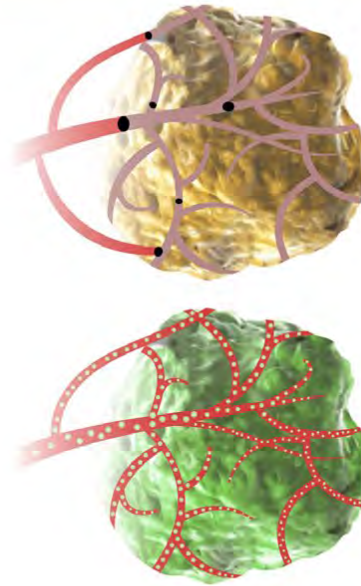
TARE

Irradiation



#### Conventional chemoembolization

- **Mechanism of action:** Delivery of a high-dose chemotherapy/ethiodized oil emulsion (yellow) followed by arterial embolisation to prevent drug washout and promote tumour ischaemia/hypoxia.
- **Particle size:** 100-500 µm



#### Radioembolization

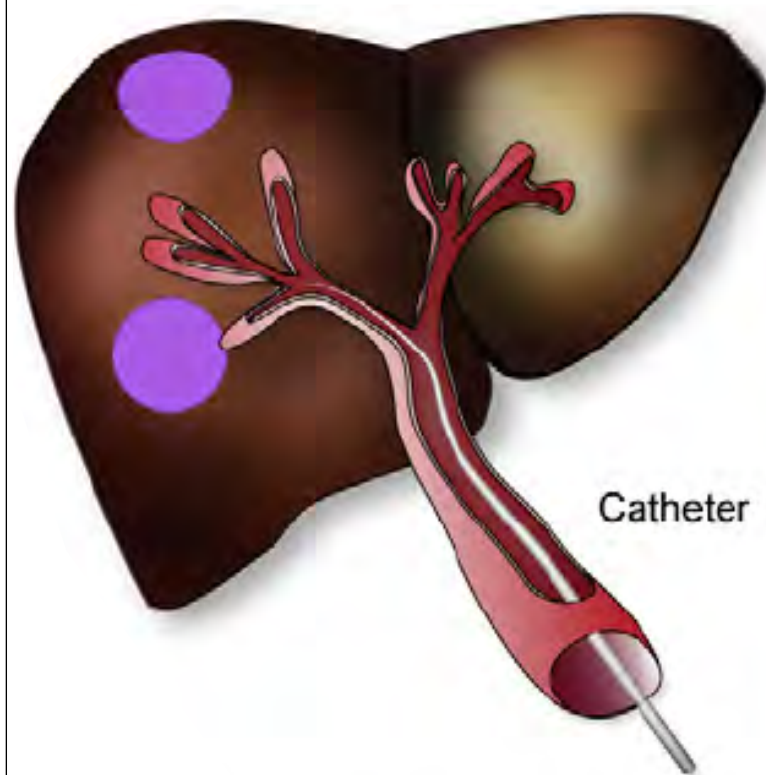
- **Mechanism of action:** Delivery of  $\beta$ -emitting microspheres that provide local, high dose tumour radiation. The radiation affects tissues 2.5-11 mm from the delivered microsphere (green)
- **Particle size:** 20-60 µm

