Carcinome hépatocellulaire = vers une nouvelle approche

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Alger 27-29 Mars 2015.

Carcinome hépatocellulaire

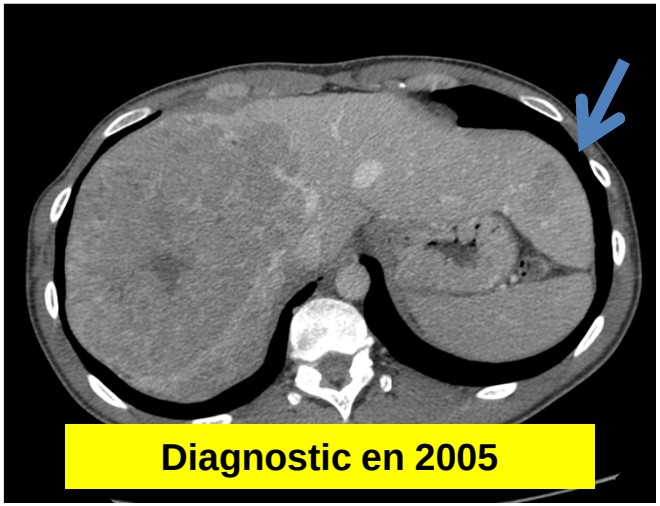
- **Moyens thérapeutiques efficaces**
  - Résection
  - Transplantation
  - Ablation (radiofréquence ou microondes)
  - Chimio-embolisation et radio-embolisation
  - Anti-angiogéniques

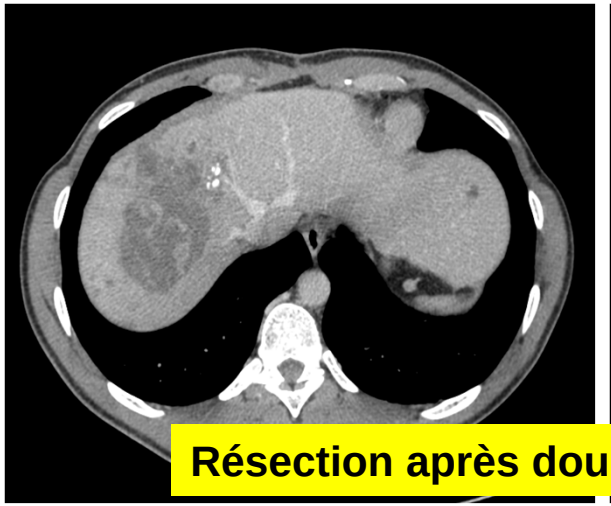
Histoire naturelle

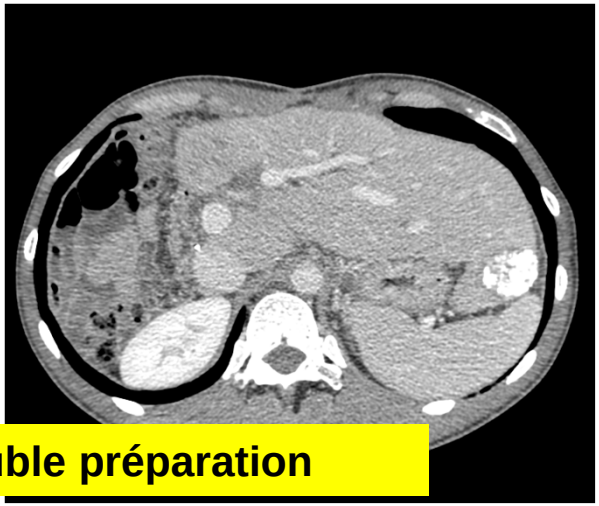
- Comme pour tout cancer (Signature génétique!)
- Chez certains malades, pas de précipitation pour opérer ou transplanter (la chirurgie est morbide!)
- Se donner du recul avec un traitement moins agressif (traitement néo-adjuvant)

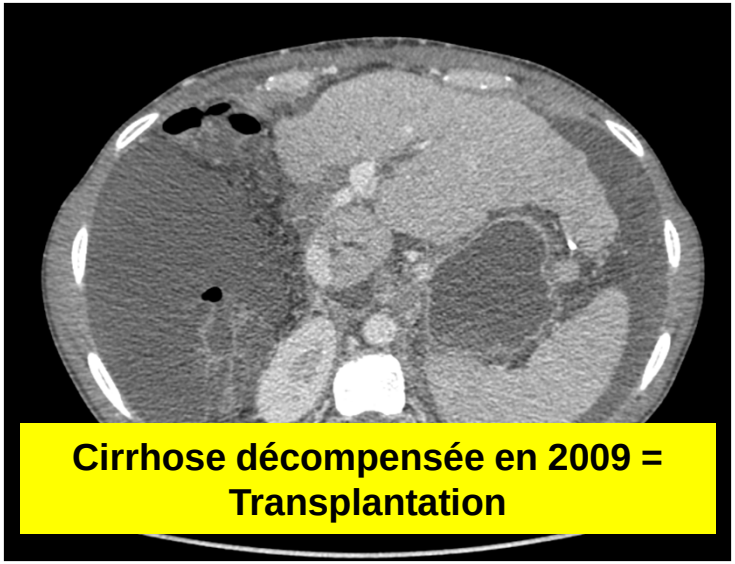
– Sélection des malades

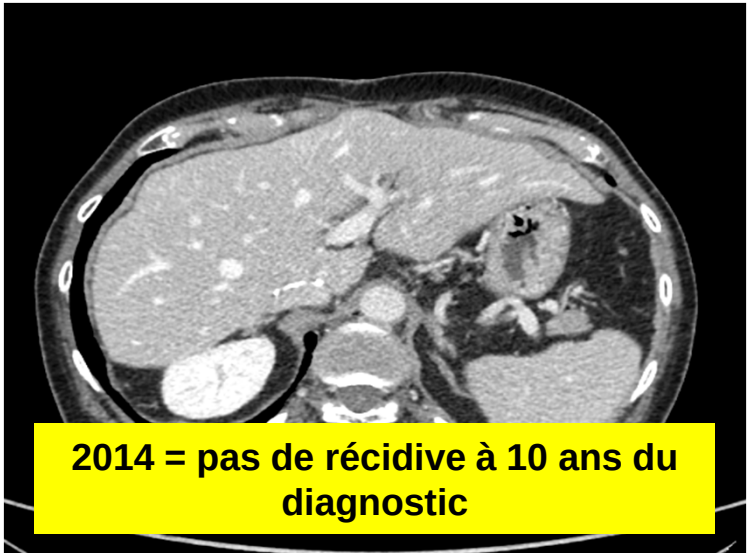
Homme, jeune, CHC, cirrhose B avec une excellente histoire naturelle



