ESMO-JSMO Joint Symposium – Recent advances in the treatment of GI tract and liver cancer in the EU and Japan

Hepatocellular carcinoma: Present treatment strategy in Japan

ESMO 2012 Congress,

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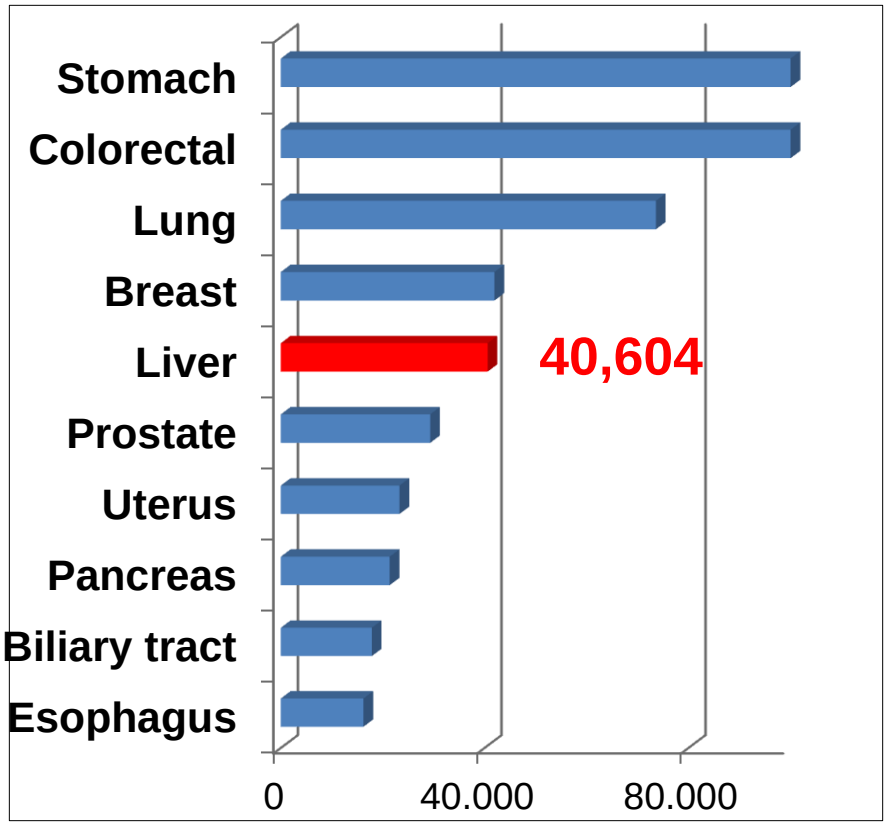
Disclosure

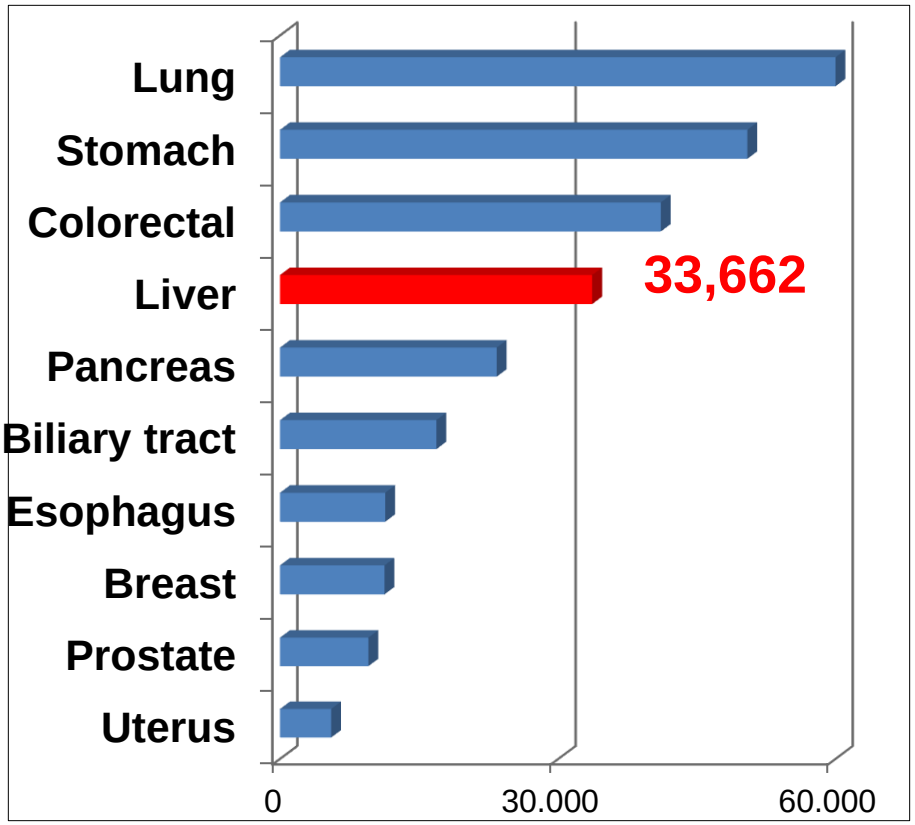
- Consulting fee or honorarium
  - Bayer, Taiho, Eli lilly, Chugai, Eisai
- Grants
  - GSK, Pfizer, Yakult, Eli lilly, Takeda, Bayer