TACE

Ischémie

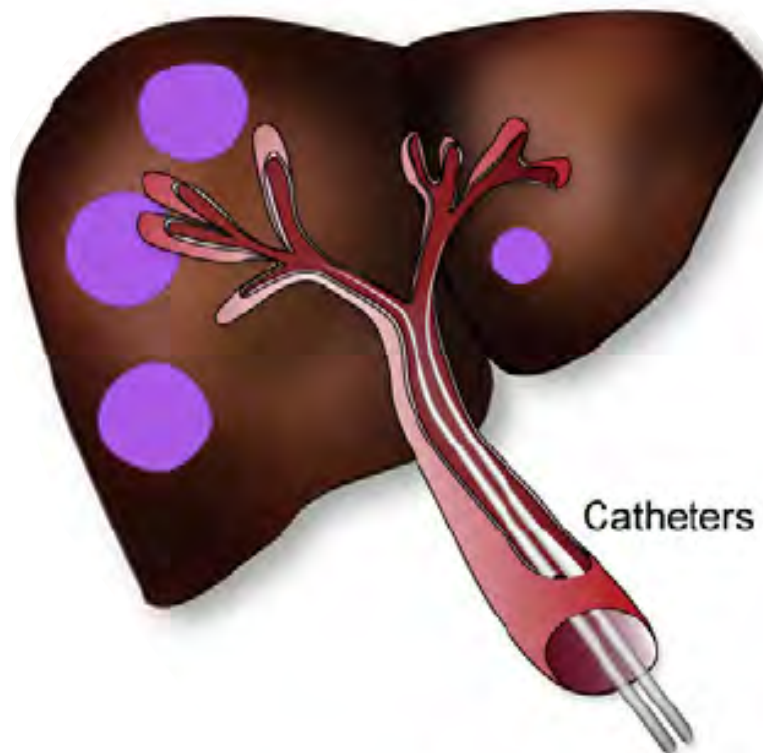


# Traitement du CHC : radio-embolisation



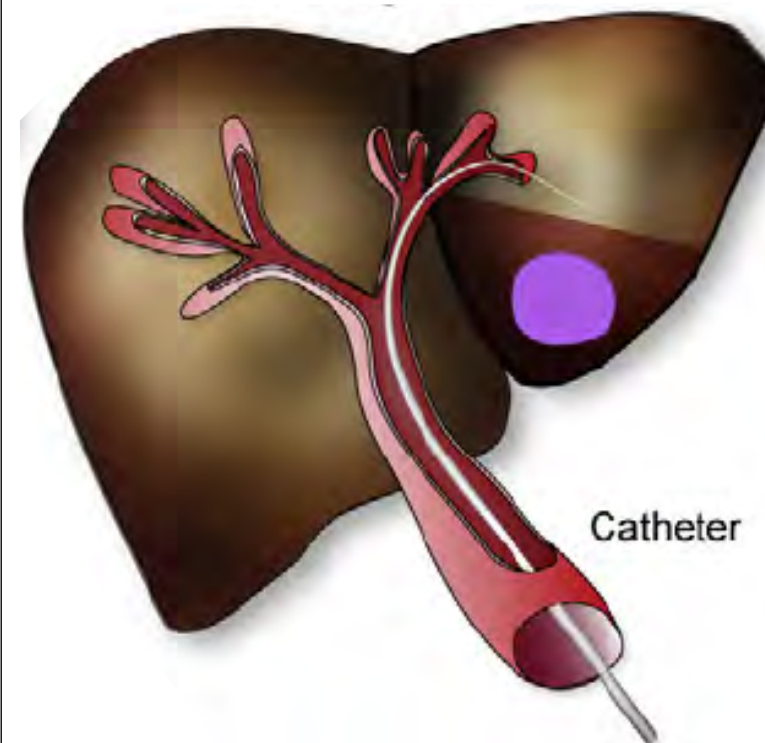
Catheter

Unilobaire