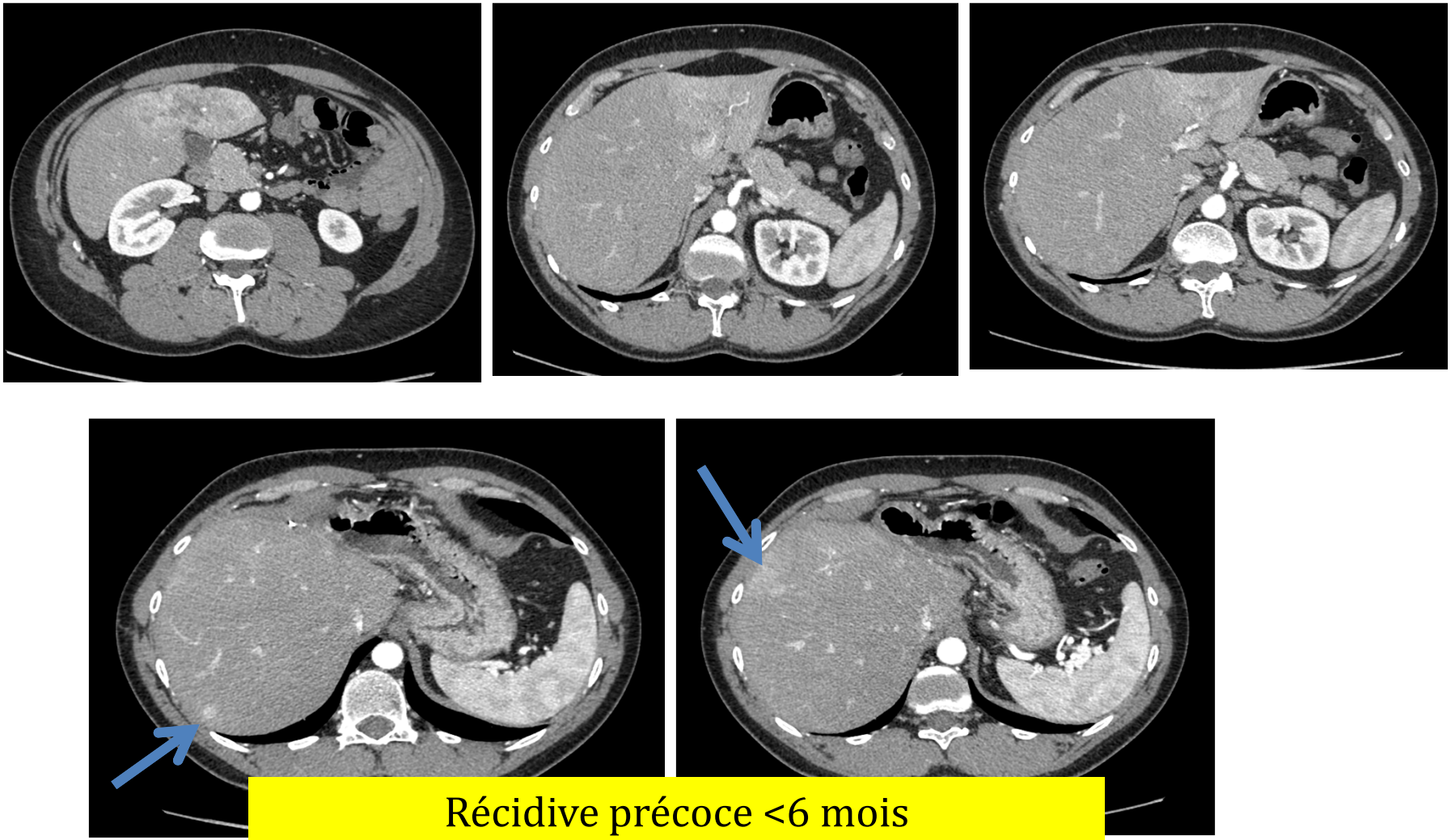








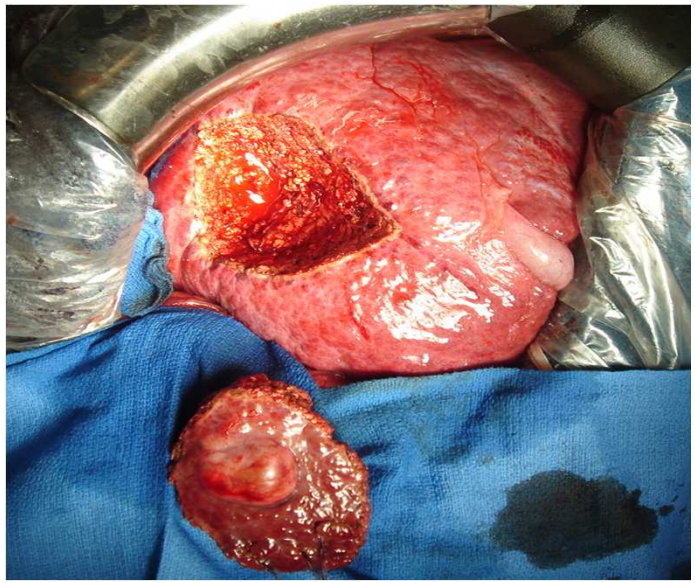
Homme, jeune, CHC opéré rapidement



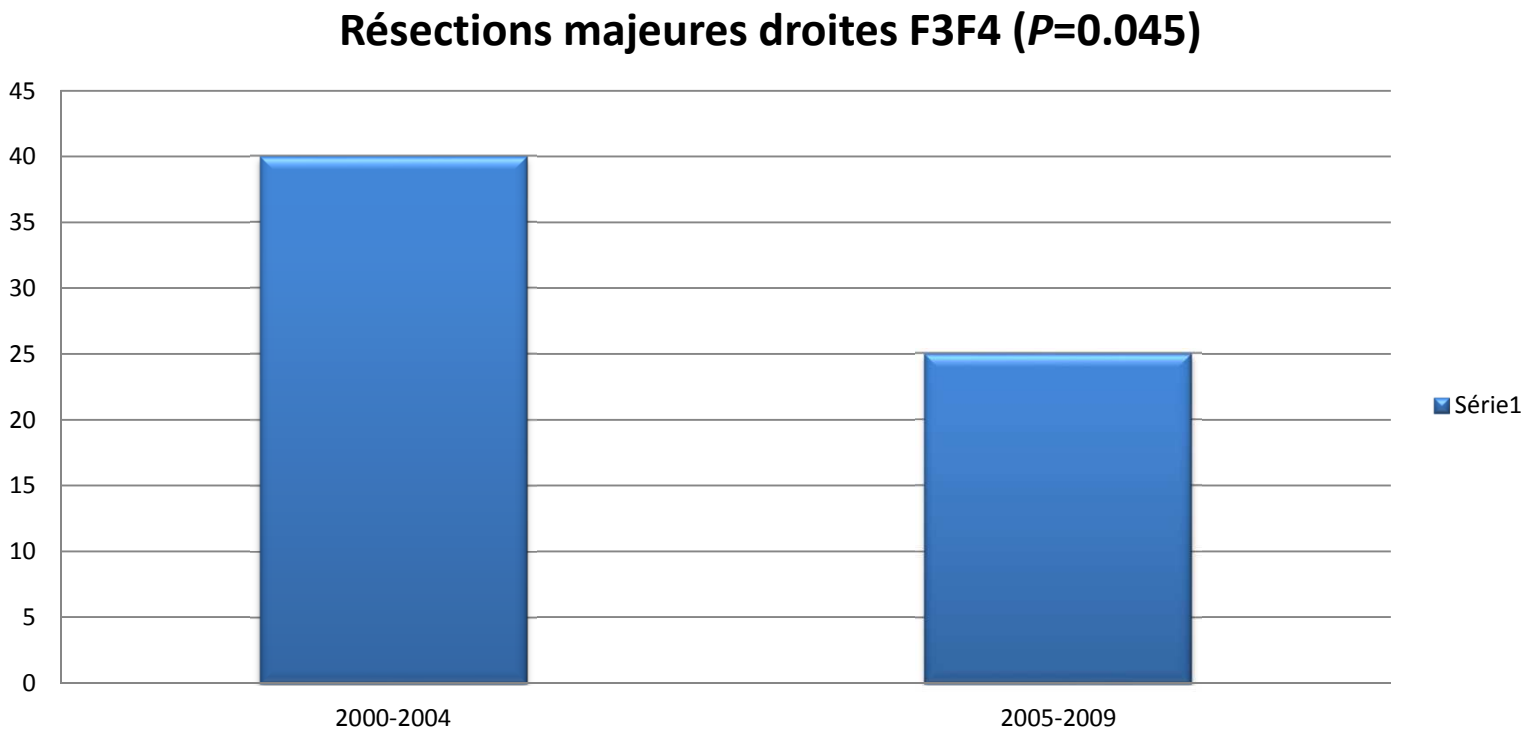
Récidive précoce <6 mois

Chirurgie à faible morbidité et mortalité

- **Sélection +++**
- **Evitez les résections majeures (Si besoin associant un autre traitement , exemple, ablation ou chimio-embolisation)**
- **Double préparation par chimio-embolisation et embolisation portale**
- **Laparoscopie**



Dans notre expérience



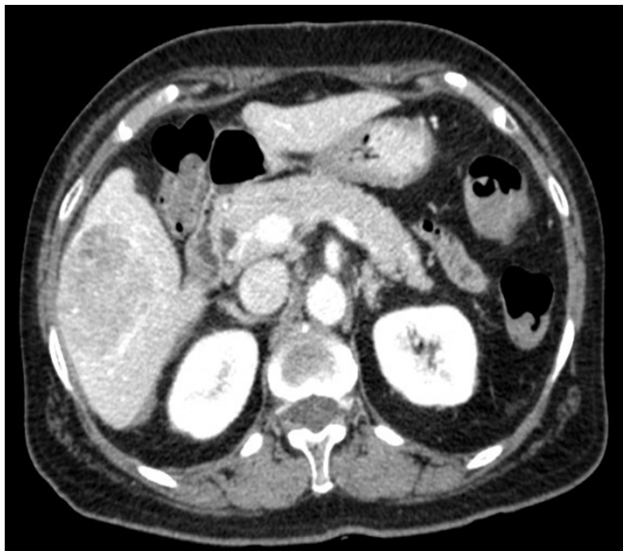
CHC = Schéma thérapeutique « en gros »

CHC <3 cm

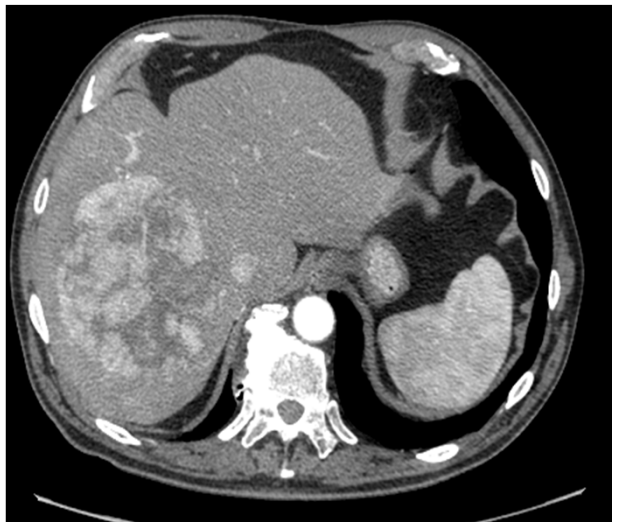
Ablation ++++

Résection si périphérique

Pas d'hépatectomie majeure

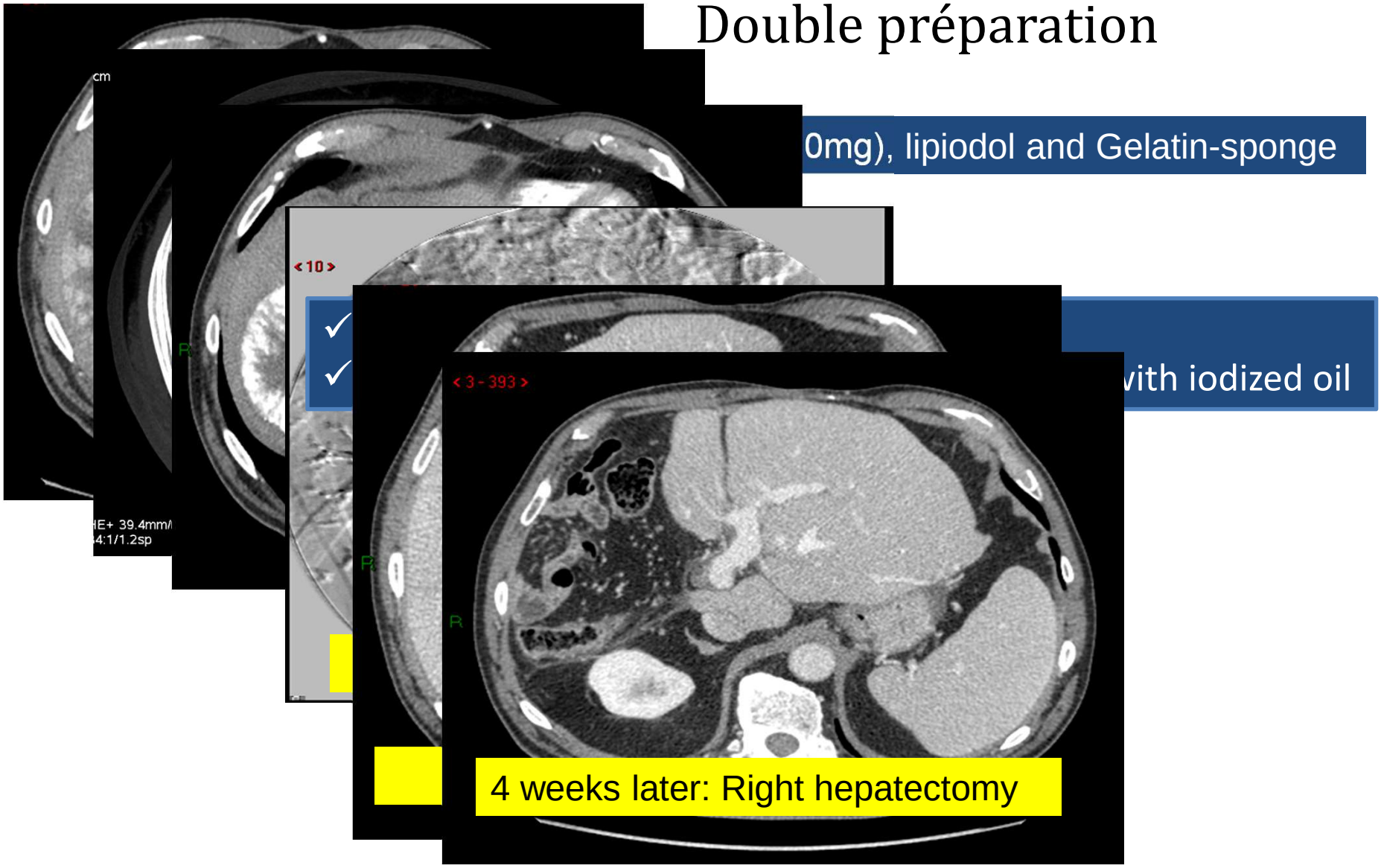


CHC de 5 cm périphérique
Résection +++
Faible risque post opératoire
Laparoscopie ou laparotomie
Sans ou traitement néo-adjuvant



Volumineux CHC ou nécessité d'une résection majeure
Résection risquée
Foie adjacent pathologique
Double préparation ++++

Double préparation



Double préparation (CE et EP)

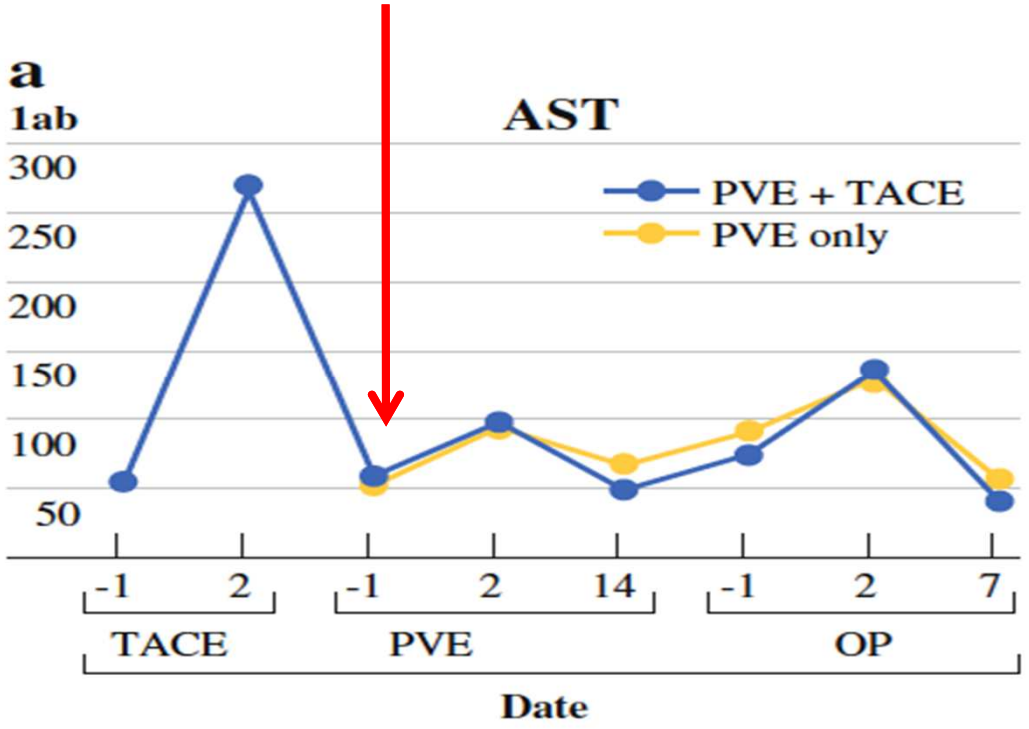
3 Questions

- Tolérance
- Efficacité sur l'hypertrophie
- Effet sur la survie à long terme

Double préparation
Tolérance: excellente clinique et biologique

	N	Period	Delay between TACE and PVE	ASAT/ALAT Peak (UI/L)	Bilirubin (mg/L)	Severe complications	Resection rate
Aoki T et al, Arch Surg 2004	17	1994-2002	9 (4-48)	600/400	<1	0	100%
Ogata S et al, BJS 2006	18	1998-2004	21(21-42)	300/200	1-1.5	0	100% ?
Yoo H ET al, Ann Surg Oncol 2011	71	1997-2008	36 (7-84)	300/250	1-1.5	1 (1.5%) liver failure	96% (PVE=91%)
Peng PD et al, HPB 2012	29	2000-2011	60 (28-102)	-		1 (3.4%)	93%
Notre expérience	47	2000-2009	23 (14-56)	285/220		2 (4%)	96%