Cancer Incidence and Mortality in Japan

Incidence in 2002

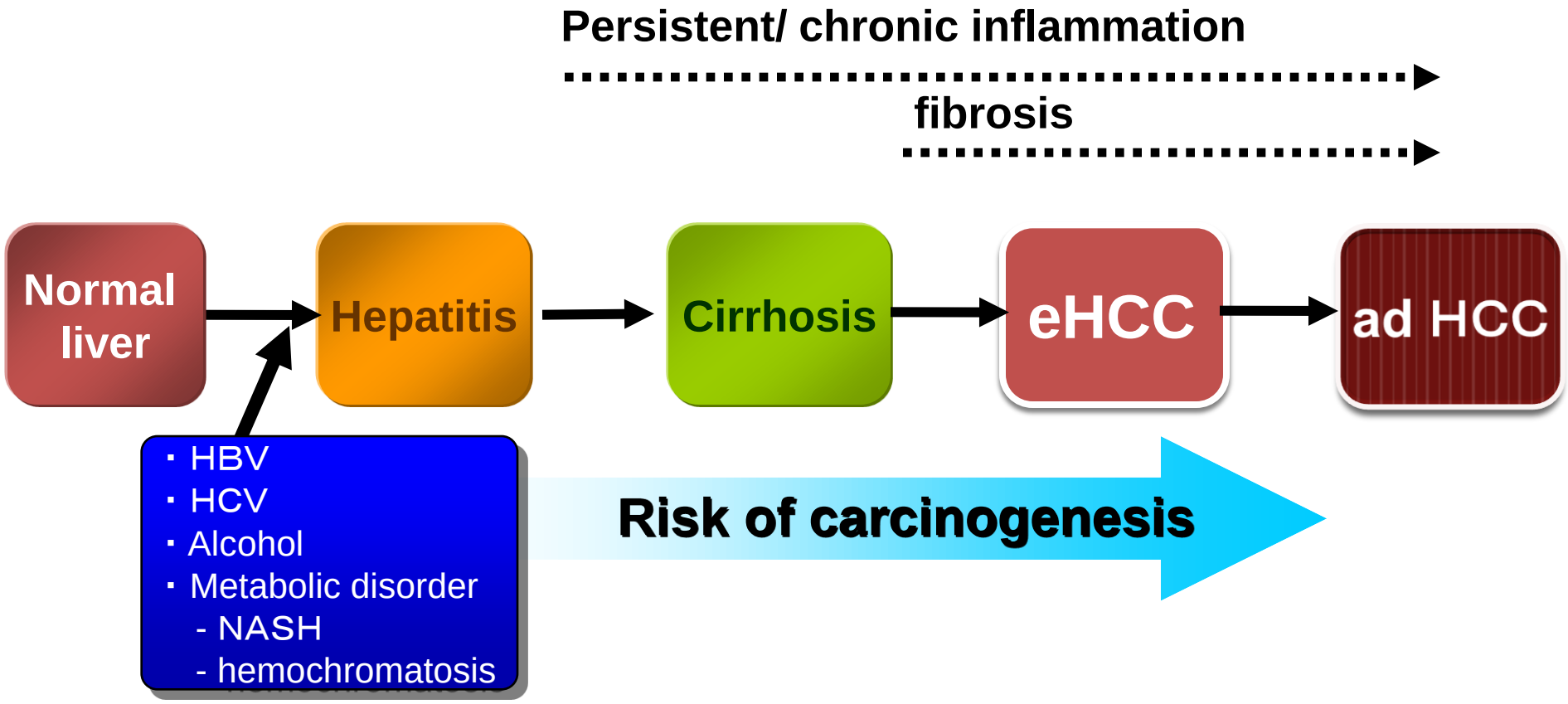


Mortality in 2006



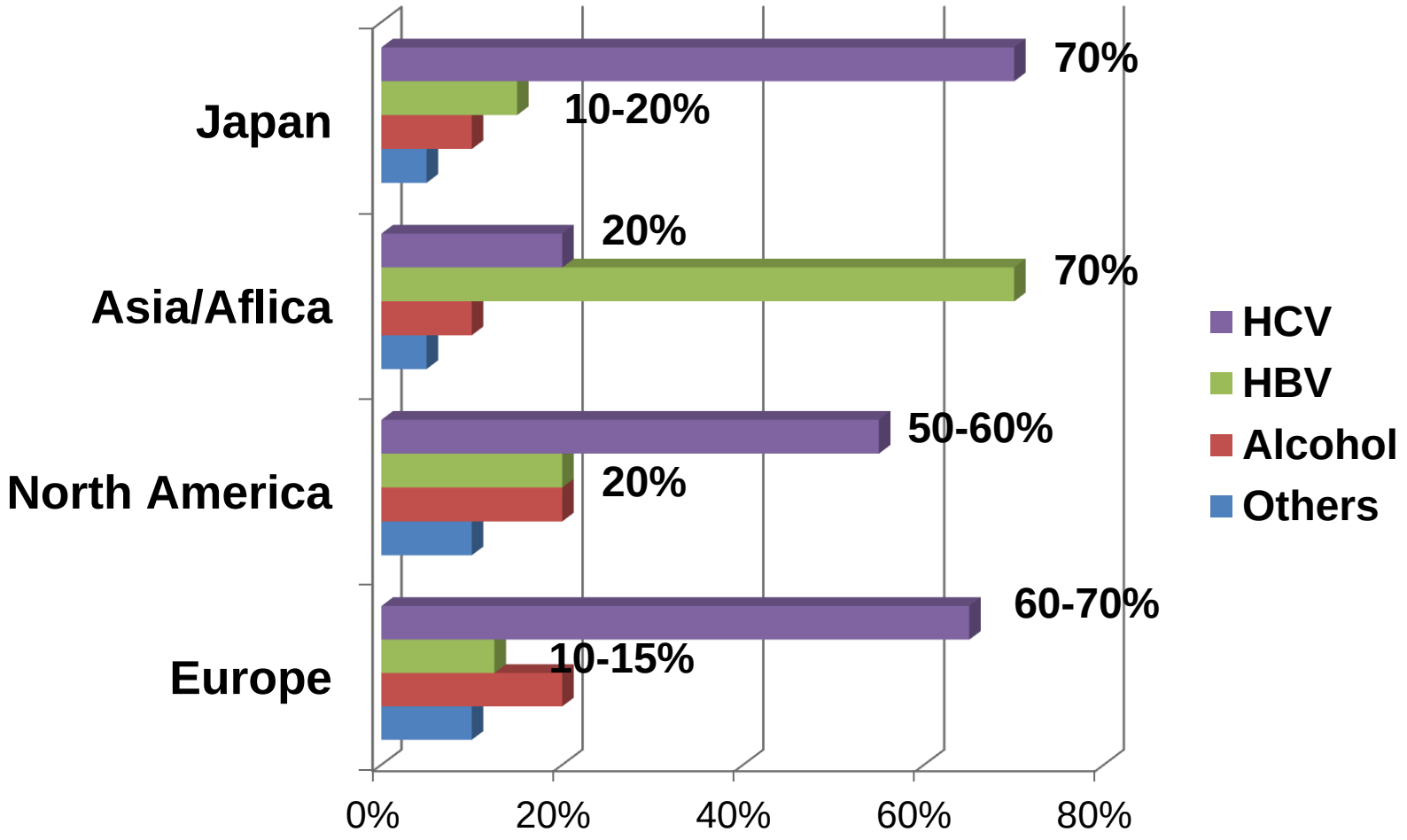
Cancer Statistics in Japan 2008

Multistep carcinogenesis in hepatocelullar carcinoma (HCC)



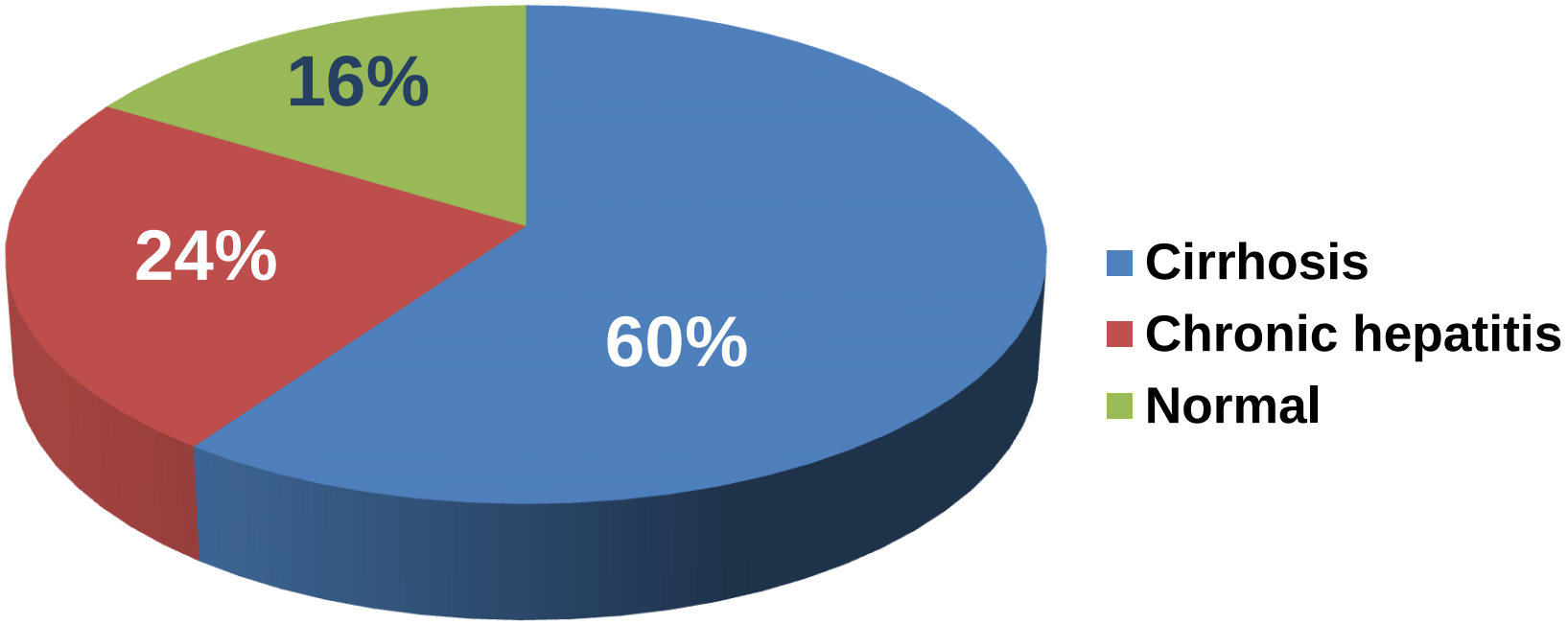
1. Adapted from Rivenbark AG, et al. *Clin Cancer Res.*13:2309（2007）
2. Marotta F, et al. *Clin Ther*.155:187（2004） 3. Thorgeirsson S, et al. *Nat Genet*. 31:339（2002）
4. Wang XW, et al. *Toxicology*.181-182:43（2002） 5. Koike K. *Hepatol Res*.33:145（2005）