Catheters

Bilobaire

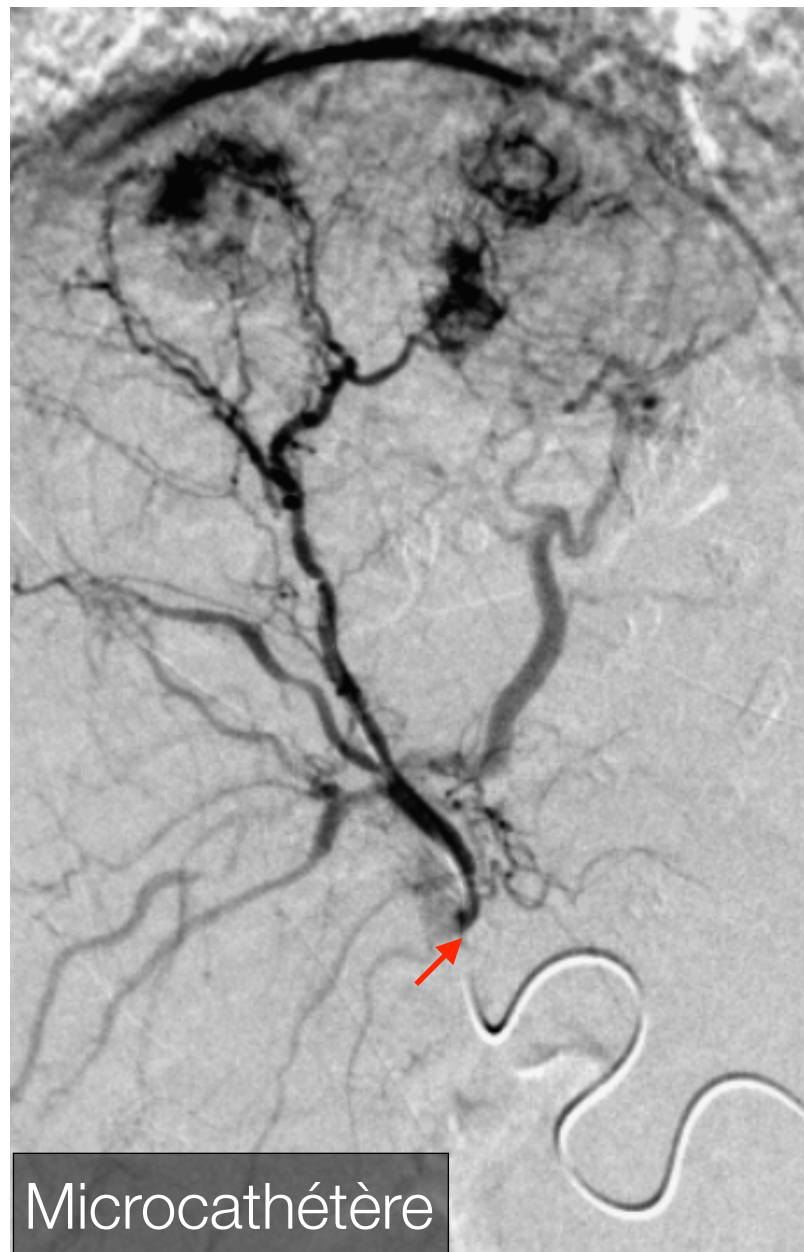


Catheter

Segmentaire

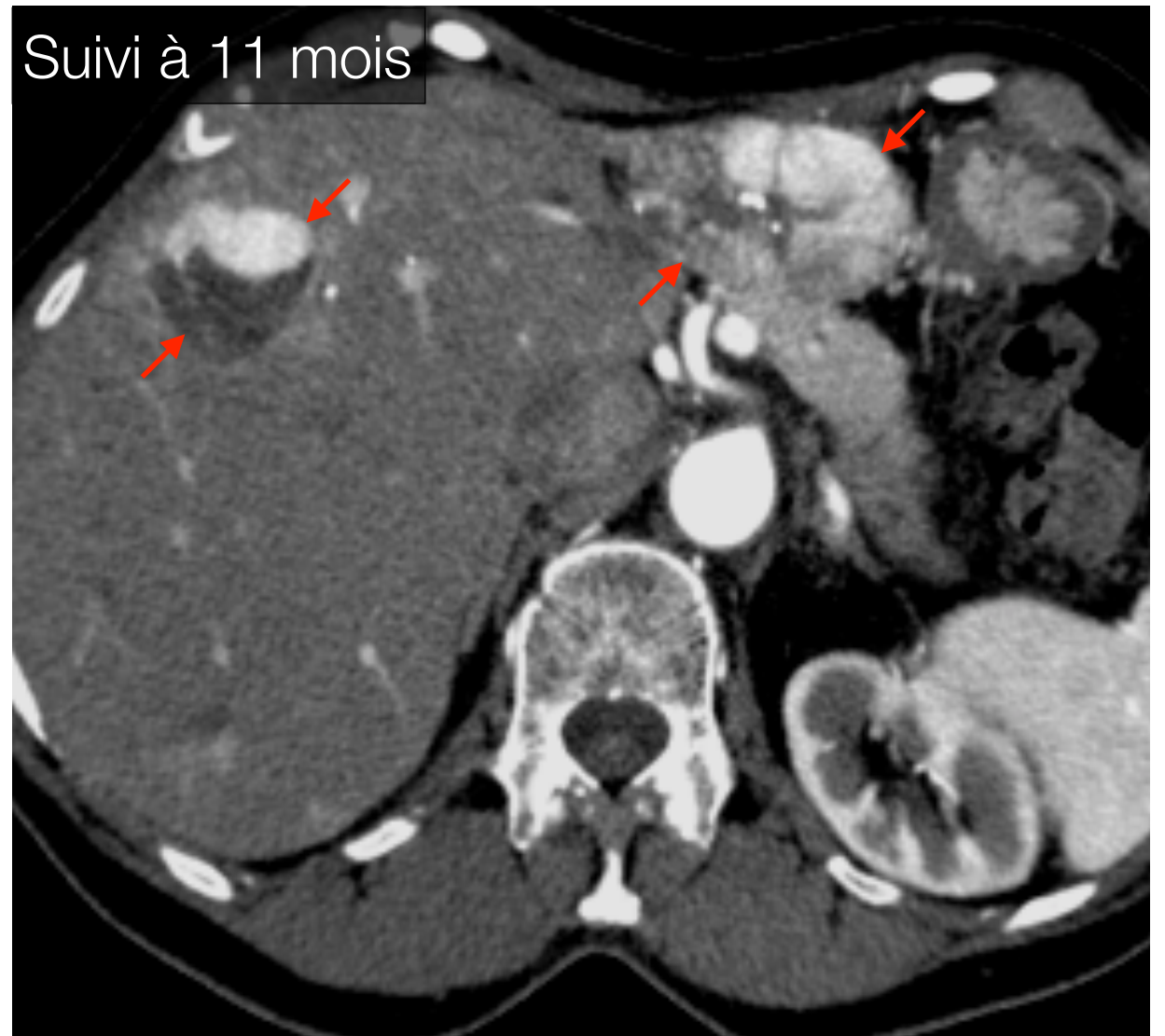
## Traitement du CHC : radio-embolisation