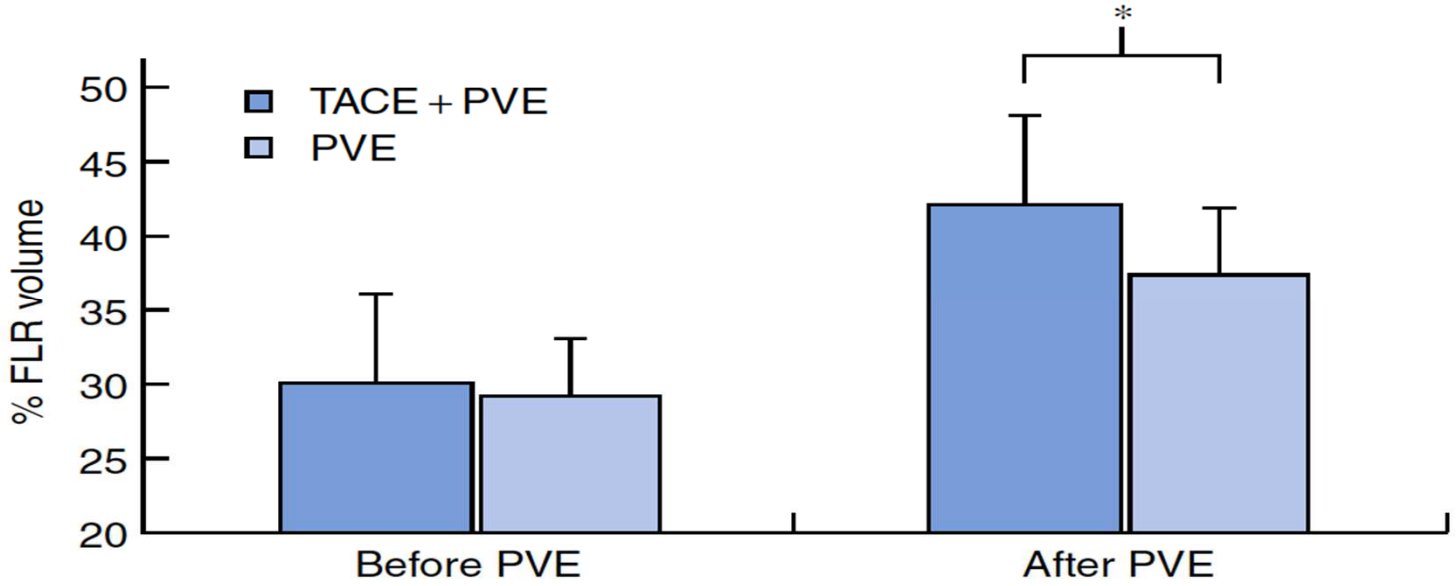
CE et EP
Normalisation du bilan hépatique avant l'EP!



yoo H et al, Ann Surg Oncol 2011

L'hypertrophie du foie restant est meilleure avec la double préparation

	CE + EP	EP	P
Yoo H, 2011	7.3 ±3.6%	5.8 ±4.5	0.035
Ogata S, 2006	12±5%	8±4	0.022
Peng PD, 2012	7.4%	7.9%	0.20
Notre expérience	11.6%	8.5%	0.04



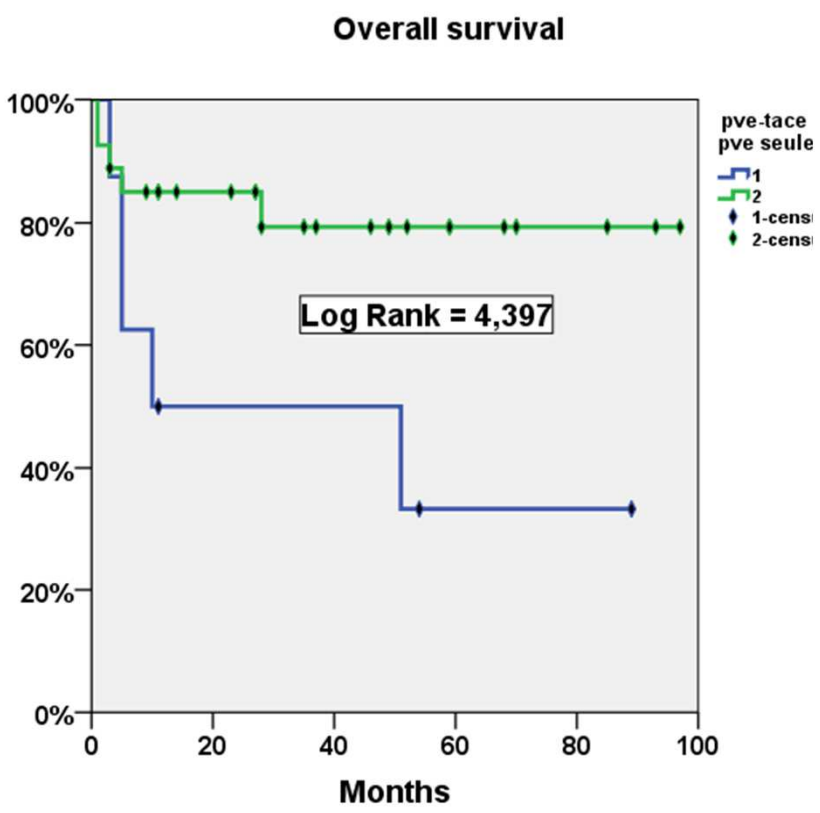
Complications post opératoire

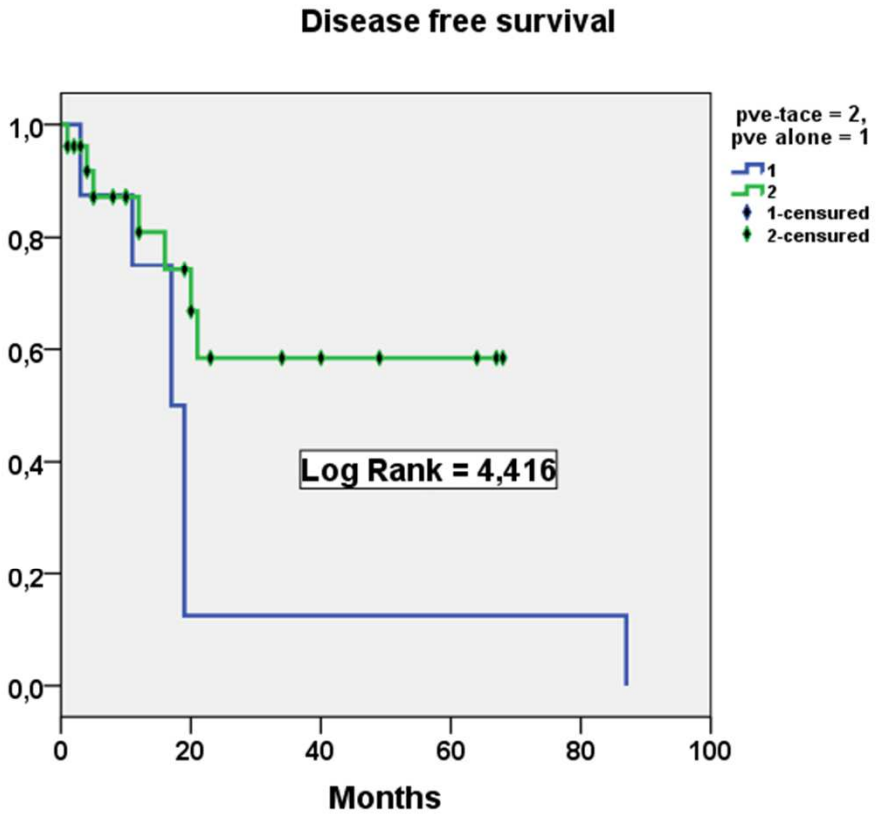
Varaibles	EP (n=22)	CE + EP (n=47)	p
Mortality	22%	11%	0.51
Major morbidity (Clavien >II)	27%	42%	0.37
Ascites	55%	27%	0.09
Liver failure	1 (4.5%)	4 (8.5%)	0.32
biliary fistula	0%	3%	0.55
Reintervention	9%	15%	0.61
collection	0%	6%	0.40
Pulmonary complications	31%	27%	0.21
Hospital stay (days)	21 (4-66)	16 (7-58)	0.44

Double préparation: nécrose tumorale ++++++

Variables	CE + EP n=47	EP n=22	P
Mean Size (cm)	7.6 (4-15)	8.5 (3-13)	0.15
Tumour >5 cm	63%	82%	0.23
Mean number	1.8 (1-5)	1.2 (1-3)	0.20
Satellite nodules	43%	55%	0.53
Vascular invasion	50%	82%	0.065

	CE + EP n=47	EP n=22	P
Mean necrosis rate	**59%**	**30%**	**0.029**
Complete necrosis (100%)	**9 (19%)**	**0%**	
Necrosis (70-99%)	13 (28%)	0%	
Necrosis (50-69%)	21(45%)	4 (18%)	
Necrosis <50%	4 (8%)	18 (82%)	





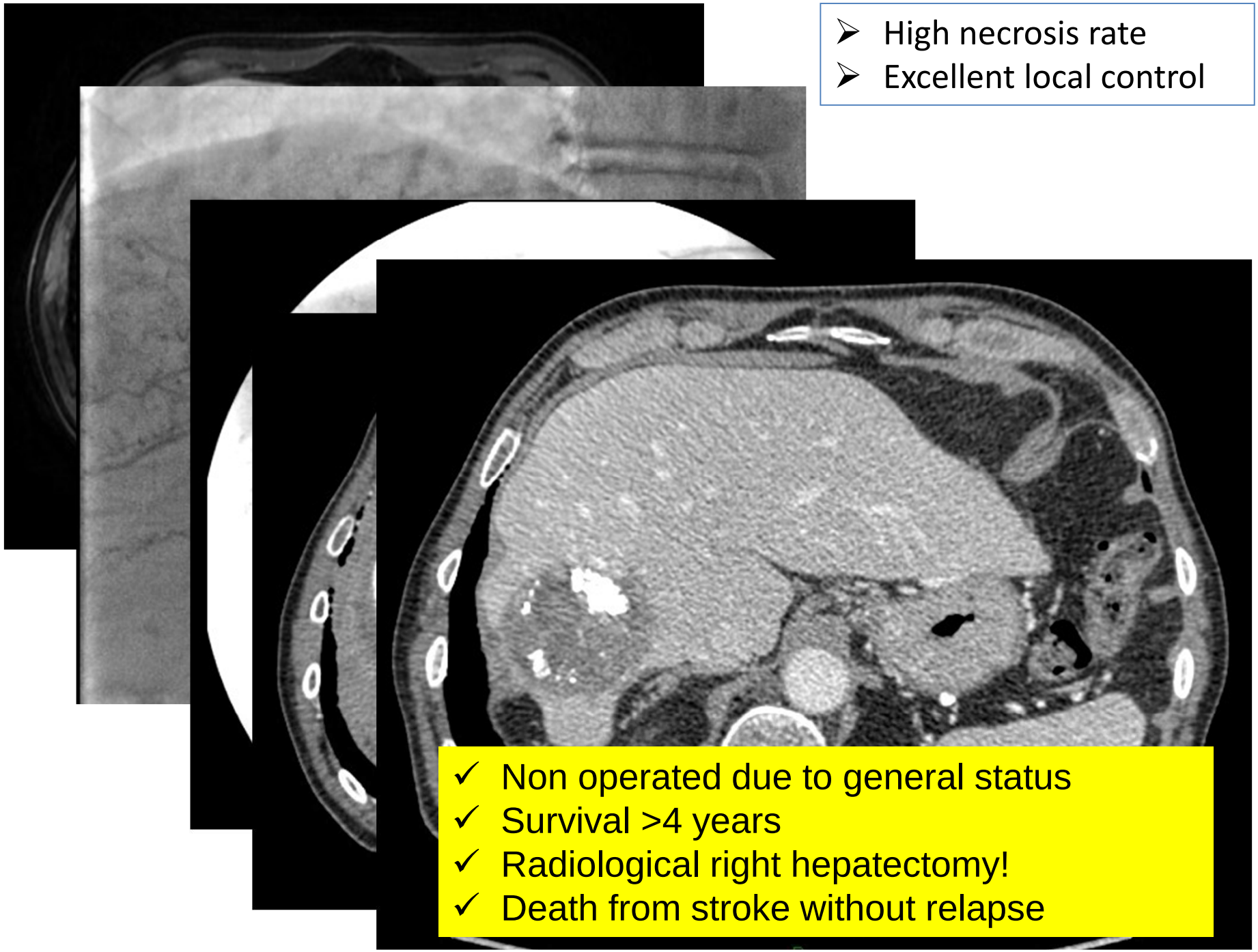
	Overall survival (mean)	Disease free survival (mean)	P
PVE	28 (3-89)	19 (1-87)	<0.05
TACE+PVE	37 (1-93)	24 (1-68)	<0.05