Etiology of HCC varies by regions



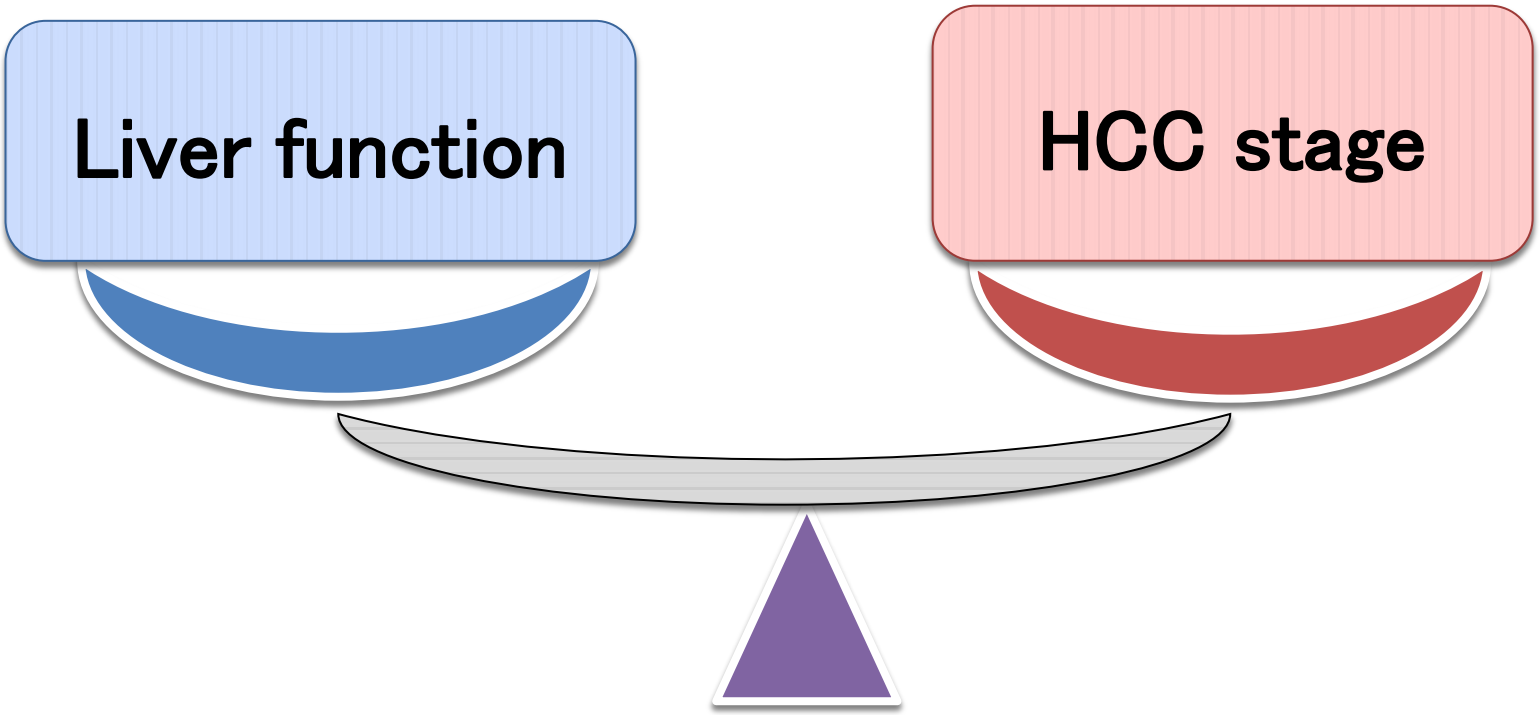
Llovet JM, et al. Lancet 2003; 362:1907

Background of the Liver in Patients with HCC



the Liver Cancer Study Group of Japan, 2007

Treatments Strategy for HCC

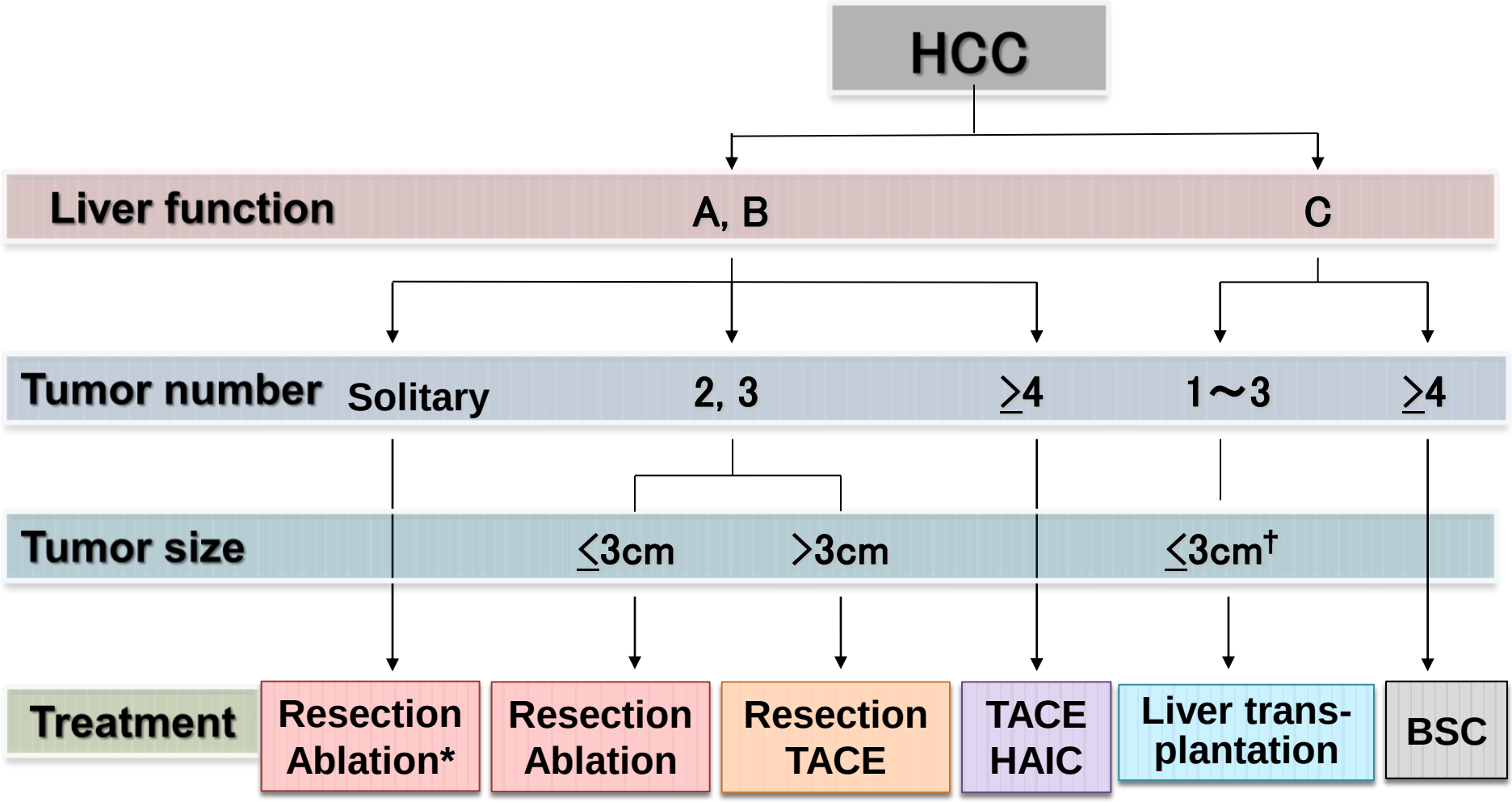


Balance between liver function and tumor stage is the most important in selection of treatments for HCC.

Contents

1. **Treatment strategy for HCC in Japan according to the Japanese guideline**
2. **Efficacy and safety of sorafenib in practice**
