

TREATMENT ALGORITHM FOR HEPATOCELLULAR CARCINOMA

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HCC treatment : A permanent challenge !

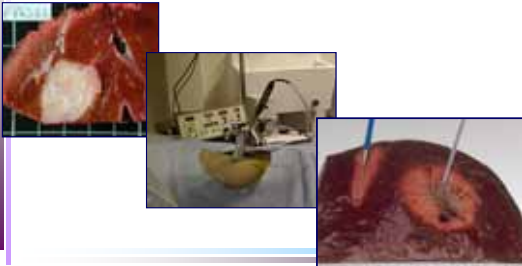
- **A low level of proof** for most of the treatments (very few phase III trials) => a great heterogeneity in classifications, practices and recommendations according to centers & countries +++
- **Two diseases** : HCC & liver disease (90% cirrhosis) which influence independently the prognosis and possibilities of treatment => classifications +++

%	HCC	5-year Survival	Treatment
20-30	In situ	90 %	Curative
	small (<3cm)	50-70 %	Curative

Llovet JM, et al. Lancet 2003 ; 362:1907-17.

Curative treatments

- Resection
- Percutaneous local destruction



Hepatic resection in HCC

- **Best Tt for HCC in non cirrhotic liver**
- **HCC in cirrhotic liver** : => specialized centers
 - mortality : 1 - 5 % (< 10 %)
 - 5-year survival # 50 %
 - 5-year recurrences : 70 - 100 %
 - indications : « small » HCC ; Child-Pugh A (« hyper A »)
- **Best candidate: one single nodule**
 - normal bilirubinemia ; + / - ALAT < 2N, ICG: nl
 - Absence of PHT (sub-hepatic KT ?)
 - 5-year survival : 74 %

Llovet JM et al. Hepatology 1999;30:1434-40.

The best curative treatment :Liver Transplantation (OLT) for small HCC

- **Using the Milan Criteria**

at 4 years :

- Overall Survival : **75 %**
- Recurrence free Survival : **83 %**

• **N = 48**

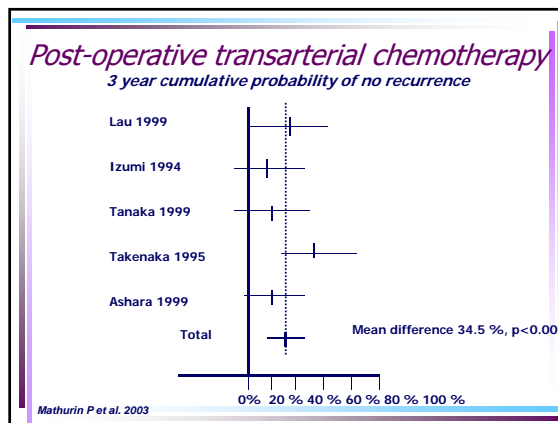
	True small HCC		False small HCC
N	35		13
OS	85 %	0.01	50 %
DFS	92 %	0.002	59 %

Mazzafero N Engl J Med 1996

Adjuvant chemotherapy after resection

Author	T+T-(n)	T+	T-
Izumi 1994	23/27	postop TACE (adm-mtc)	Ø
Li 1995	47/47	postop TACE (dxr-mtc)	Ø
Ueno 1989	10/11	postop TAC (cddp-mtc)	Ø
Kohno 1996	48/40	postop TAC (5fu) + 5FU po	5FU po
Lau 1999	21/22	postop TAC (1131)	Ø
Yamasaki 1996	50/47	preop TACE (adm)	Ø
Wu 1995	24/28	preop TACE (dxr)	Ø
Lygidakis 1996	49/42	pre+postop TACE (chimio-il2-ifng)	Ø
Ono 1997	29/27	postop TAC (epi) + 5FU po	Ø
Lai 1998	30/36	postop TACE (adm) + EPR iv	Ø
Osaka 1989	22/15	preop TAC (adm) + 5FU po	preop CIA
Yamamoto 1996	35/32	postop 5FU po	Ø

Mathurin P et al. 2003



%	HCC	5-year Survival	Treatment
20-30	In situ small (<3cm)	90 % 50-70 %	Curative Curative
10	limited, non complicated	30 %	TACE

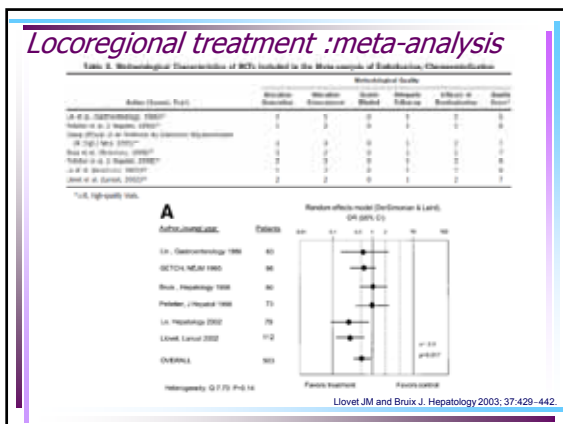
Llovet JM. et al. Lancet 2003 ; 362:1907-17.