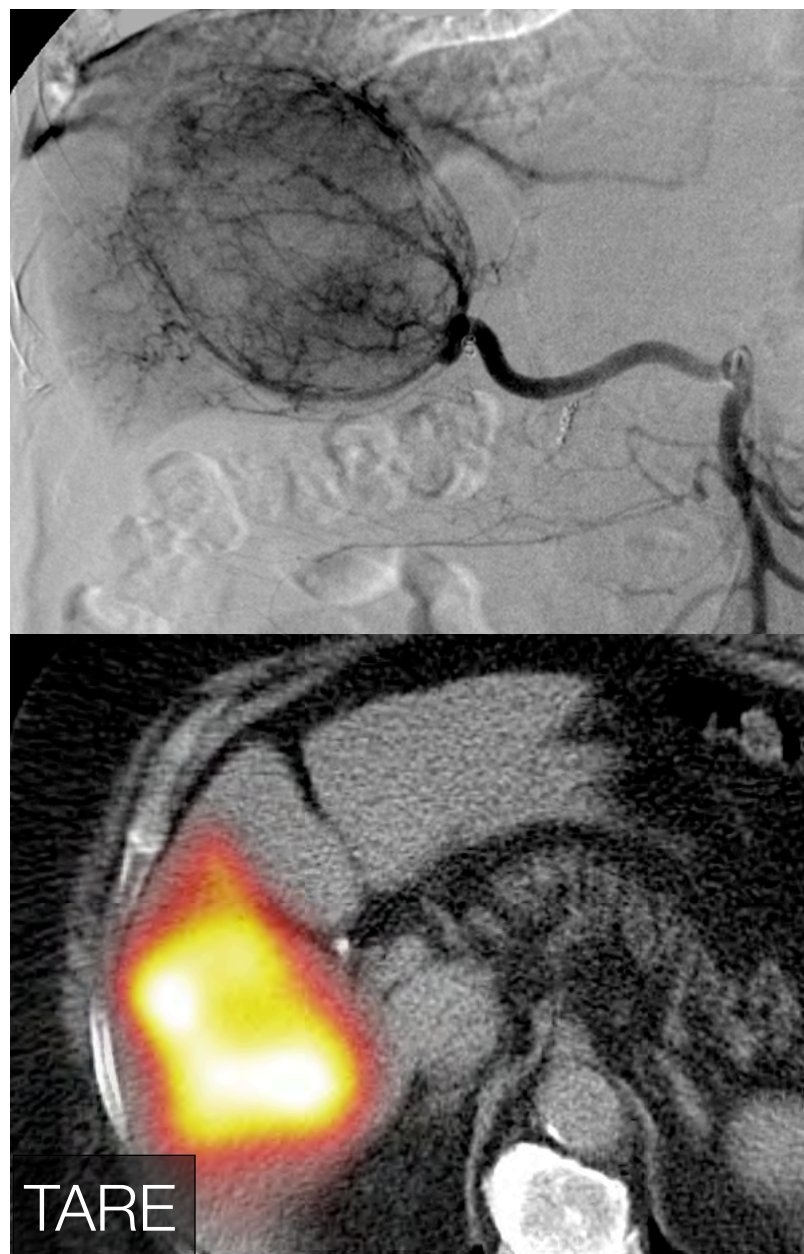


Traitement du CHC : radio-embolisation

# Traitement du CHC : radio-embolisation





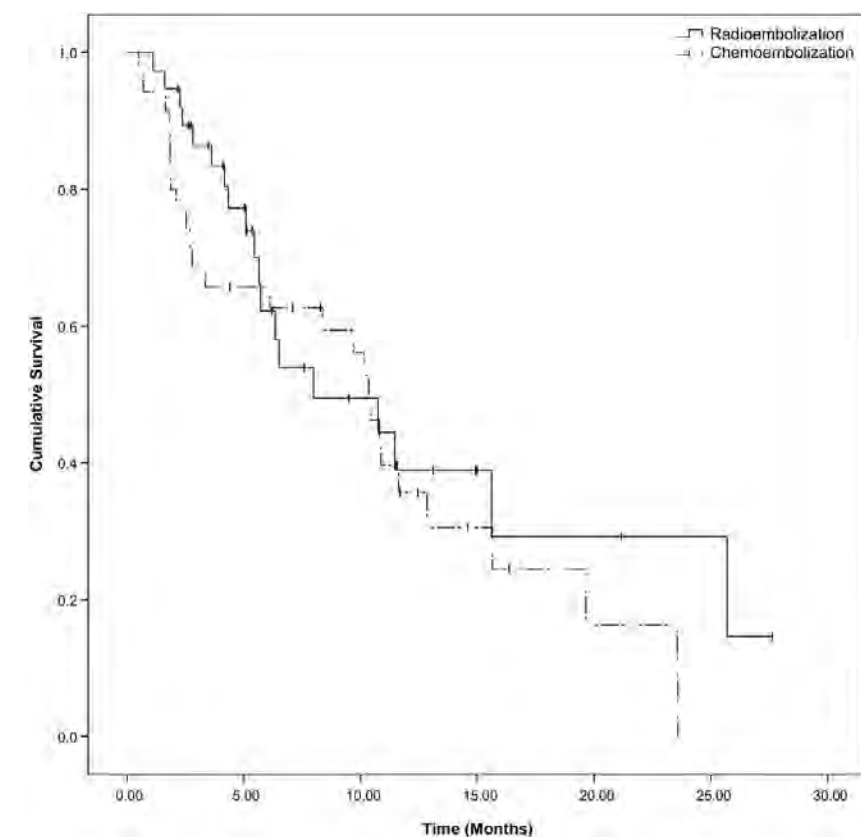


Traitement du CHC : radio-embolisation

# Safety and efficacy

Lance J Vasc Interv Radiol 2011

- ▶ Comparative analysis of the safety and efficacy of TACE and  $Y^{90}$  in 73 patients with unresectable HCC
  - ▶ TACE had significantly higher rates of hospitalization as a result of postembolization syndrome
  - ▶  $Y^{90}$  therapy is much more tolerated by patients over TACE

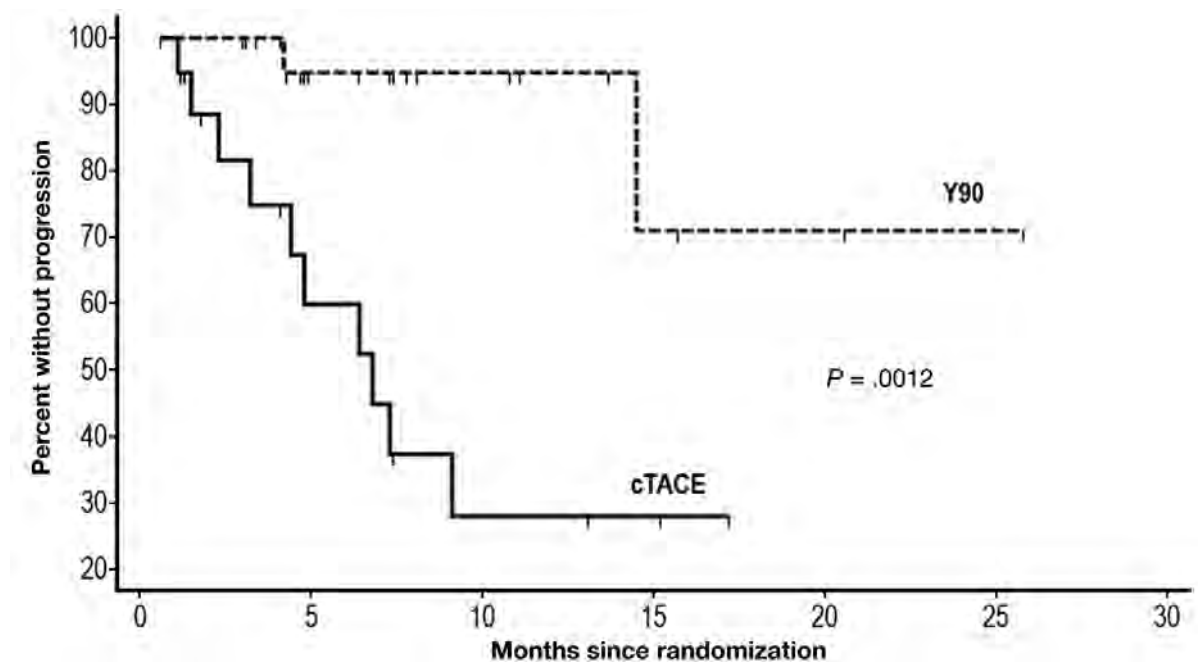


**Figure 2.** Kaplan-Meier survival curve depicting patient survival for the chemoembolization (n = 35) and radioembolization (n = 38) cohorts. There was no difference in overall survival (log-rank test,  $P = .33$ ).

# $^{90}\text{Y}$ vs TACE

Salem R, *Gastroenterology* 2016

- ▶ prospective randomized study.  
BCLC A & B
- ▶ no PVT / Child Pugh A/B
- ▶ longer TTP ( $p = 0.012$ )
  - $^{90}\text{Y}$ : > 26 months
  - TACE: 6.8 months
- ▶ no difference in median OS