Survie globale
Facteurs pronostiques

Variables	Univariate		multivariate	
	logrank	p	logrank	p
Sex	0.22	0.63	-	-
Age>65	1.45	0.22	-	-
AFP >200	13.20	0.004	14.20	**0.002**
Taille >5 cm	14.53	0.003	12.86	**0.04**
Necrosis >50%	14.21	0.003	-	-
satelittes nodules	4.51	0.028	-	-
Vasular invasion	4.98	0.017	-	-

Survie sans récidive
Facteurs de risque

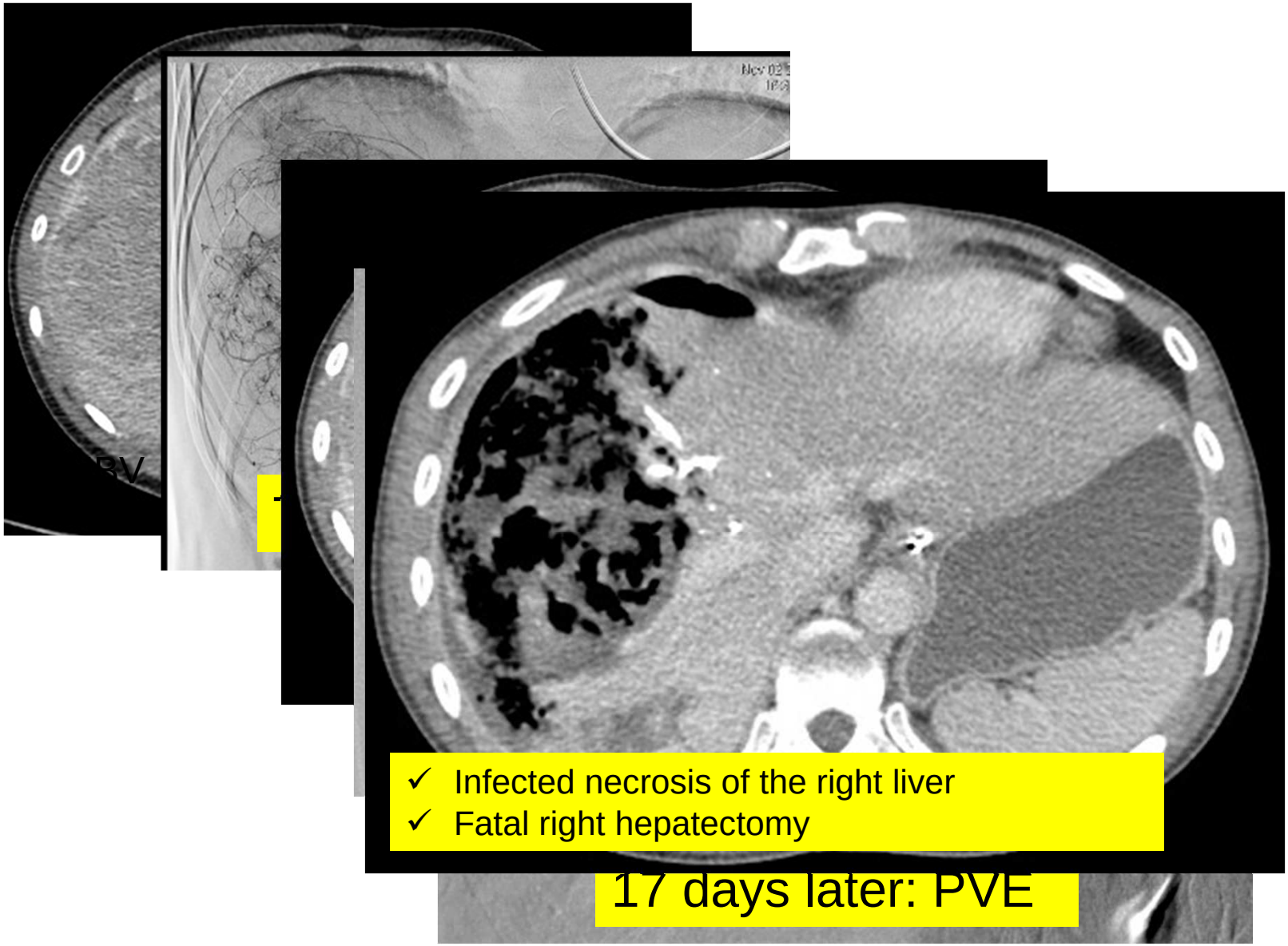
Variables	Univariate		multivariate	
	logrank	p	logrank	p
Sex	0.50	0.82	-	-
Age>65	2.32	0.15	-	-
AFP >200	13.23	0.038	-	-
Taille >5 cm	15.78	0.028	14.75	**0.017**
Necrosis >50%	16.32	0.007	17.68	**0.002**
satelittes nodules	6.01	0.001	7.44	**0.001**
Vasular invasion	2.28	0.06	-	-



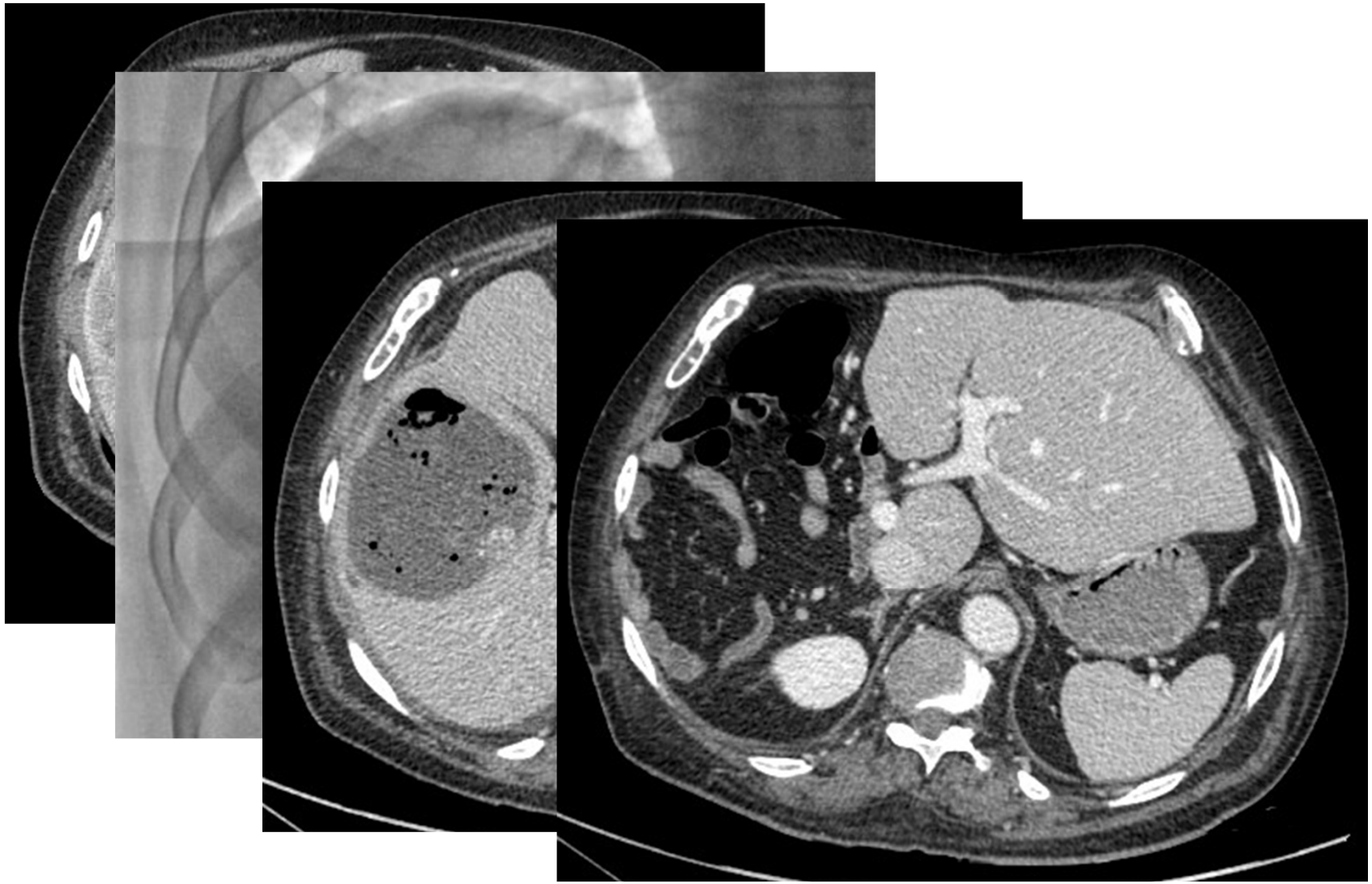
- High necrosis rate
- Excellent local control

- ✓ Non operated due to general status
- ✓ Survival >4 years
- ✓ Radiological right hepatectomy!
- ✓ Death from stroke without relapse

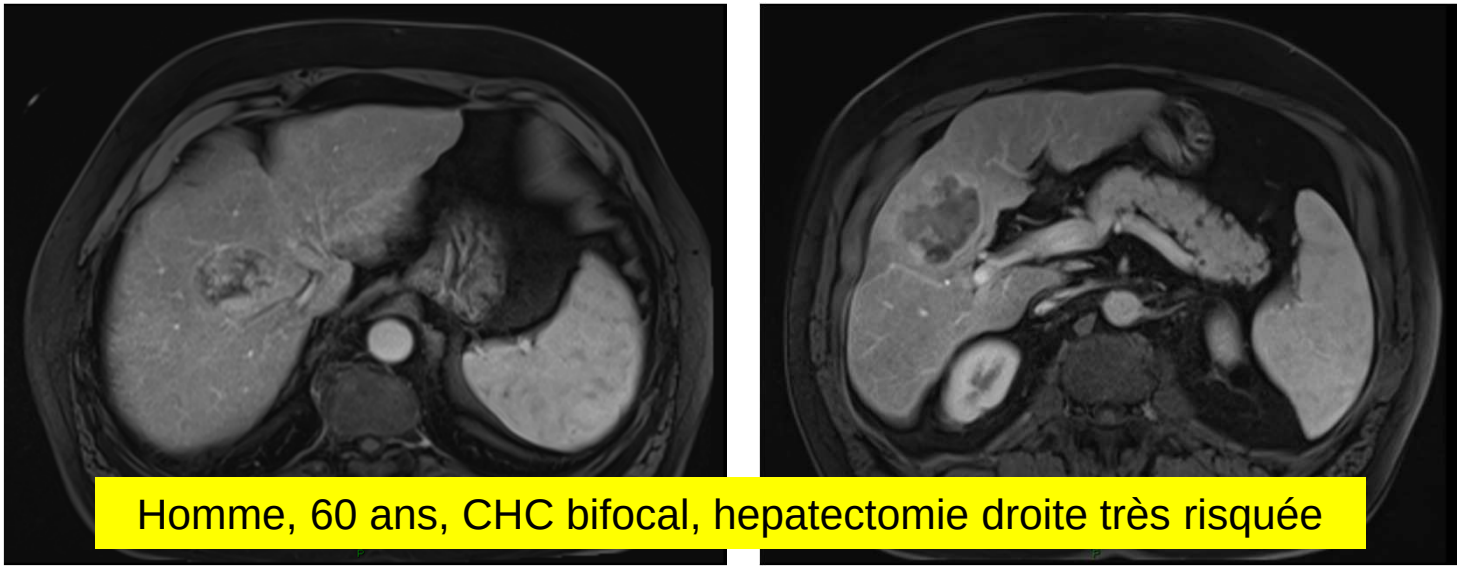
Double préparation: Complications graves (<5%)