Locoregional treatment of hepatocellular carcinoma

- Locally advanced disease with good hepatic function
- Two positive recent randomized studies

Ref	n pts	Virus LD	Okuda stage 1	OS 2-year
Lai 2002	79	80%	47%	31% vs 11% p = 0.005
Llovet 2002	112	90%	63%	63% vs 27% p = 0.009

Lai et al, Hepatology 2002 ; Llovet et al, Lancet 2002



%	HCC	5-year Survival	Treatment
20-30	In situ small (<3cm)	90 % 50-70 %	Curative Curative
10	limited, non complicated	30 %	TACE
40-50	Extended metastatic	< 10 %	Medical Tt

Llovet JM. et al. Lancet 2003 ; 362:1907-17.

Systemic chemotherapy. No clear proof of efficacy. Monotherapy

Table 2 Systemic chemotherapy for hepatocellular carcinoma (single agents)

Study	Agent	No. of patients	Response rate (%)
Johnson et al. [103]	Doxorubicin	44	32
Scarpignin et al. [111]	Doxorubicin	109	0
Melloni et al. [104]	VP-16	24	13
Hochster et al. [36]	Epirubicin	19	17
Lauri et al. [105]	Mitomycin	20	0
Falkson et al. [106]	Cisplatin	33	17
Chao et al. [45]	Fluorouracil	20	0
Pratt et al. [48]	Fluorouracil	11	11
Yang et al. [17]	Gemcitabine	28	18
Fuchs et al. [40]	Gemcitabine	30	0
O'Reilly et al. [49]	Irinotecan	14	7
Helm et al. [107]	Tyrosyl-Dipicolyl-D-glutamate	18	0
Soussi et al. [52]	Paclitaxel	26	6
Lowage et al. [55]	T30067	21	19
Falcon-Lizasoain et al. [107]	Irinotecan	29	7

Systemic chemotherapy. No clear proof of efficacy. Polychemotherapy

Table 3 Systemic chemotherapy for hepatocellular carcinoma (combination regimens)

Study	Regimen	No. of patients	Response rate (%)
Al-Jawad et al. [108]	Doxorubicin, 5-FU, mitomycin C	10	13
Ravy et al. [109]	Doxorubicin, bleomycin	60	16
Patel et al. [37]	5-FU, interferon	28	14
Si et al. [110]	Cisplatin, interferon	30	13.3
Bobbio-Palavicini et al. [111]	Epirubicin, cyclophosphamide	36	39
Leung et al. [50]	PIAF	50	26
Tsai et al. [51]	GEMOX	23	19
Lee et al. [112]	Cisplatin, doxorubicin	37	18.9
Bando et al. [113]	Mitomycin, 5-FU, cisplatin	21	27

Abbreviations: 5-FU, 5-Fluorouracil; GEMOX, gemcitabine and oxaliplatin; PIAF, cisplatin, interferon, doxorubicin, and 5-fluorouracil.

Polychemotherapies: synthesis

- A very few randomised trials (vs BSC)
- All negatives
- No meta-analysis
- tolerance ?
 - Grade toxicity ≥ 3 : 10 à 30 %
 - acceptable ?
 - Toxic death : 0 - 20 %

➡ Phase II and III TRIALS + + + +

Targeted therapies : the future of the medical treatment of HCC ?

Targeted Biotherapies: rationale

-EGF-R/TGF α involved in hepatic regeneration and carcinogenesis

- ➔ Cetuximab
- ➔ Erlotinib
- ➔ Gefitinib

Miura et al. J Hepatol 1997
Hisaka et al. Int J Oncol 1999
...