TTP

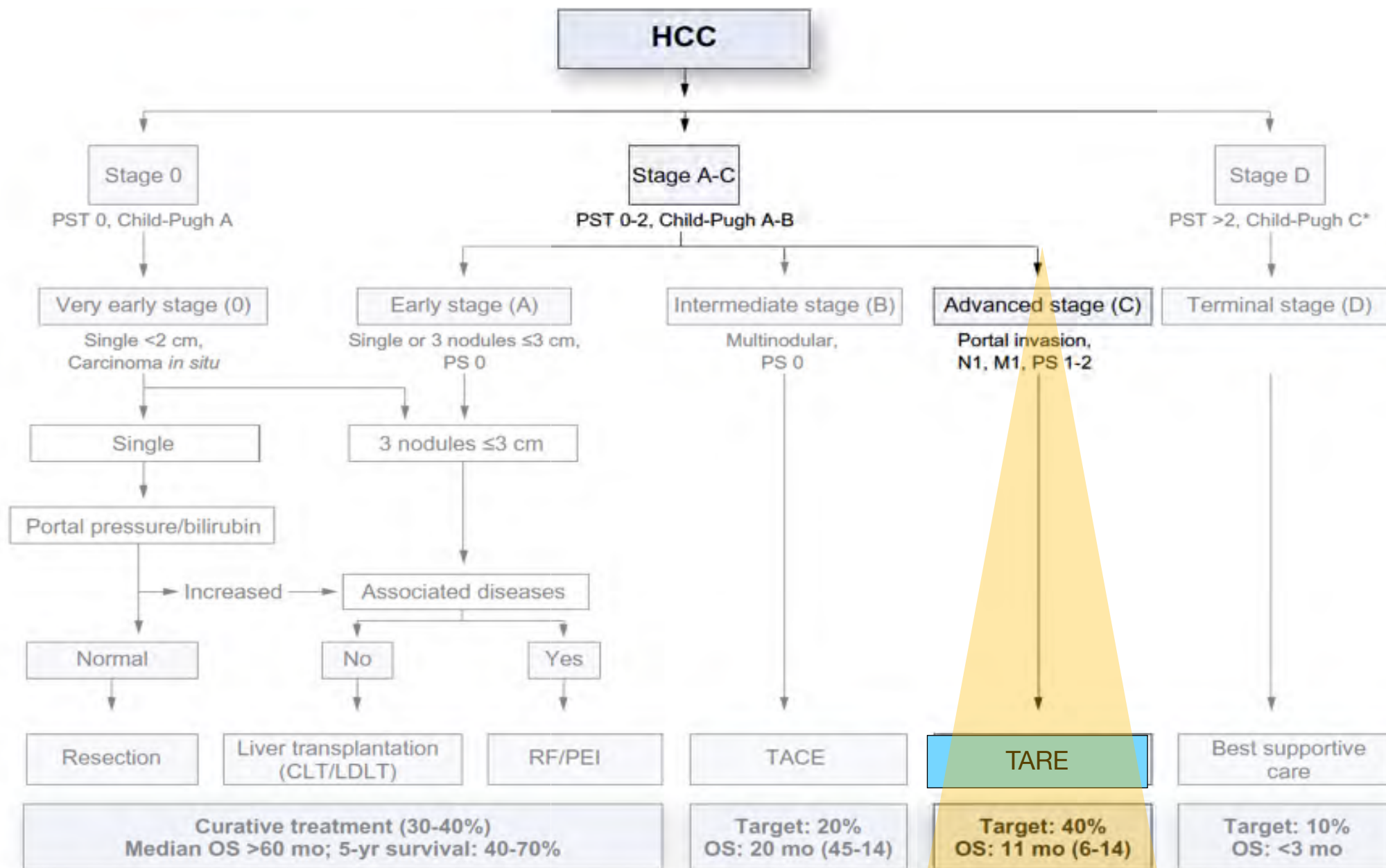
# $^{90}\text{Y}$ and TACE



Kolligs Liver Int 2015

- ▶ SIRTACE : 28 patients with unresectable HCC and without PVT assigned to  $^{90}\text{Y}$  or TACE. primary end-point : Health-related quality of life (HRQoL)
  - ▶ no difference in HRQoL,
  - ▶ no difference in local control of liver tumor according to RECIST 1.0
  - ▶ no difference in the frequency of adverse events
- ▶ The investigators to suggest  $^{90}\text{Y}$  as an alternative treatment option for TACE





# Traitement du CHC

EASL-EORTC, *J Hepatol* 2012



# $^{90}\text{Y}$ and Sorafenib

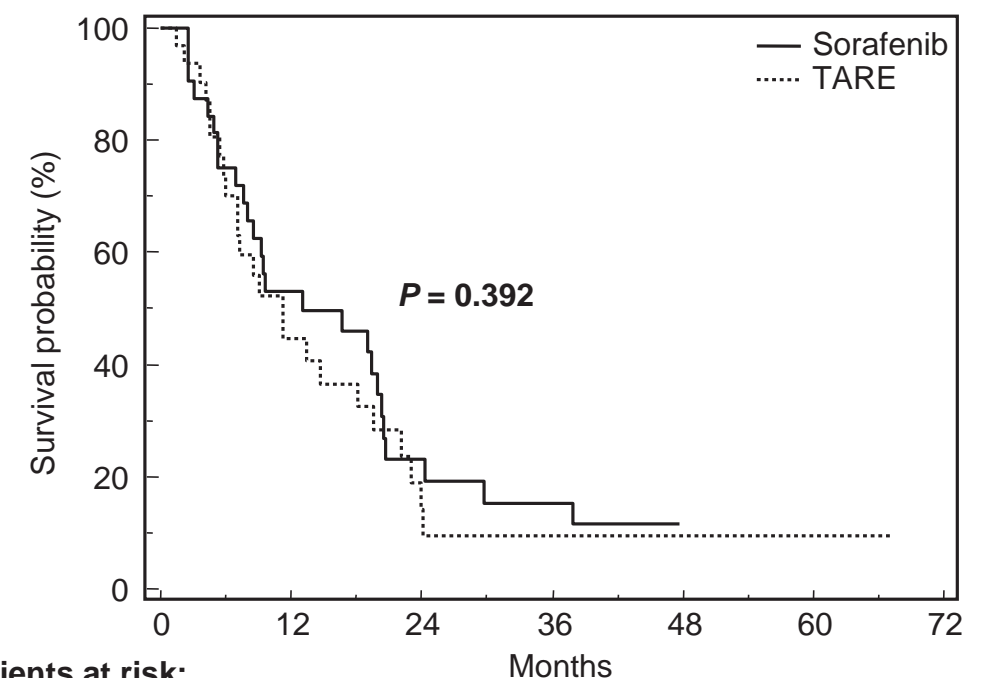
Gramenzi Liver Int 2015

- ▶ HCC cohort not amenable to curative treatment 137 patients

- ▶ No CR with Sorafenib

- ▶ 12 patients achieved CR in  $^{90}\text{Y}$  and 2 patient were able to OLT

- ▶  $^{90}\text{Y}$  for downstaging



Patients at risk:

Months	0	6	12	18	24	30	36	42	48	54	60
Sorafenib group	32	24	15	12	6	4	4	3	0	0	0
TARE group	32	20	12	9	4	1	1	1	1	1	1