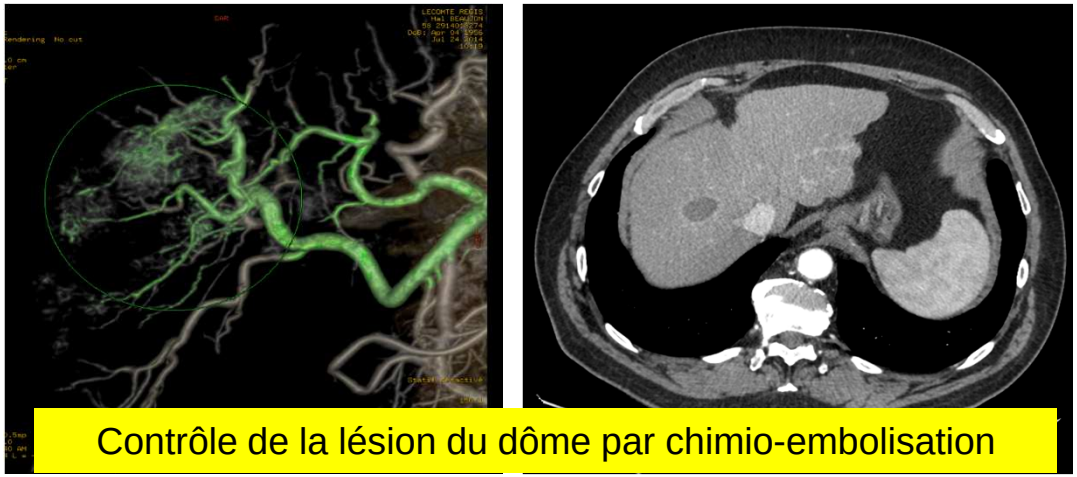
HCC/NASH: Necrosis post TACE
Complicated Right hepatectomy



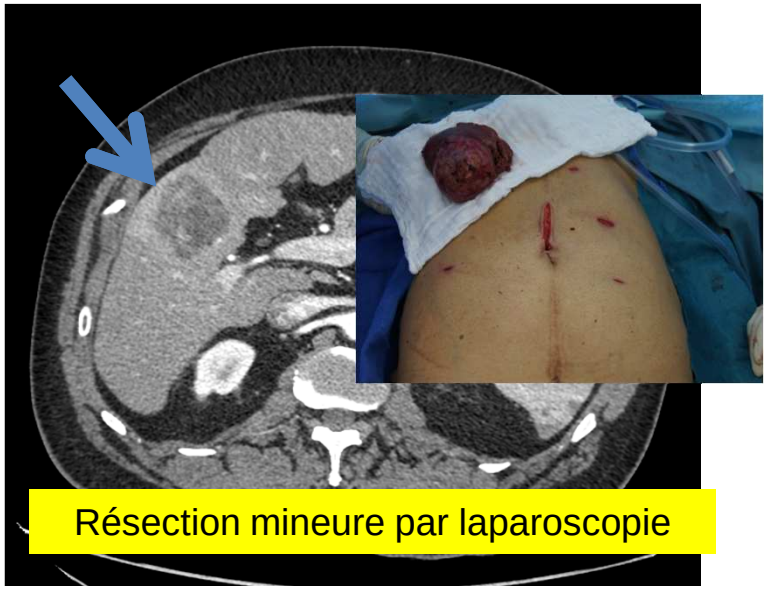
Association des moyens thérapeutiques



Homme, 60 ans, CHC bifocal, hepatectomie droite très risquée

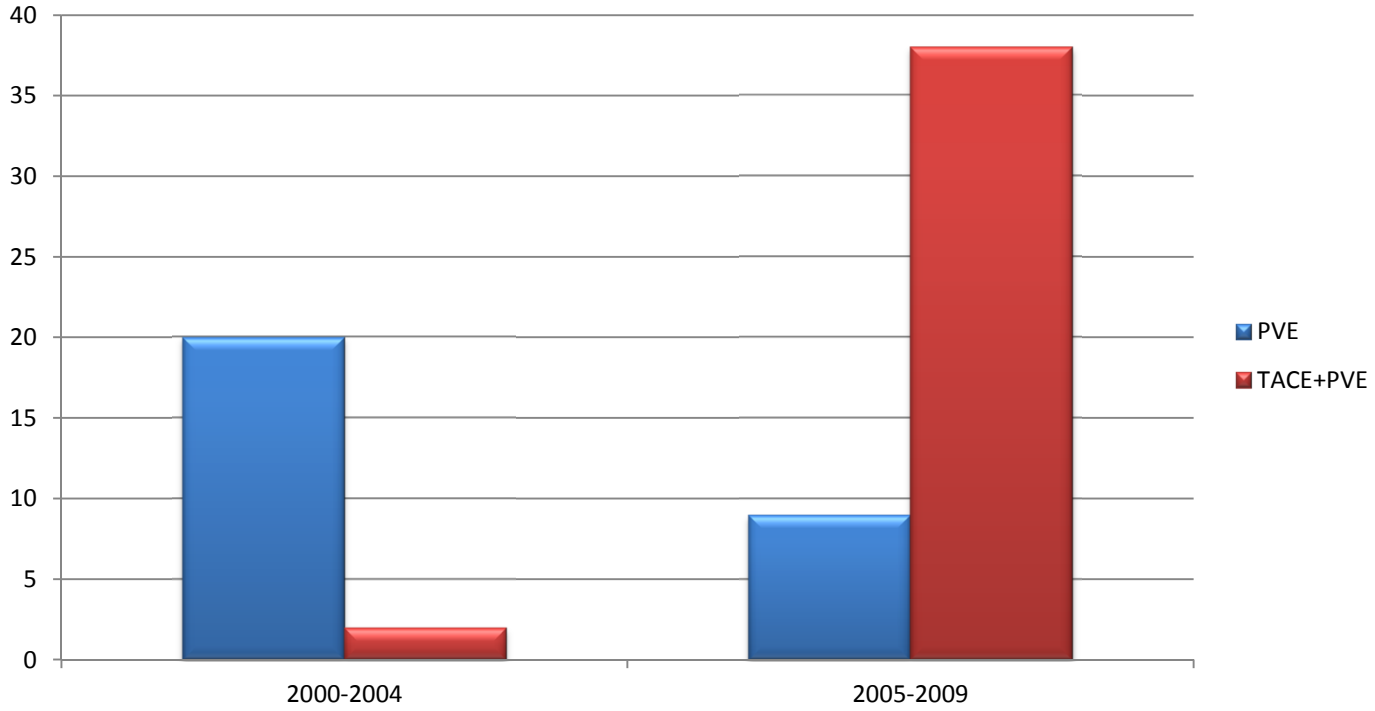


Contrôle de la lésion du dôme par chimio-embolisation



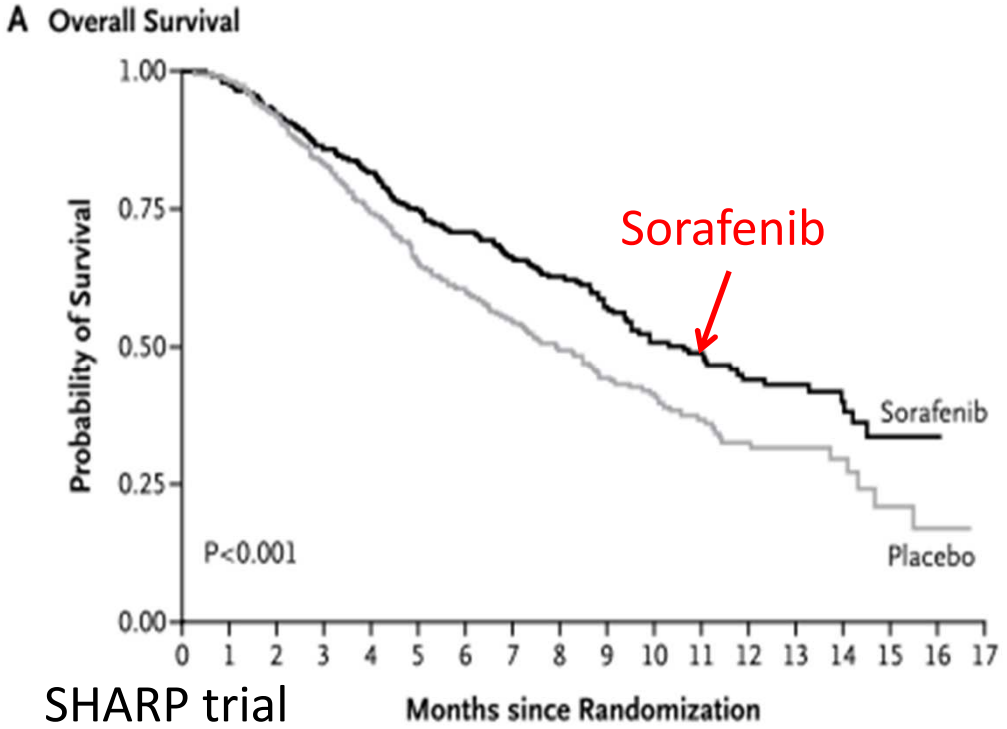
Résection mineure par laparoscopie

Evolution des moyens thérapeutiques



	2000-2004	2005-2009
Safe surgery	++++	++++++
Ablation therapy	++ (No microwaves)	++++++++
Antiangiogenic	No	Yes
Radioembolization	No	Yes

Antiangiogénique (Sorafénib): Peut rendre certains malades résécables



SHARP trial

Réponse morphologique partielle:

Llovet, NEJM 2008 (2%)
Cheng, Lancet Oncol 2009 (3.3%)

Chez certains malades = réponse spectaculaire

Barbier L et al, Ann Surg Oncol 2014

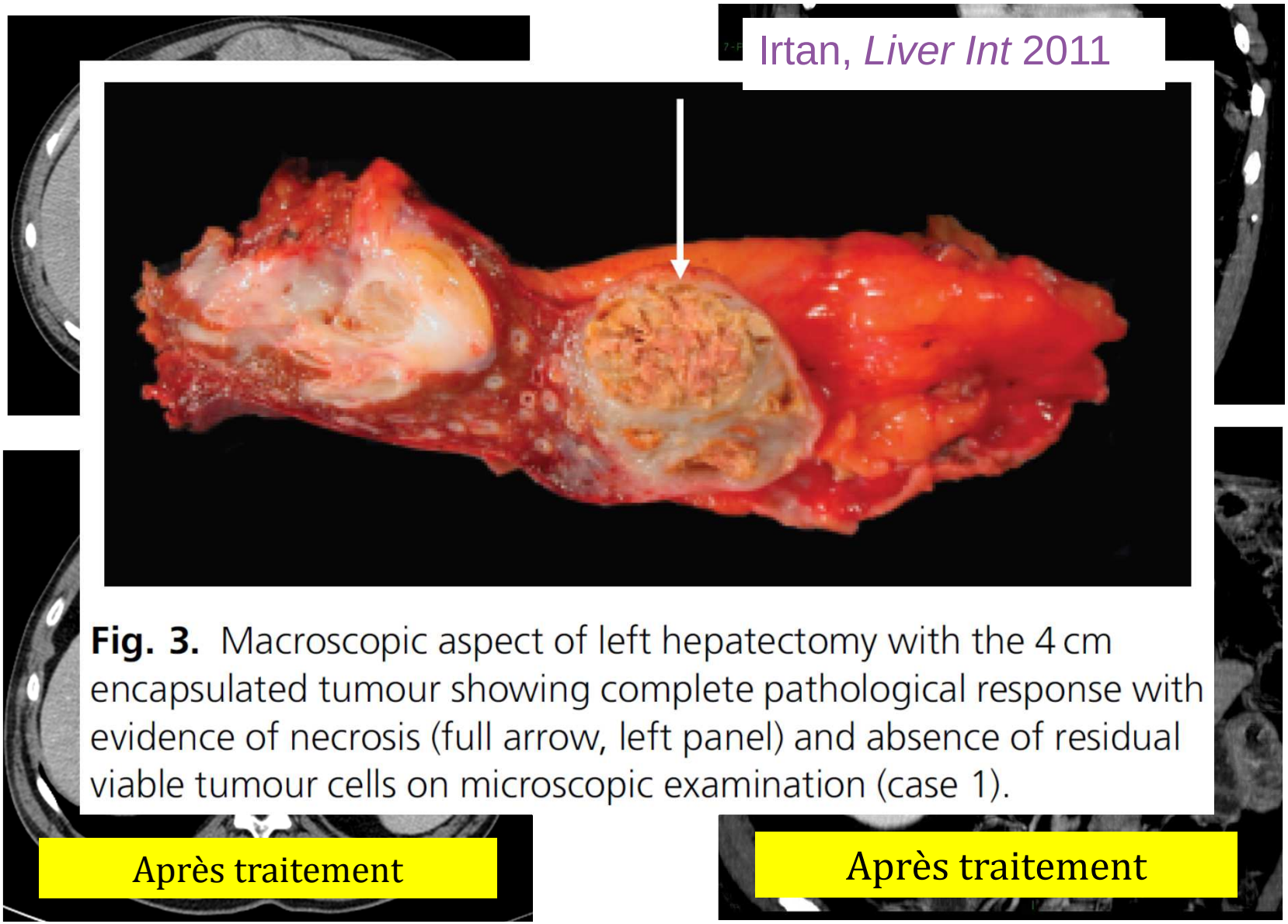


Fig. 3. Macroscopic aspect of left hepatectomy with the 4 cm encapsulated tumour showing complete pathological response with evidence of necrosis (full arrow, left panel) and absence of residual viable tumour cells on microscopic examination (case 1).