-Angiogenesis and VEGF involved in metastatic spread of this highly vascularized tumor

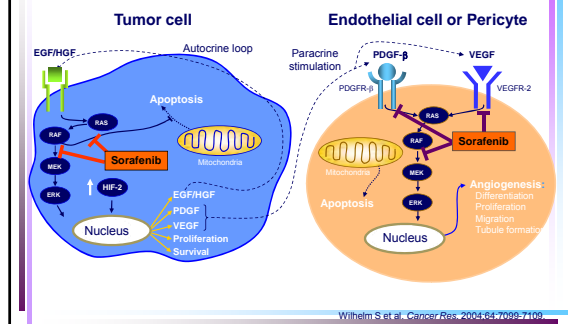
- ➔ Bevacizumab
- ➔ Sorafenib

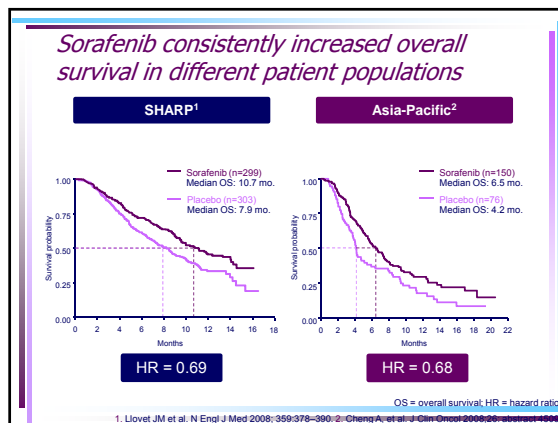
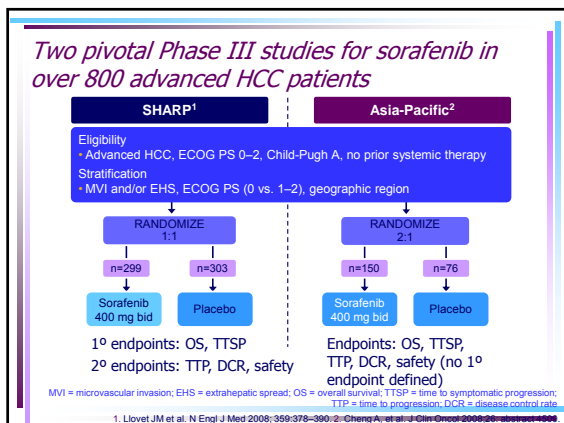
Poon et al. Ann Surg 2001
Torimura et al. Hum Pathol 1998
...

-Other pathways: Cell cycle/cyclin, KIT/PDGF-R, Cox...

-Others approaches: gene therapy, MMP inhibitors and antisense agents

Sorafenib Targets Both Tumor-Cell Proliferation and Angiogenesis





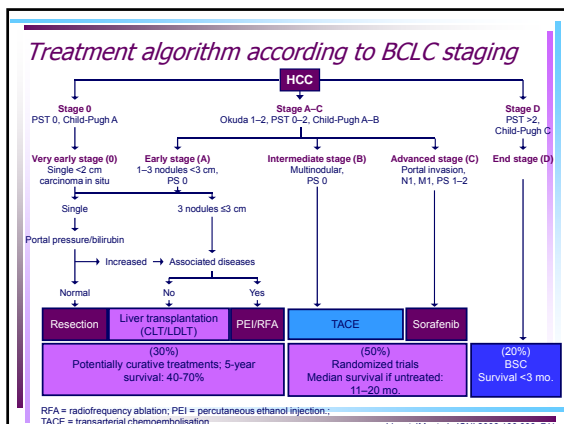
Phase III SHARP Trial Response assessment: Independent review

	Sorafenib (n=299)	Placebo (n=303)
Overall response		
Complete response (CR)	0	0
Partial response (PR)	7 (2.3%)	2 (0.7%)
Stable disease (SD)	211 (71%)	204 (67%)
Progressive disease	54 (17%)	73 (24%)
Progression-free rate at 4 months	62%	42%
Duration of treatment (median, weeks)	23	19

Llovet JM, et al. Lancet 2003; 362:1907-17.

%	HCC	5-year Survival	Treatment
20-30	In situ small (<3cm)	90 %	Curative
10	limited, non complicated	50-70 %	Curative
40-50	Extended metastatic	< 10 %	Sorafenib
20	Terminal	0%	BSC

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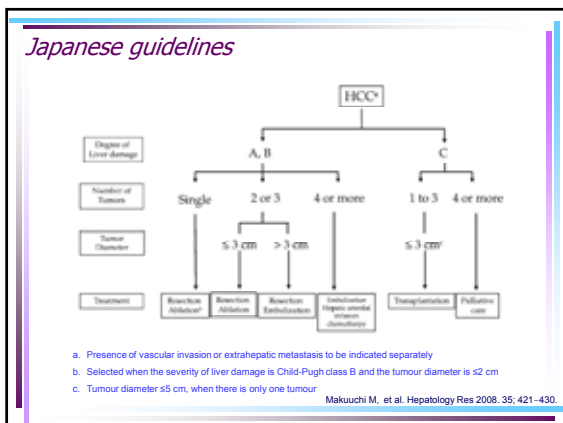
HCC guidelines/recommendations (2001 to present day)