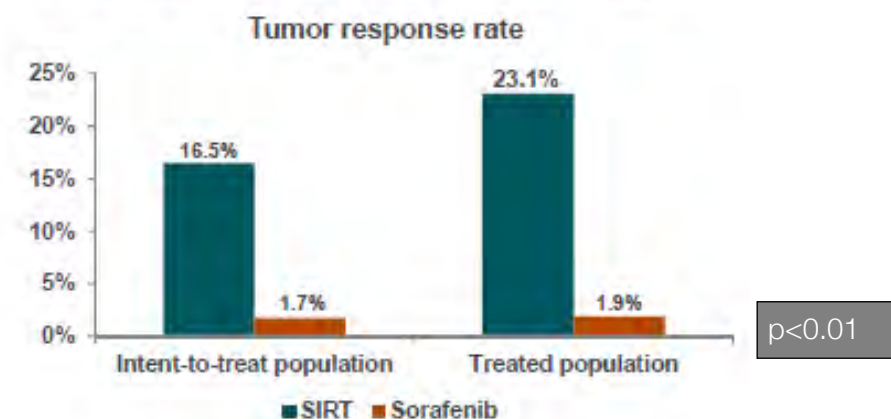
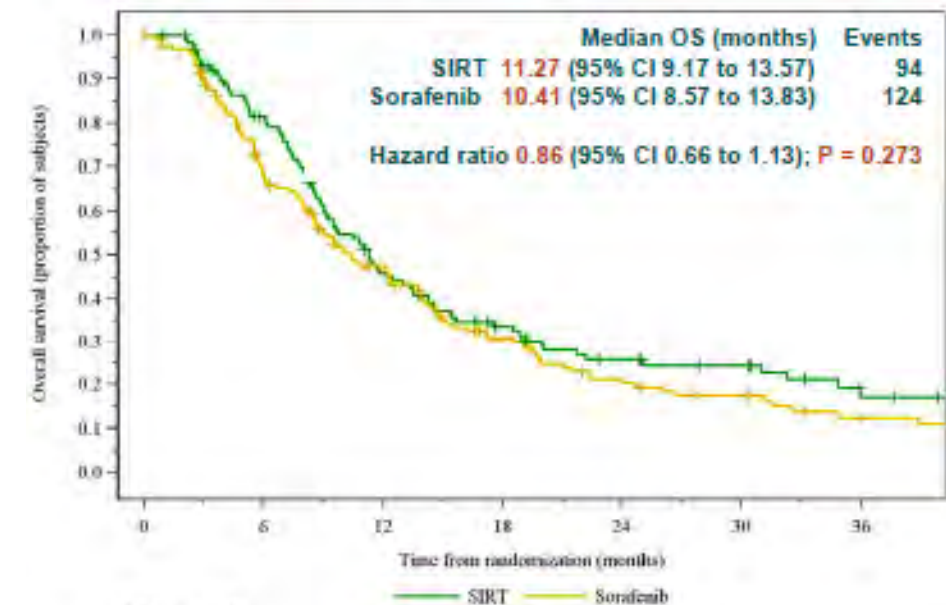
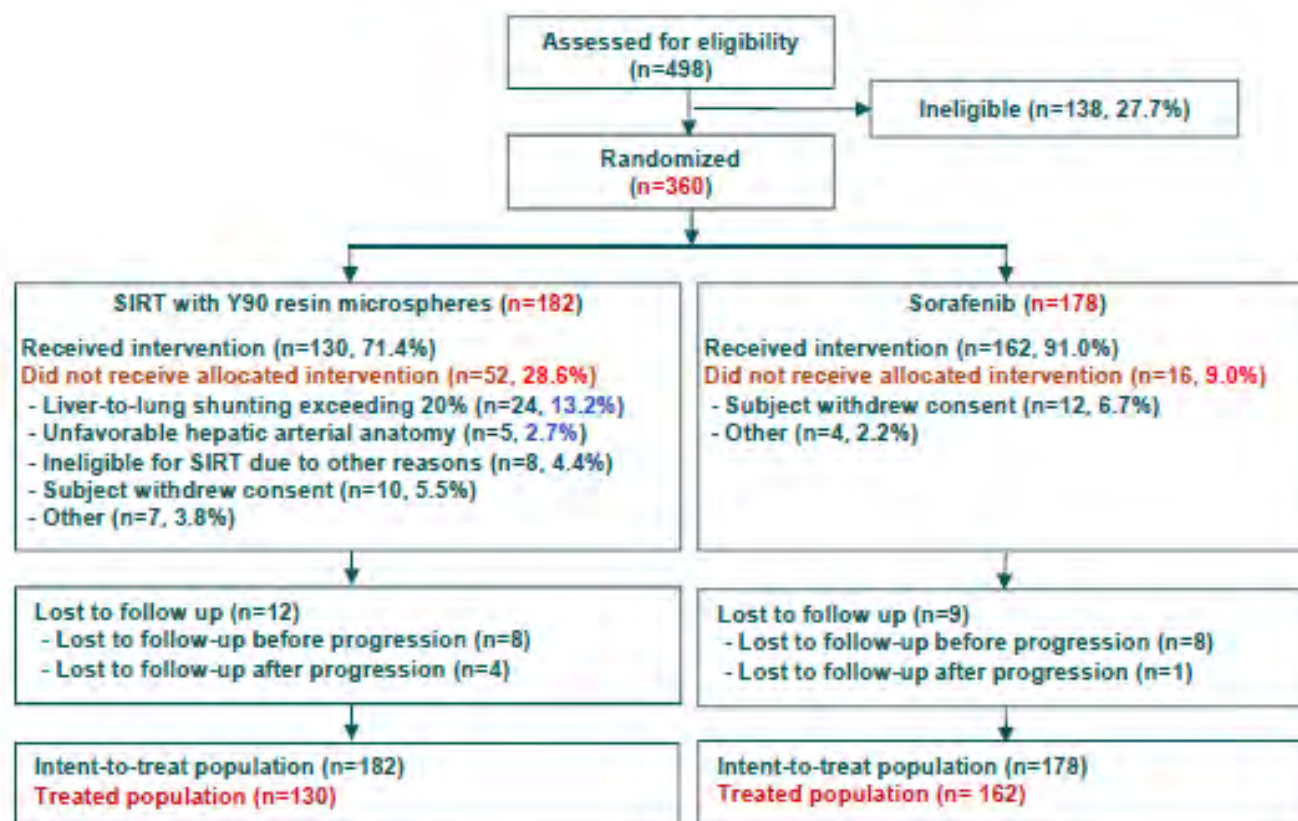
**Fig. 3.** Overall survival of sorafenib and TARE patients after matching with the propensity analysis score.