Dans l'avenir !
Radio-embolisation = double préparation

Radiation Lobectomy: Preliminary Findings of Hepatic Volumetric Response to Lobar Yttrium-90 Radioembolization.

- Hypertrophie controlatérale extensive
- Réponse tumorale
- Survie prolongée

Ron C. Gaba et al, Ann Surg Oncol 2009.

Amélioration du pronostic à long terme
Prévention de la récidive

- Traitement de la maladie sous jacente
  - Hépatites virales
  - Syndrome métabolique
  - Autres
- Transplantation de principe ou en cas de récidive

Posthepatectomy HBV Reactivation in Hepatitis B–Related Hepatocellular Carcinoma Influences Postoperative Survival in Patients With Preoperative Low HBV-DNA Levels

Gang Huang, MD, Eric C. H. Lai, MBChB, MRCSEd, FRACS,*† Wan Yee Lau, MD, FRCS, FACS, FRACS(Hon),*† Wei-ping Zhou, MD, PhD,* Feng Shen, MD,* Ze-ya Pan, MD,* Si-yuan Fu, MD,* and Meng-chao Wu, MD**

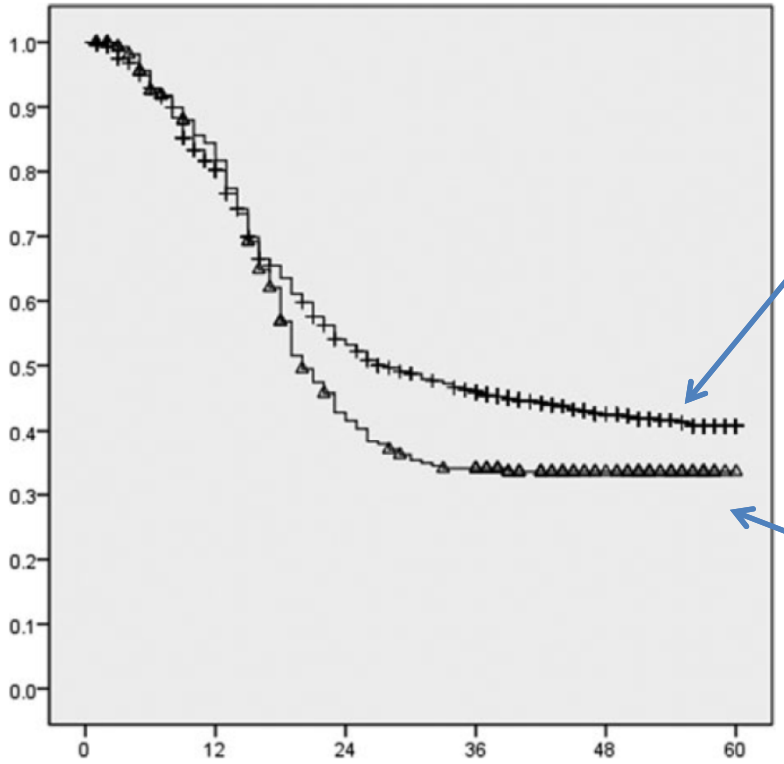


FIGURE 1. Comparison of DFS between patients with HBV reactivation (△; n = 280) and patients without HBV reactivation (+; n = 1329). Log-rank test: $P = 0.009$.

Pas de réactivation virale

P=0,009

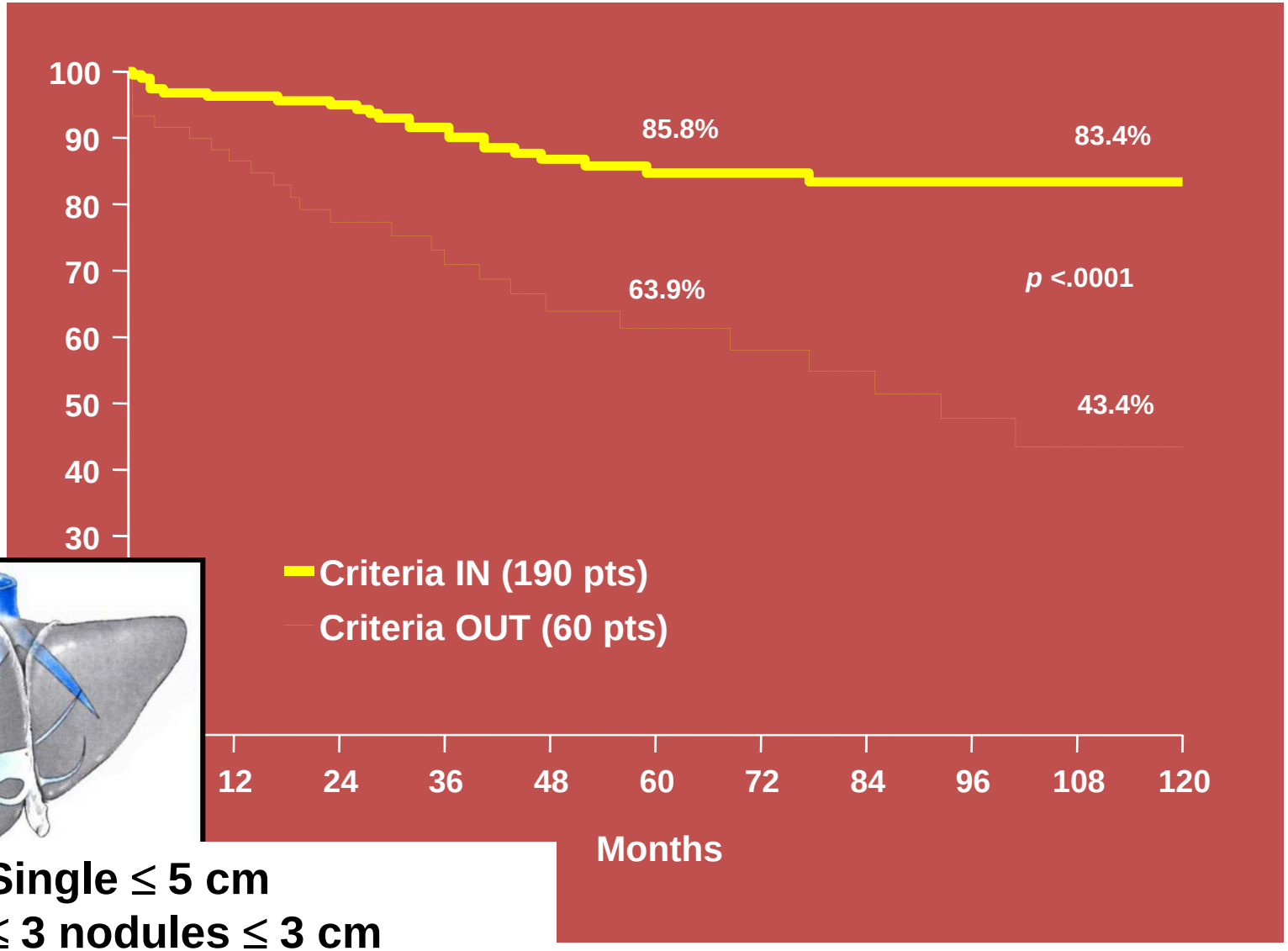
Avec réactivation virale

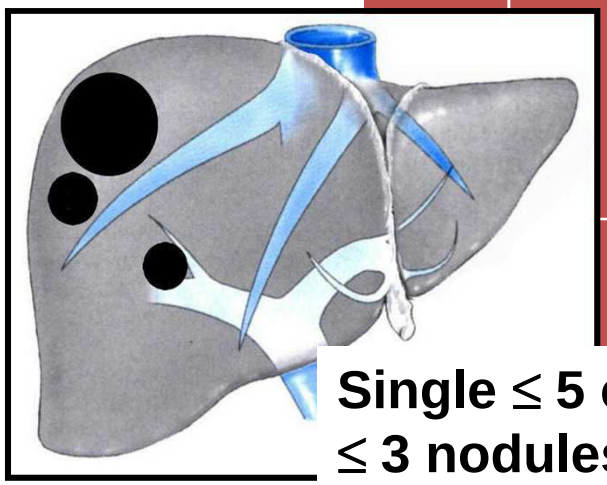
Ann Surg 2013

Transplantation hépatique

- Traite le cancer et la maladie sous jacente
- Meilleure résultats par rapport à la chirurgie chez des malades très bien sélectionnés
- Obstacle majeur
  - Pénurie de greffons hépatiques