Organisation	Country	Year	Evidence base
NCCN ¹	US	2009	Mainly level 2A evidence (phase II, cohort/case studies & experience)
HUG ²	UK	2009	All study types*
Spanish consensus ³	Spain	2009	All study types*
Austrian consensus ⁴	Austria	2008	All study types* & expert opinion/experience
AJFF Prodige ⁵	France	2008	Expert opinion/experience
J-HCC ⁶	Japan	2008	All study types*
AASLD ⁷	US	2005	All study types* & expert opinion/experience, Update in development
BASL ⁷	UK	2004	Superseded by HUG guidelines (2009)
BSG ⁸	UK	2003 ¹	All study types* & expert opinion/experience
EASL ¹⁰	EU	2001	All study types*, Update in development together with EORTC
Italian guidelines ¹¹	Italy	2001	-

*Data from randomized controlled trials, controlled trials without randomization, cohort/case studies, uncontrolled retrospective studies, meta-analysis; ¹Data from randomized controlled trials, controlled trials without randomization, cohort/case studies, controlled retrospective studies, meta-analysis

Abbreviations: AASLD, American association for the study of liver diseases; BASL, British association for study of the liver; BSG, British society of gastroenterology; EASL, European association for the study of the liver; EORTC, European organization of research on cancer; NCCN, National comprehensive cancer network

1. NCCN practice guidelines version 2.2009. 2. Ryder S. 2nd HUG meeting 2009. <http://www.medicalnewstoday.com/story/143444.php>. 3. Gomez Sanchez S. *Med Clin (Barc)* 2007; 132:272-27. 4. Wainwright D, et al. 5. BSG. 6. European Association for the Study of the Liver. 7. BSG. 8. British Society of Gastroenterology. 9. European Association for the Study of the Liver. 10. European Association for the Study of the Liver. 11. Italian guidelines 2001.



NCCN guidelines (2009)

Therapy	Guidelines
Surgical resection	<ul style="list-style-type: none"> Adequate liver function (Child-Pugh class A with mild or moderate portal hypertension) Solitary mass without MVI Adequate future liver remnant (at least 20% without cirrhosis and at least 30-40% with Child-Pugh class A cirrhosis, adequate vascular and biliary inflow/outflow) Controversial but can be considered in multifocal disease with MVI
Liver transplantation	<ul style="list-style-type: none"> UNOS criteria: single lesion $\le 5\text{ cm}$, or 2 or 3 lesions $\le 3\text{ cm}$ (cadaveric or living donation) Controversial if tumour characteristics are marginally outside the UNOS guidelines and may be considered at some institutions for living-related liver transplantation
PEI/RFA	<ul style="list-style-type: none"> Accessible location for percutaneous/laparoscopic/open approaches for ablation Optimal tumour size is $\le 3\text{ cm}$ Lesions $\ge 3\text{ cm}$ may be treated using combination embolisation and ablation as long as the tumour location is favourable Unresectable/inoperable lesions $> 5\text{ cm}$ should be treated using arterial embolic approaches Caution advised when ablating lesions near major vessels, major bile ducts, and other intra-abdominal organs
TACE	<ul style="list-style-type: none"> All tumours irrespective of location may be amenable provided that the arterial blood supply to the tumour may be isolated without non-target embolisation Contraindications: <ul style="list-style-type: none"> Bilirubin $> 3\text{ mg/dL}$, unless segmental injections can be performed Major portal vein thrombosis Child-Pugh class C
Sorafenib	<ul style="list-style-type: none"> Selected patients with Child-Pugh class A or B liver function with disease characterised as: <ul style="list-style-type: none"> Unresectable and endovascular/not suitable for liver transplantation Local disease only in patients who are not operable due to performance status or comorbidity Metastatic Inadequate safety and dosing data of sorafenib in patients with Child-Pugh Class B and extreme caution recommended when considering sorafenib for patients with elevated bilirubin levels

MVI: microvascular invasion; PEI: percutaneous ethanol injection; RFA: radiofrequency ablation; TACE: transarterial chemoembolisation; UNOS: United Network for Organ Sharing