# $^{90}\text{Y}$ and Sorafenib

evidence  
level I

Chow ASCO 2017

## SIRveNIB trial

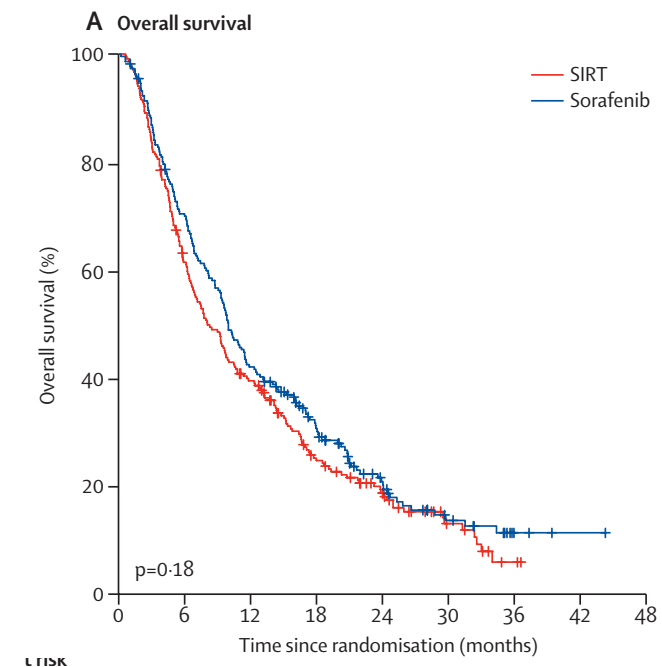
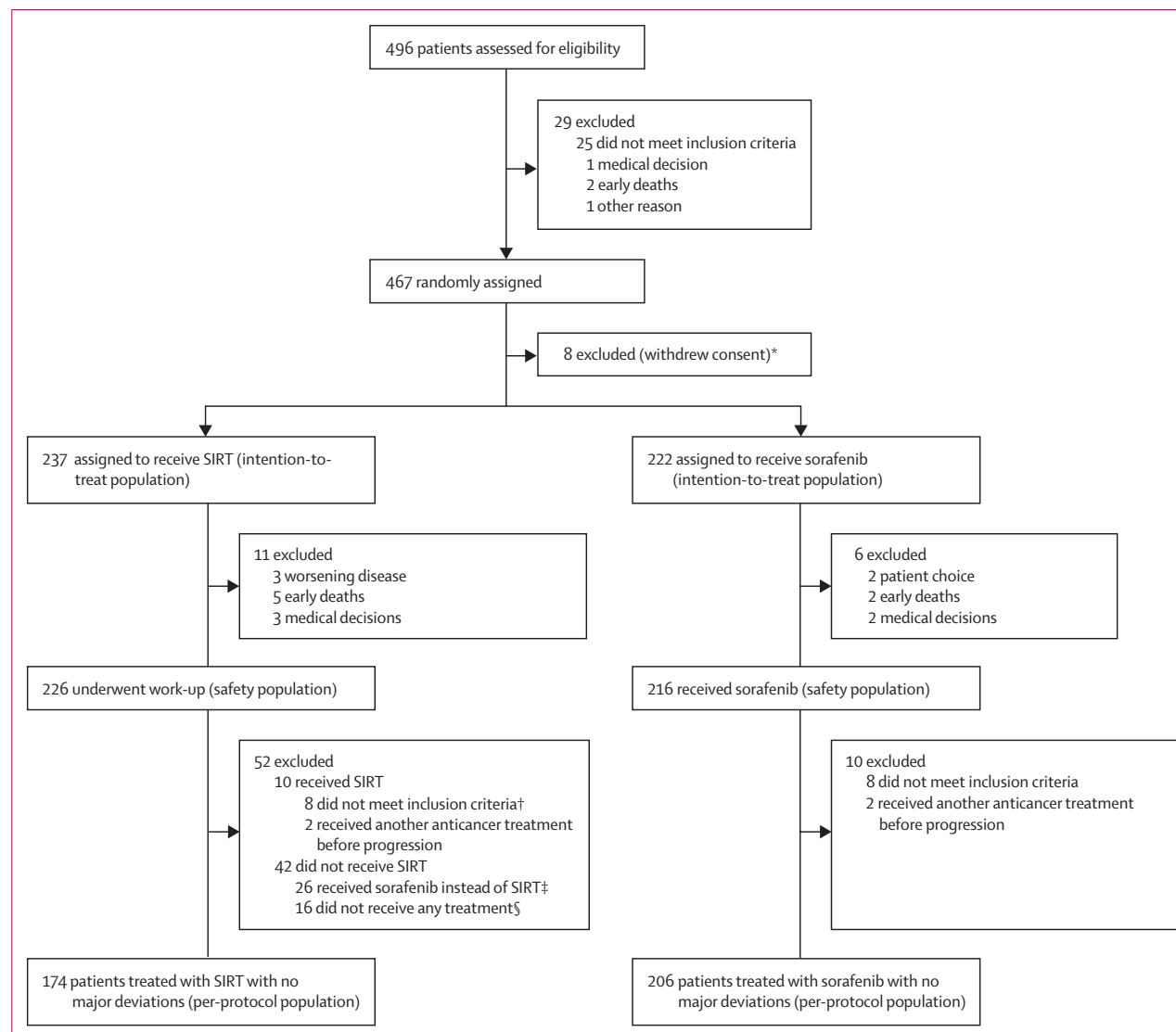