3. **Clinical trials using sorafenib in Japan, especially combination with hepatic arterial infusion chemotherapy**

Algorism of HCC Treatments



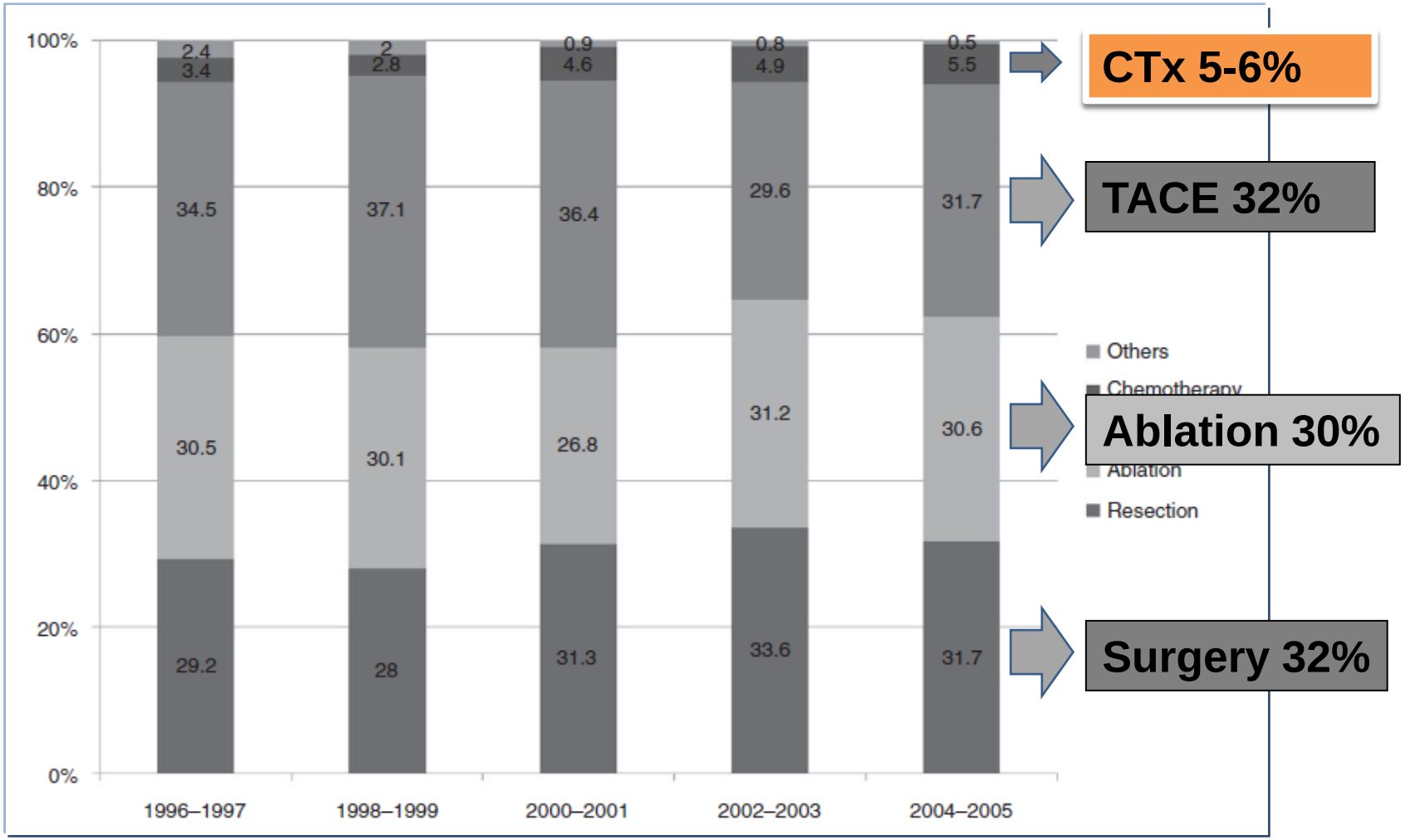
*Ablation should be applied to patents with liver damage B and ≤2 cm

† In case of solitary tumor, <5 cm

Japan HCC Treatment guideline revised, 2009

Changes of treatment methods as the first line treatment for HCC in Japan

From Nationwide Survey by the Liver Cancer Study Group of Japan



Arii S, et al: Hepatol Res 2010; **40**: 667

The efficacy of local treatments

- **Surgical resection**
- **Local ablation**
- **Transarterial chemoenbolization**