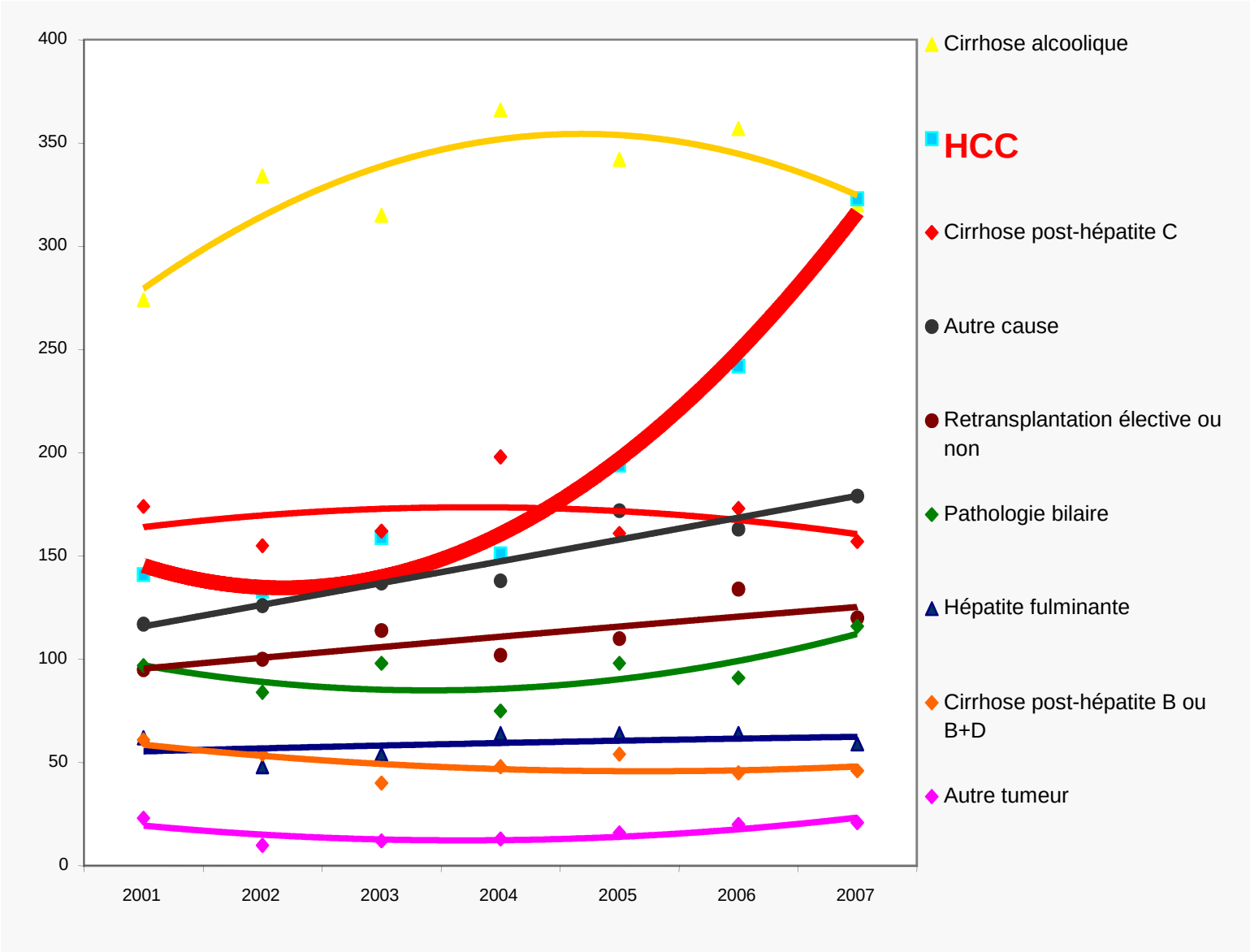
Mazzaferro experience 2006 : LT for HCC



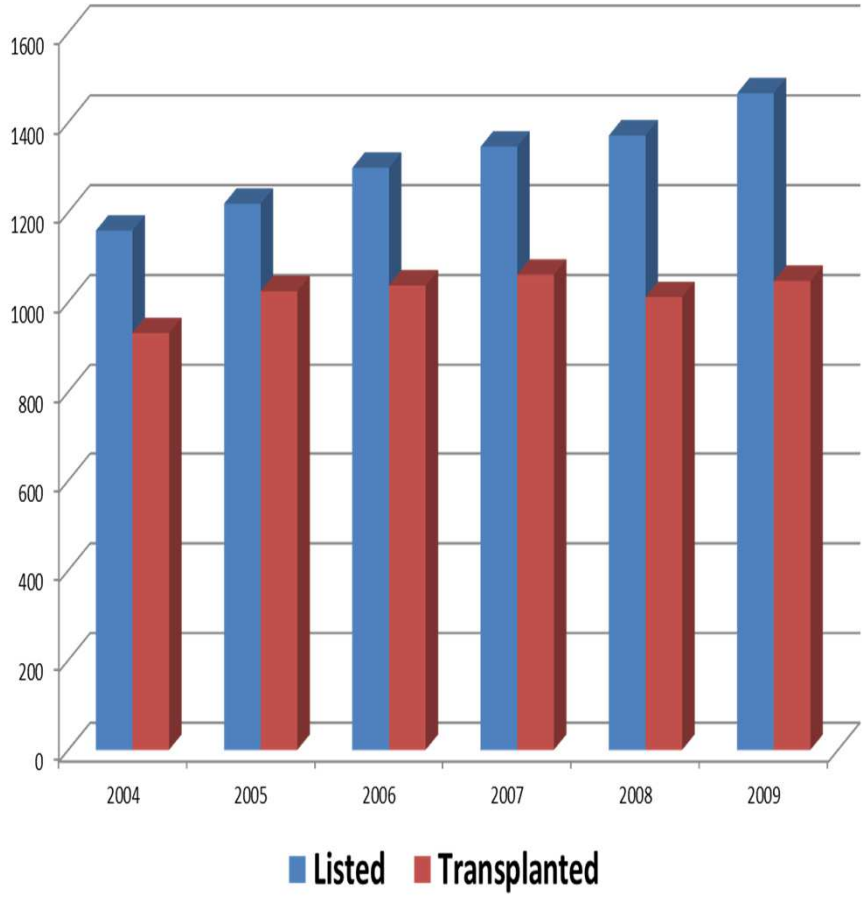


Single ≤ 5 cm
≤ 3 nodules ≤ 3 cm
No vascular Invasion

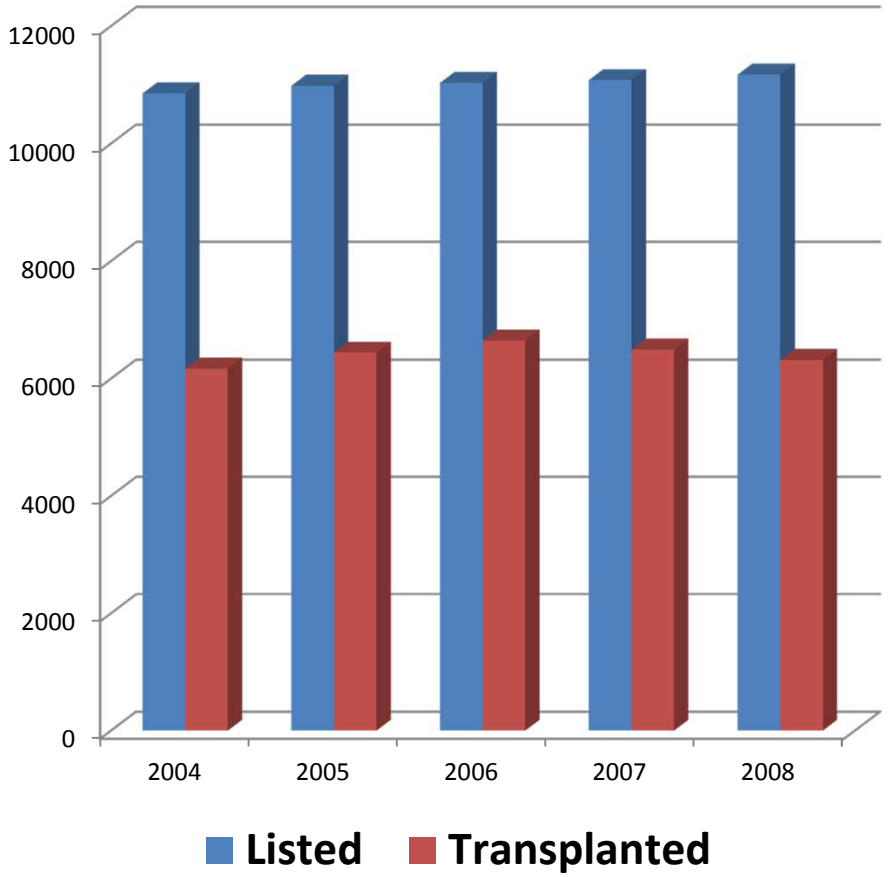
Patients Listed for LT: 2001 - 2007



Organ shortage

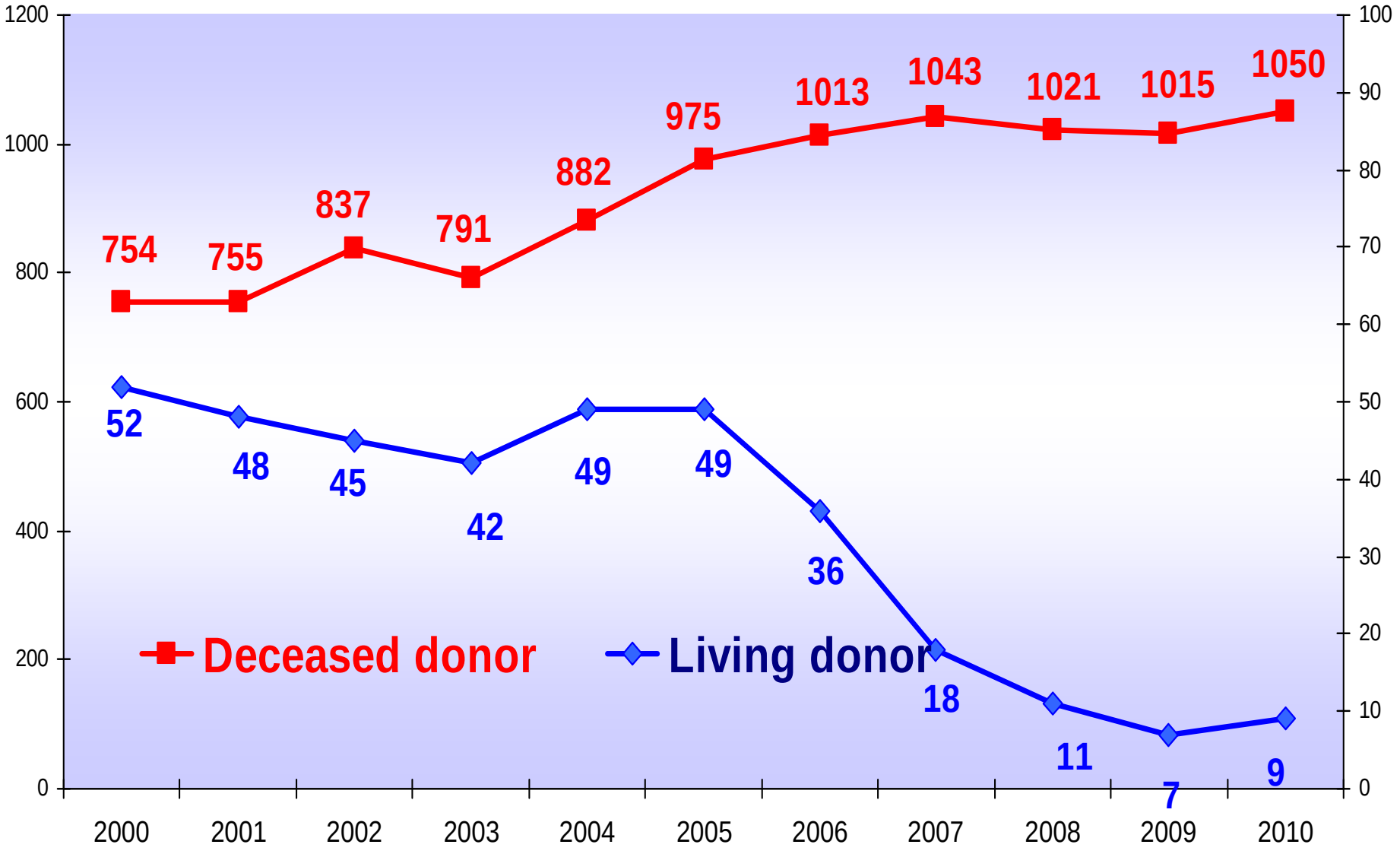


Data Agence de la Biomédecine



Data UNOS

Adult-to-adult LDLT in France

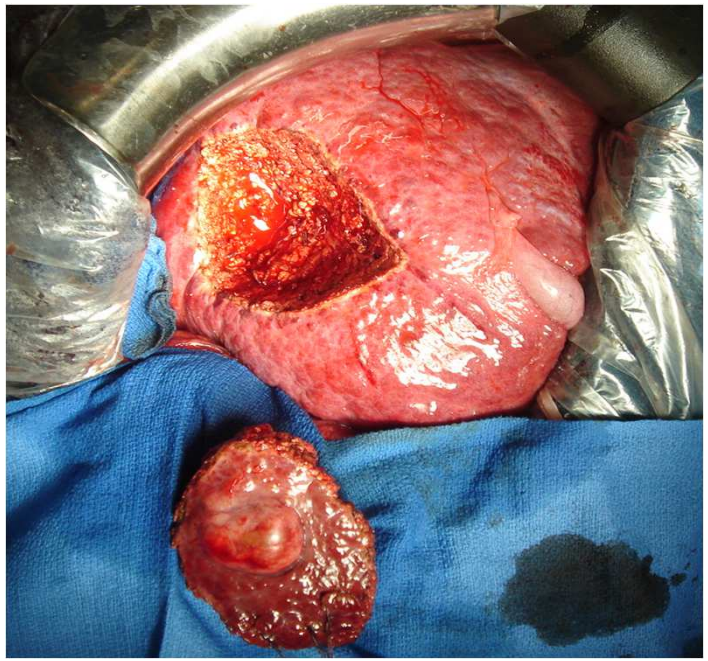


Résection avant la transplantation
Avantages

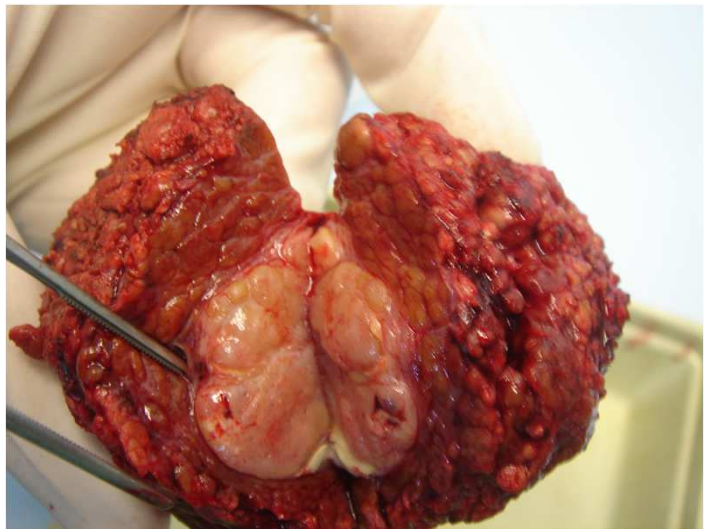
1)Traitement curatif immédiat à faible risque