# $^{90}\text{Y}$ and Sorafenib

evidence  
level I

Vilagrain Lancet 2017

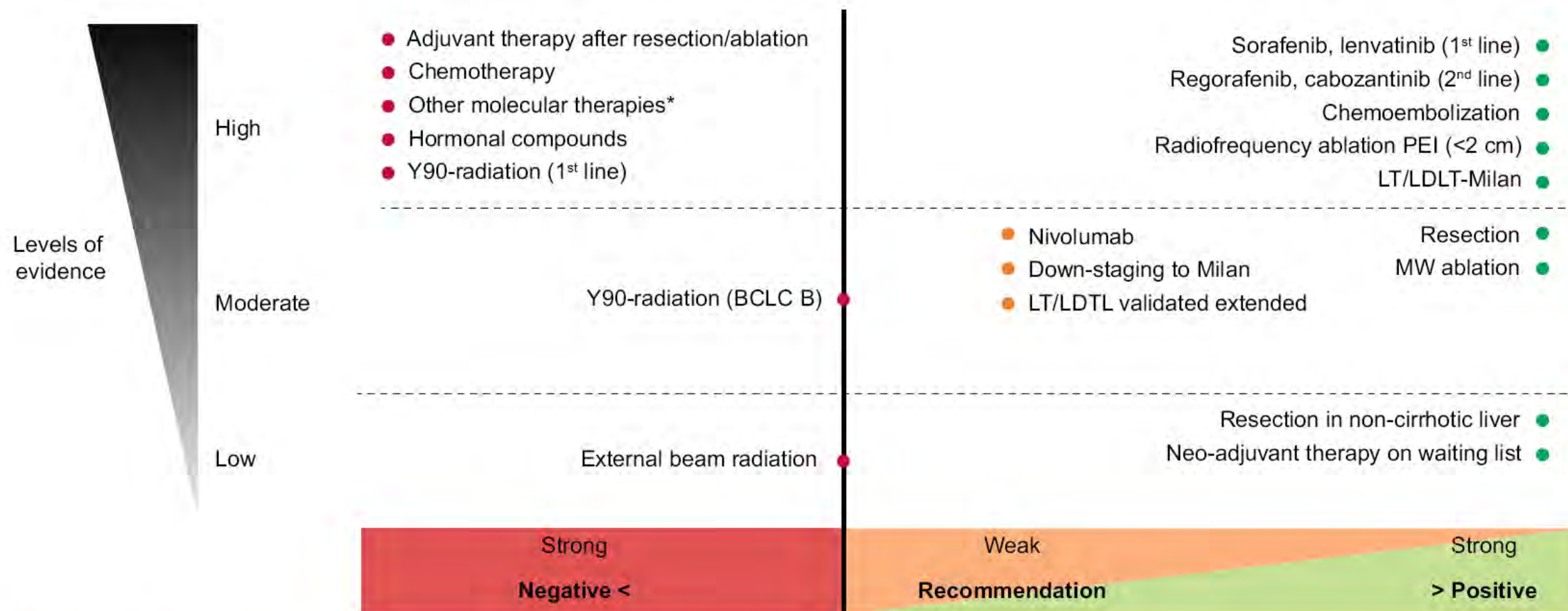
## SARAH trial



	SIRT (n=190)	Sorafenib (n=198)	p value
Best overall response			
Complete response	5 (3%)	2 (1%)	0.0077
Partial response	31 (16%)	21 (11%)	..
Stable disease	93 (49%)	131 (66%)	..
Progressive disease	60 (32%)	44 (22%)	..
Disease control*	129 (68%)	154 (78%)	0.0346

Data are n (%). SIRT=selective internal radiotherapy. RECIST=Response Evaluation Criteria in Solid Tumors. \*Disease control is the percentage of patients who had a best response of complete response, partial response, or stable disease.

**Table 3: Comparison of treatment responses (RECIST 1.1) among evaluable patients in the intention-to-treat population**

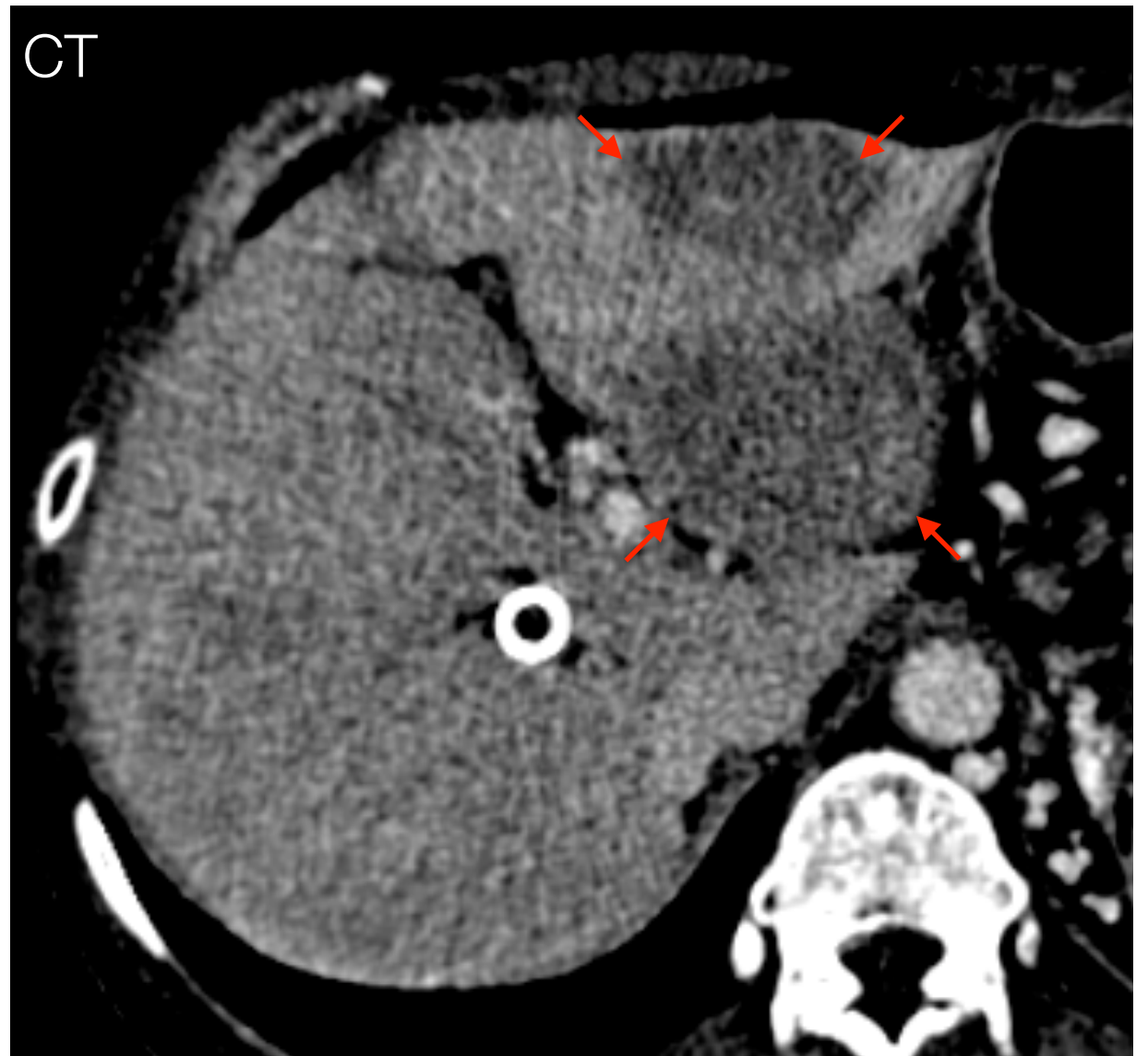


- \*Other molecular therapies: sunitinib, linifanib, brivanib, tivantinib, erlotinib, everolimus
- Weak recommendation: more evidence needed

# Traitement du CHC : évidence

# Suivi post-traitement

- ▶ CT à 24 h pour thermo-ablation (complications)
- ▶ CT / MRI à 1 mois puis tous les 3 mois la 1ère année et tous les 6 mois la 2ème année.
- ▶ IRM > CT







MERCI !