The efficacy of local treatments

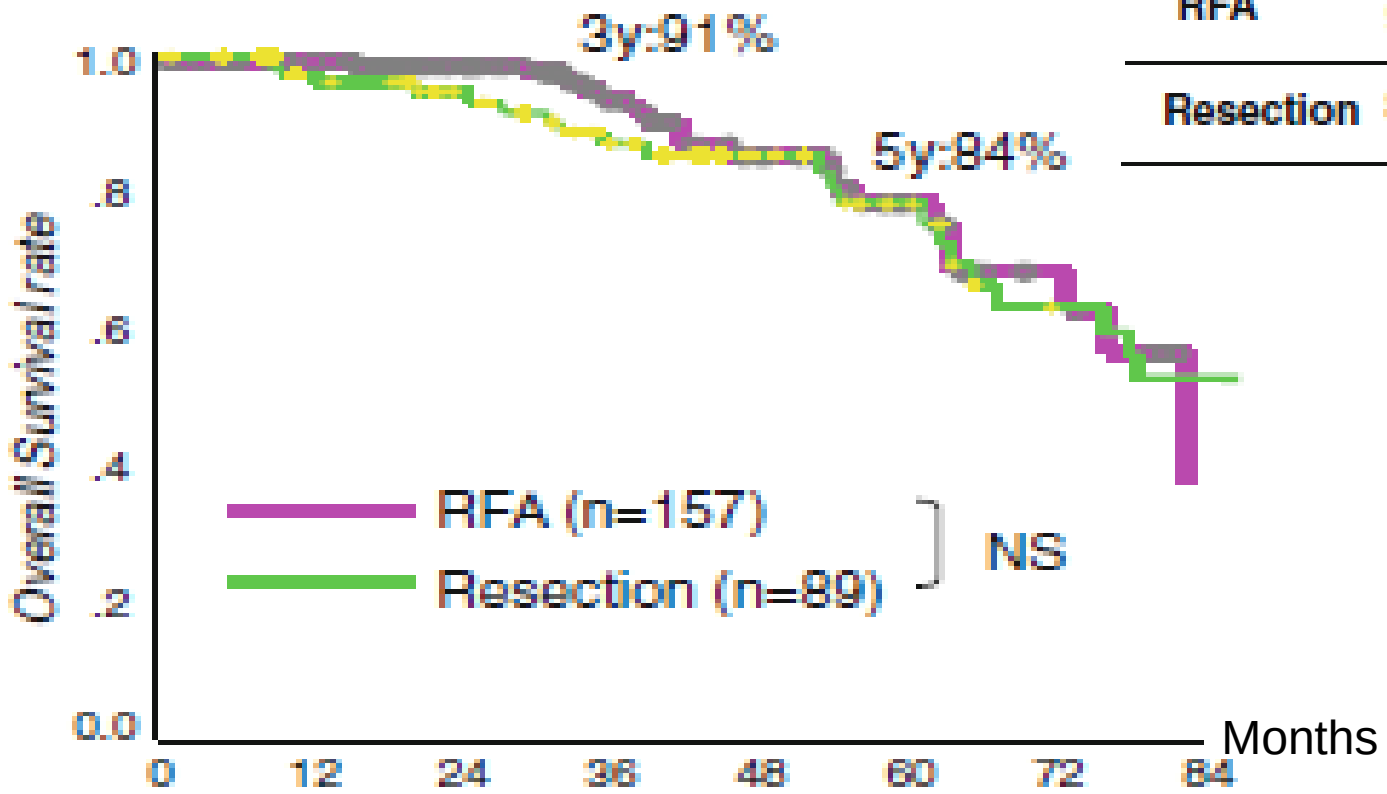
- **Surgical resection**
- **Local ablation**
- **Transarterial chemoenbolization**

Overall Survival of Resection and RFA

the 17th nationwide survey of the Liver Cancer Study Group of Japan

Solitary HCC smaller than 5 cm, Child-Pugh A

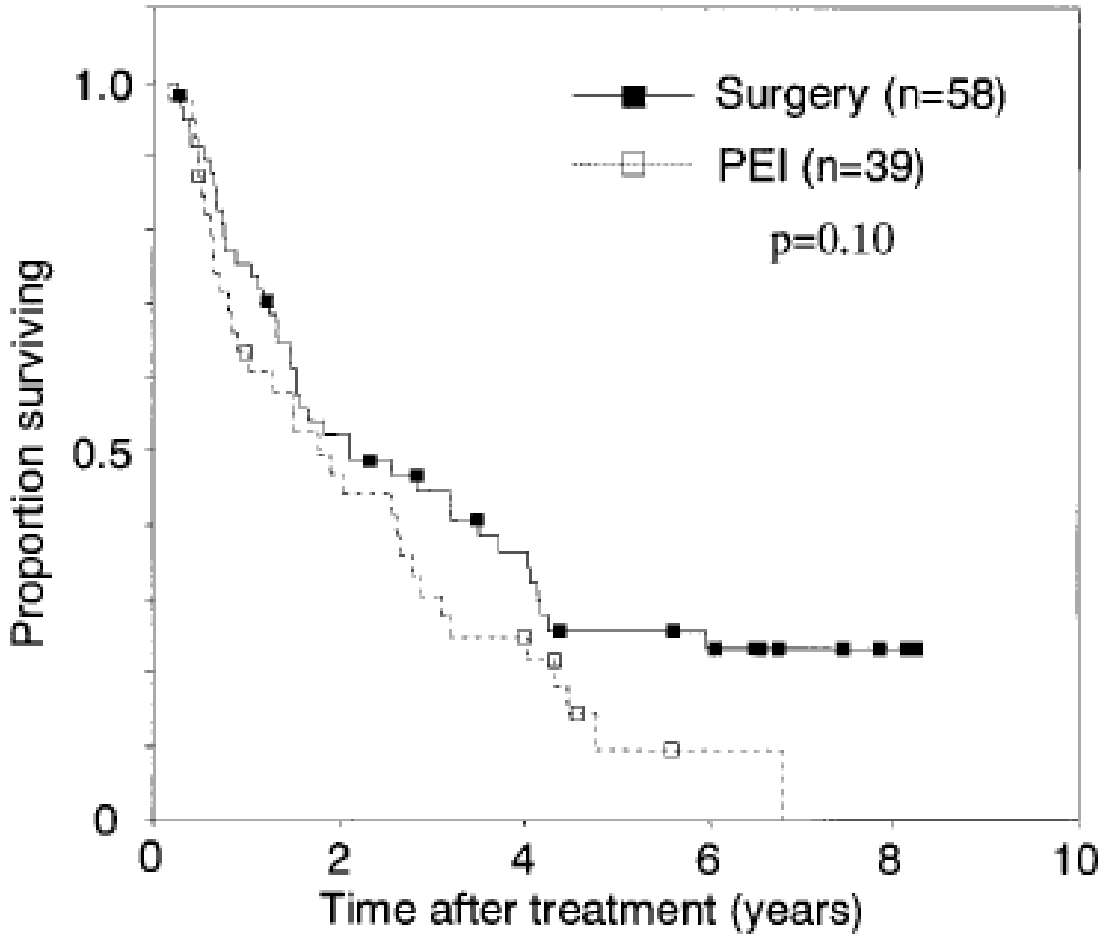
	3y	5y
RFA	91%	84%
Resection	87%	78%



Kudo M, Chung H. J Hepatobiliary Pancreat Surg 2009

Disease-free survival after surgery or ablation therapy

Recurrence rate of HCC is very high even in patients with HCC who can receive curative treatments.