Survie à 5 ans =75%

Excellente qualité de vie (pas de traitement immunosuppresseur)



2)Sélection sur la pièce et l'histoire naturelle (+++)

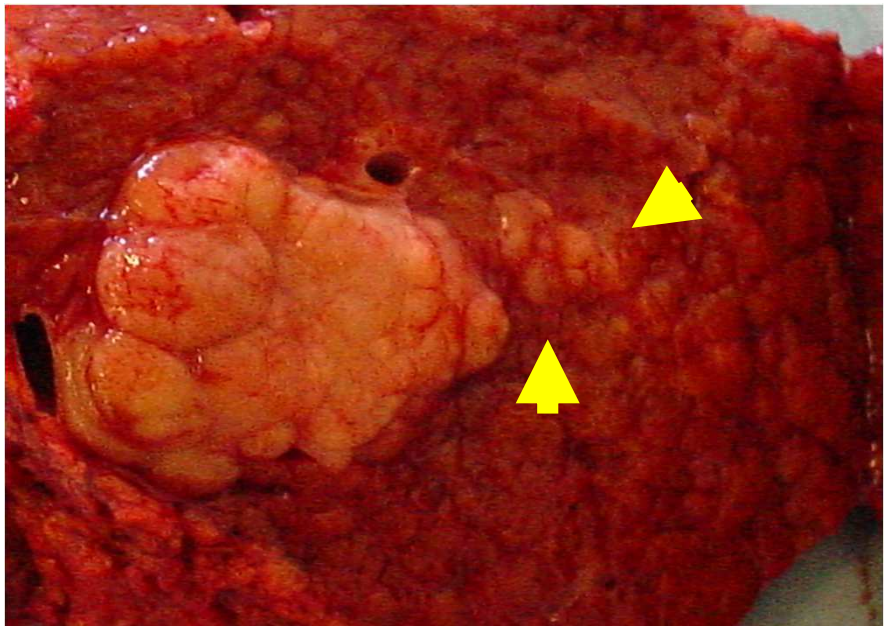


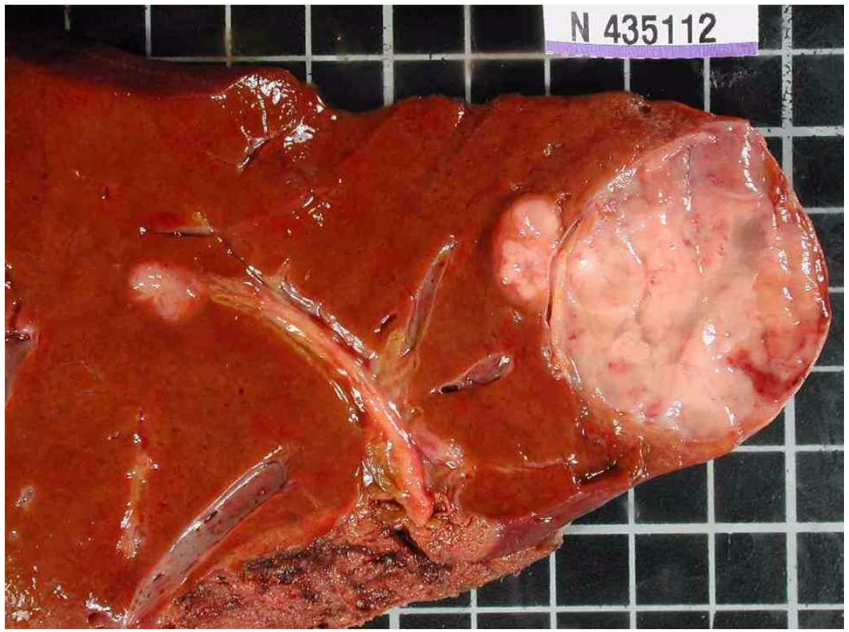
3)Préservez des greffons hépatiques pour autres pathologies(?)

Résection avant transplantation

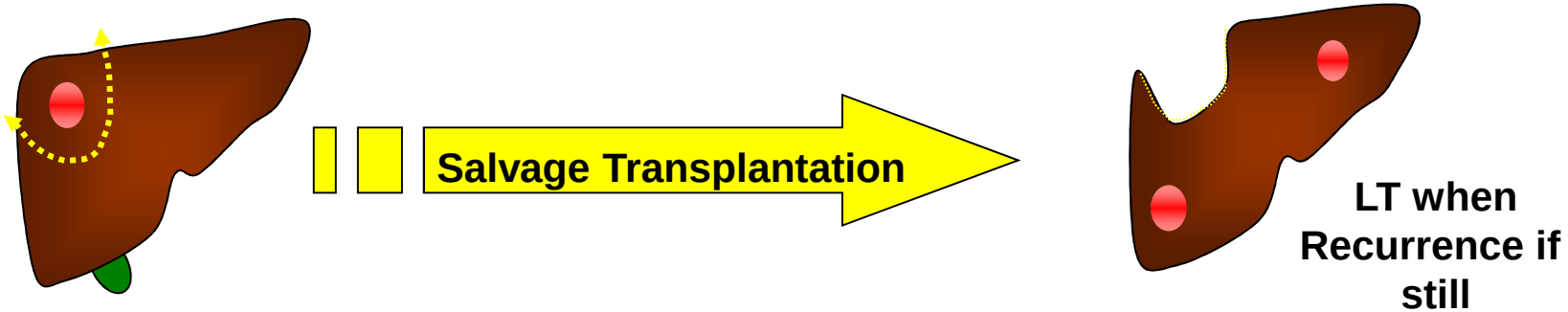
Avantages: données histologiques nécessaires pour la sélection

Differentiation, vascular invasion, satellite nodules

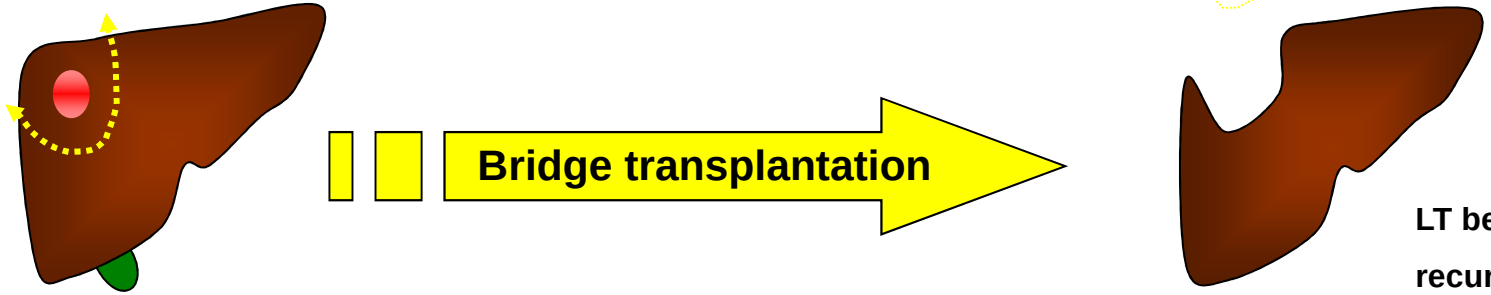




Résection avant la transplantation
2 modalités

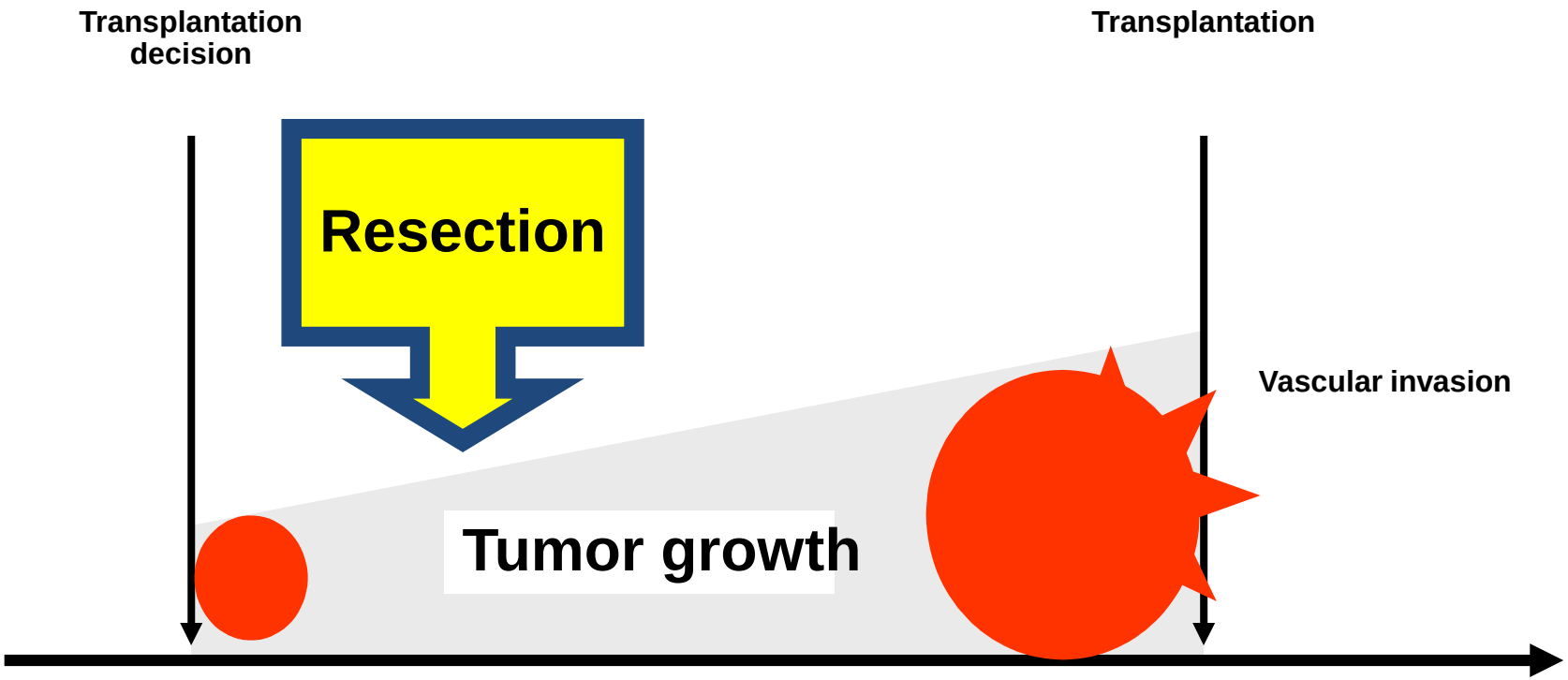


LT when Recurrence if still Within LT Criteria ?



LT before recurrence

Resection as a Bridge Treatment of HCC before LT



- Considered as other treatments (Radiofrequency & TACE)
- Good liver function & peripheral single tumor
- Patient remains on the waiting list !

Salvage Transplantation: an attractive concept

Requires:

- Recurrence within Milan criteria
- Compliance of follow-up with careful regular imaging
- Tolerance of LT at the time of recurrence

- Could be a loss of chance for the subgroup initially transplantable

Benefit of initial resection of hepatocellular carcinoma followed by transplantation in case of recurrence: an intention-to-treat analysis.
Fuks D, Dokmak S, Paradis V, Diouf M, Durand F, Belghiti J.

- 1998-2008

- 138 = resected
- 191 = listed for LT

- Among the 138 resected patients
- **51 (37%) = with recurrence were not transplanted**
  - 21 within Milan criteria (advanced age, comorbidities and refusal)
  - 30 Recurrence beyond Milan criteria =
    - Negative predictives factors (microscopic vascular invasion, satellite nodules, size >3 cm, poorly differentitated and liver cirrhosis)

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Conclusions

- Le traitement chirurgical d'un CHC doit prendre compte de l'histoire naturelle de la maladie et les autres modalités de traitement

- Dans cette période de pénurie de greffons hépatiques, salvage transplantation garde une place très importante