Recurrence rate

1 year : 20-30%

3 year : 50-60%

5 year : 70-90%

Yamamoto J, et al: Hepatology 34:707, 2001

The efficacy of local treatments

- Surgical resection
- Local ablation
- **Transarterial chemoenbolization**

Transarterial chemoemoblization (TACE): Tumor response

National Cancer Hospital East (2000-2006): N=118

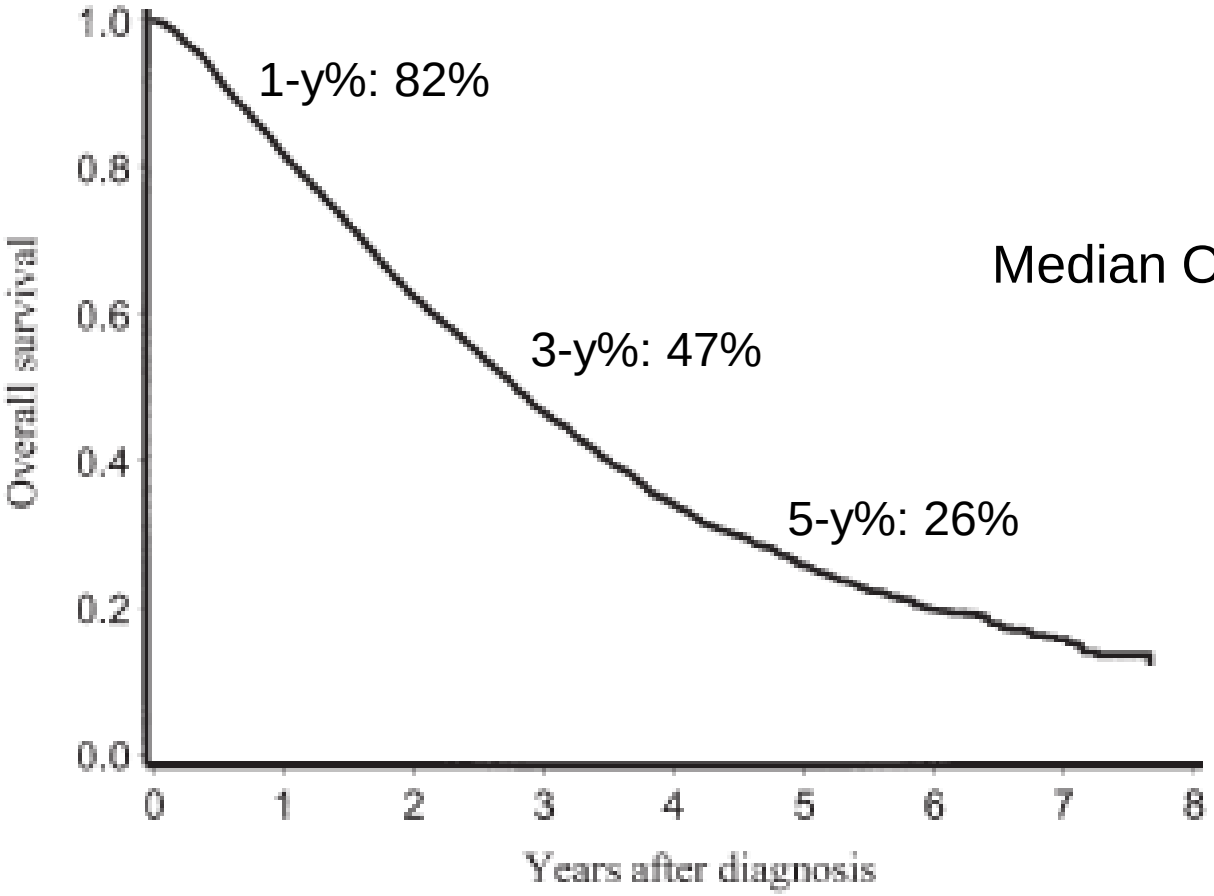
Response	N (%)
CR	39 (33%)
PR	43 (36%)
SD	21(18%)
PD	8 (7%)

CT, PR include tumor necrosis of lipiodol accumulation

Furuse J, et al. ILCA 2007

Overall survival of TACE

the 17th nationwide survey of the Liver Cancer Study Group of Japan

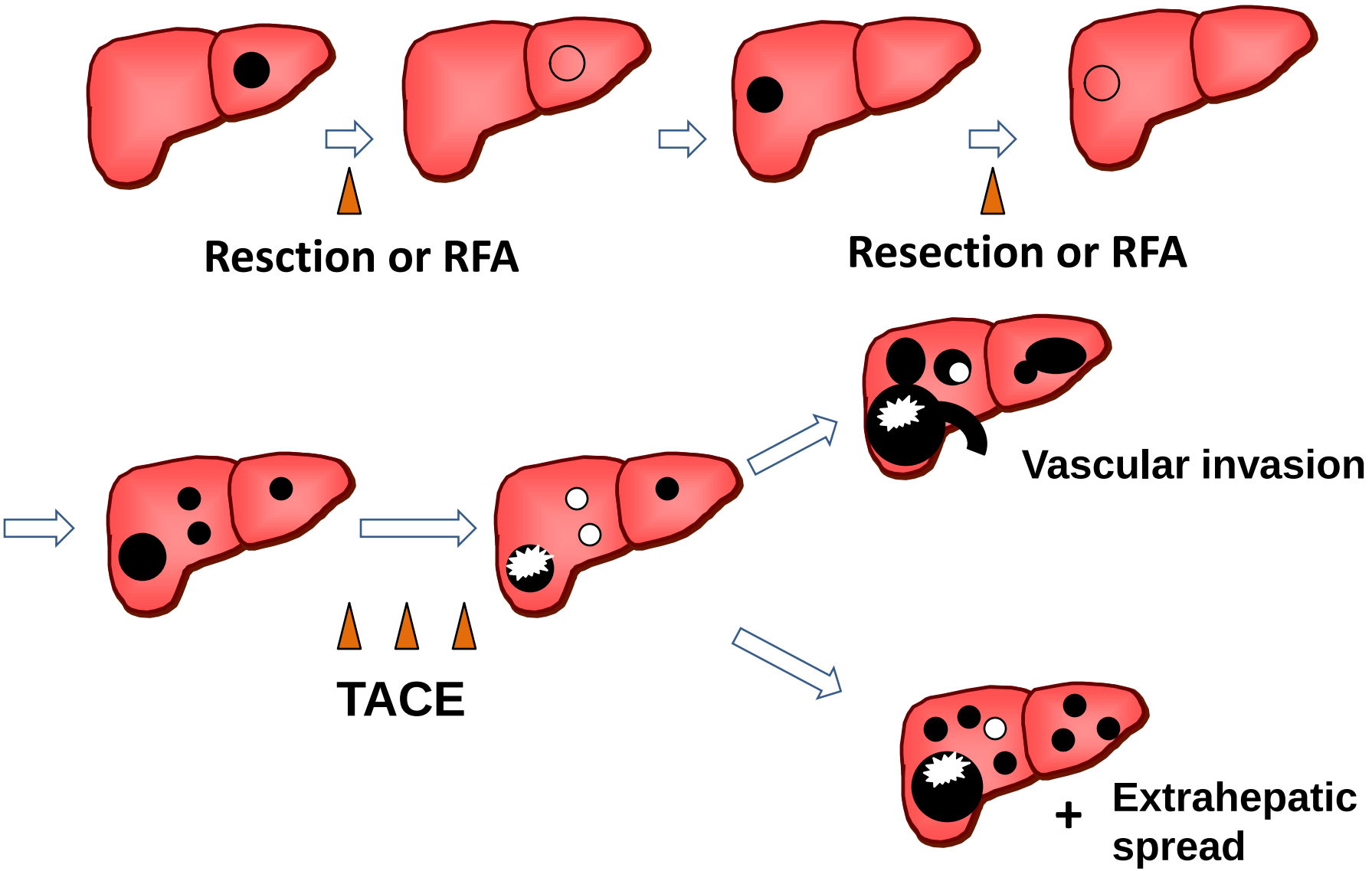


N=8,542

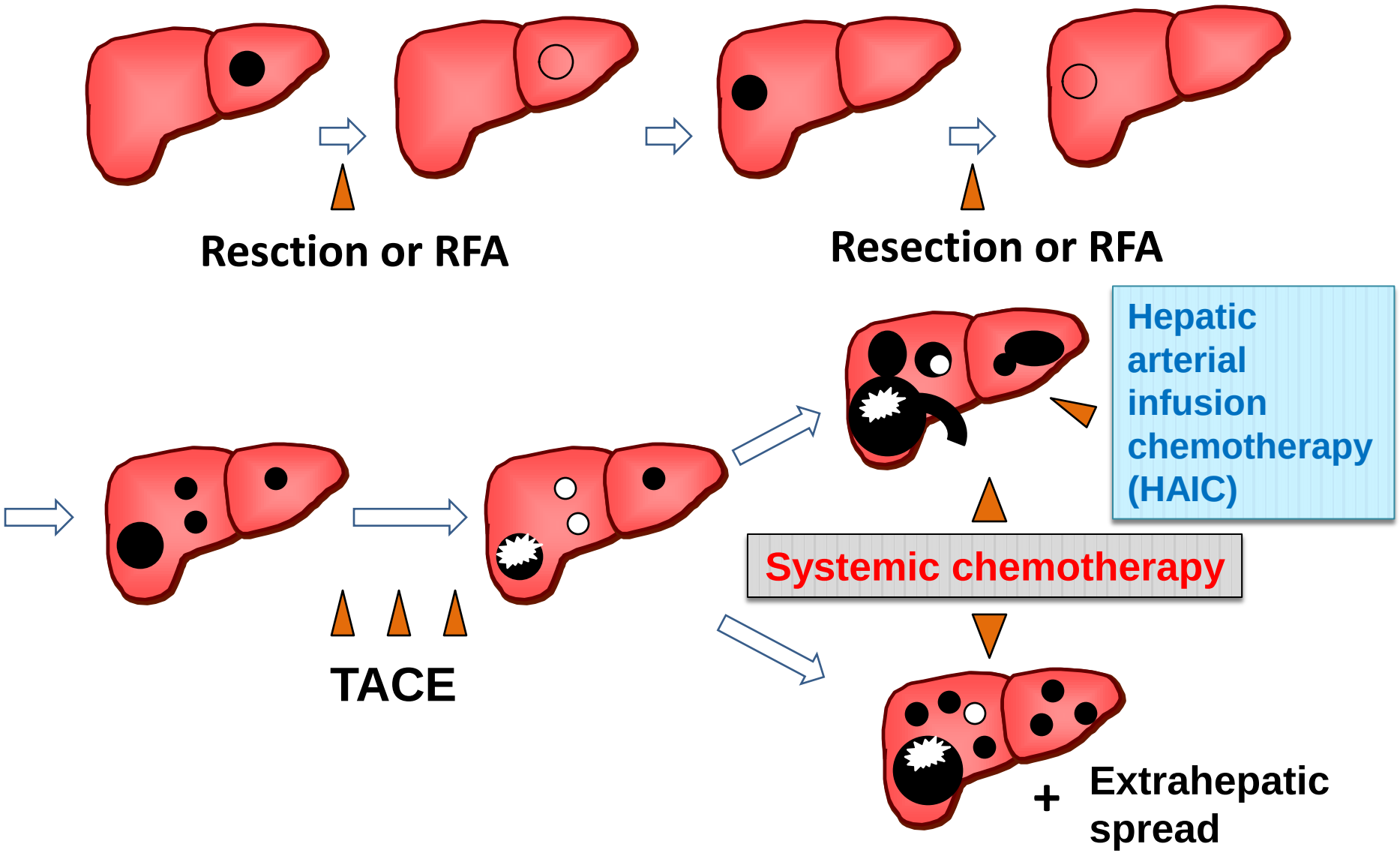
Median OS: 34 months

Takayasu K, et al. Gastroenterol 131: 461-469, 2006

Selection of treatments according to tumor condition



Selection of treatments according to tumor condition



Indication of chemotherapy

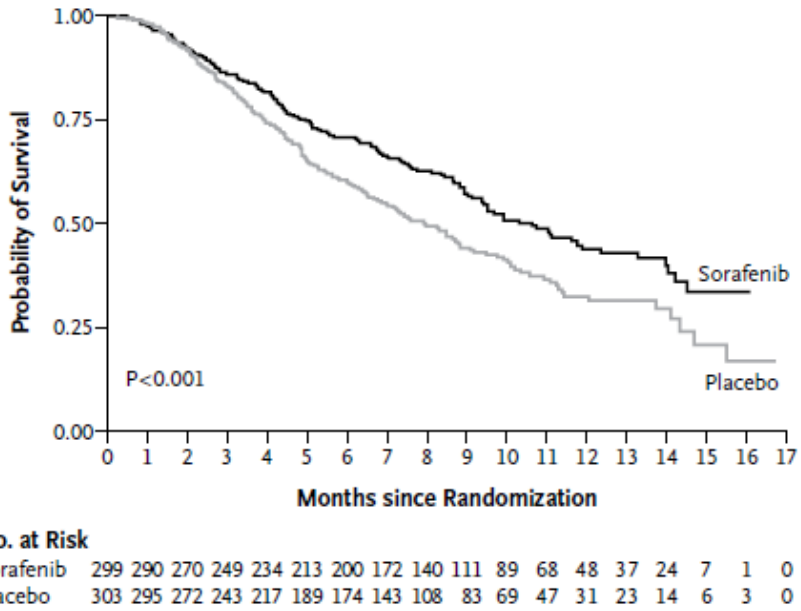
- Extrahepatic spread
- Vascular invasion (portal vein)
- TACE refractory

- Systemic chemotherapy
  - Sorafenib
  - New agents in clinical trials
- Hepatic arterial infusion chemotherapy (HAIC)
  - Japanese guideline: recommended
  - EASL–EORTC guideline: not recommended

Overall survival in RCTs of sorafenib vs. placebo

SHARP trial

N=602



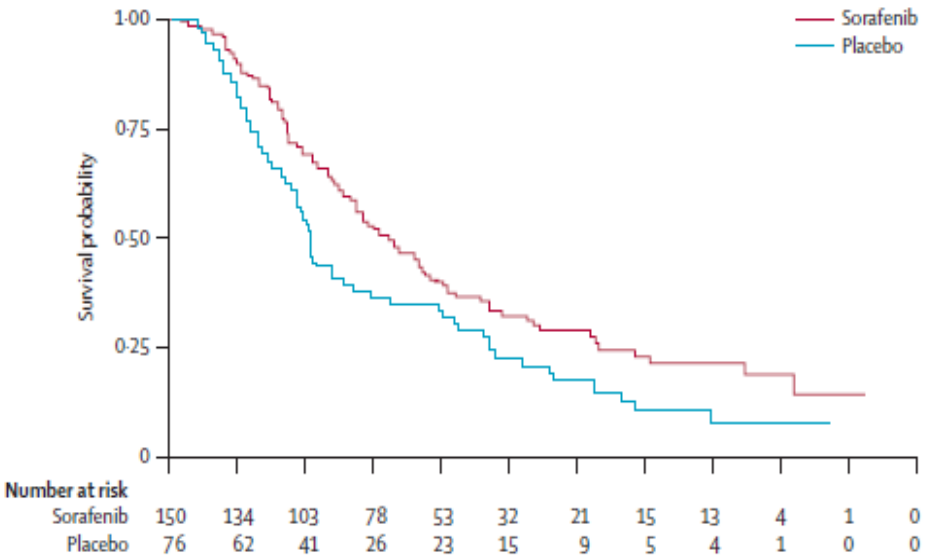
No. at Risk

Sorafenib	299	290	270	249	234	213	200	172	140	111	89	68	48	37	24	7	1	0
Placebo	303	295	272	243	217	189	174	143	108	83	69	47	31	23	14	6	3	0

	Median OS
Sorafenib	10.7 mo
Placebo	7.9 mo
HR	0.69
P-value	<0.001

Asia-Pacific trial

N=226

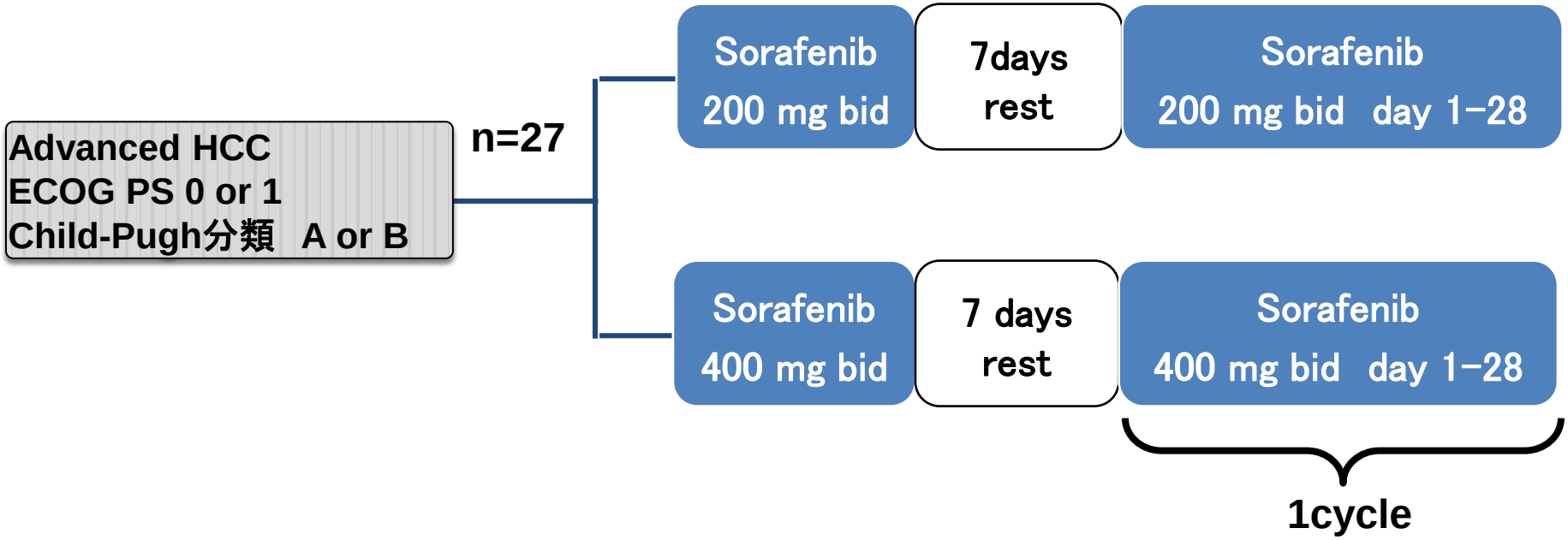


	Median OS
Sorafenib	6.5 mo
Placebo	4.2 mo
HR	0.68
P-value	0.014

Llovet JM, et al. NEJM, 2008

Cheng AL, et al, Lancet Oncol, 2009

Phase I study of sorafenib for Japanese patients with HCC



DLT: hand-foot skin reaction in 1/12 patients of 400 mg bid
Recommended dose: 400 mg bid

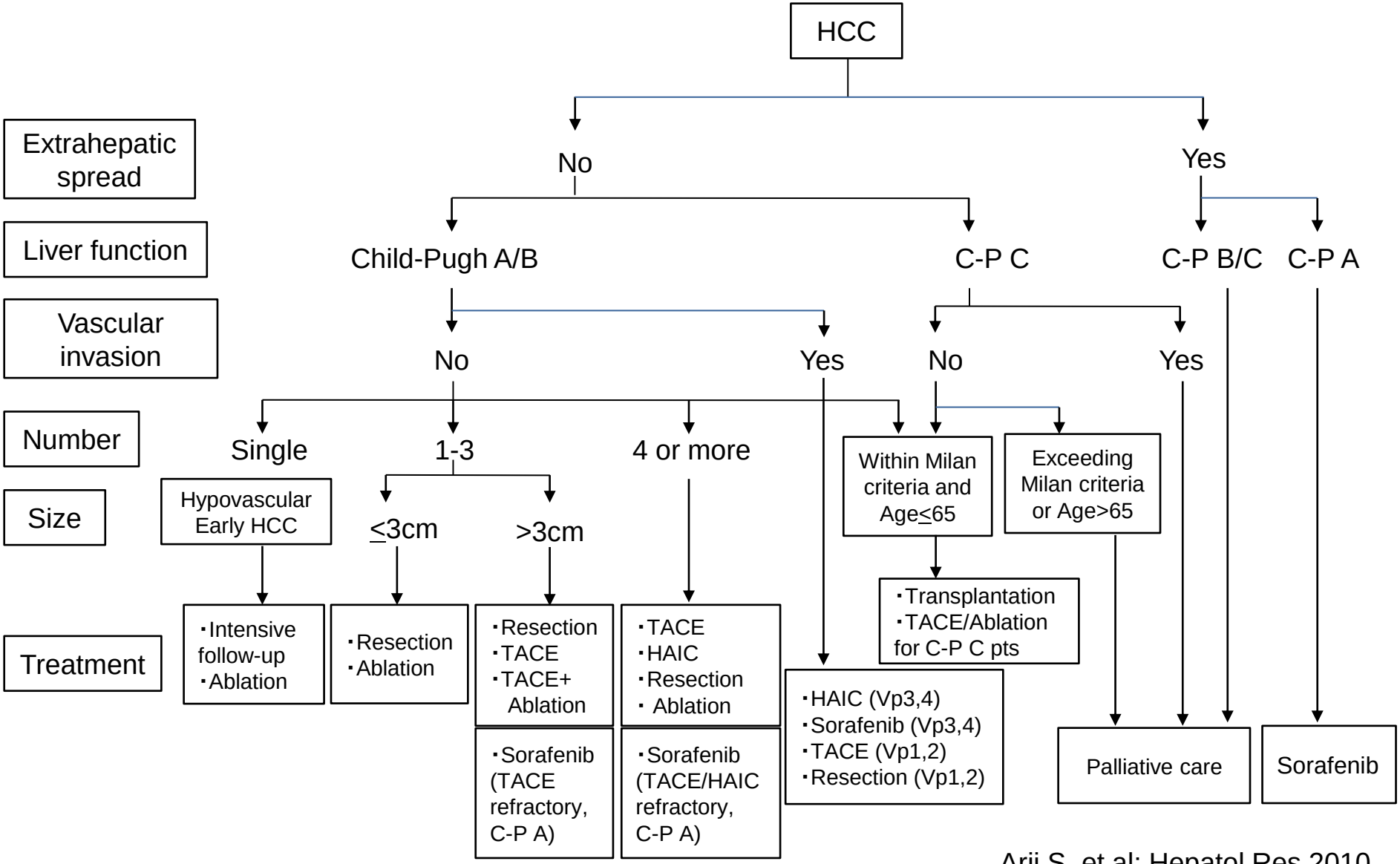
Furuse J, et al. Cancer Sci 2008;99:159-165.

Adverse Events: all grade

Adverse Event	SHARP	A-P	Jpn P-1
Fatigue	22%	20%	37%
Weight loss	9%	-	30%
Alopecia	14%	25%	29%
Dry skin	8%	-	11%
Hand–foot skin reaction	21%	45%	44%
Pruritus	8%	-	30%
Rash or desquamation	16%	20%	56%
Anorexia	14%	13%	22%
Diarrhea	39%	26%	56%
Nausea	11%	11%	-
Vomiting	5%	-	-
Voice changes	6%	-	-
Hypertension	5%	19%	19%
Liver dysfunction	<1%	-	-
Abdominal pain not specified	8%	-	-
Bleeding	7%	-	-

In 2009, sorafenib was approved to unresectable advanced HCC in Japan

Consensus-based treatment algorithm proposed by the Japan Society of Hepatology



Arii S, et al: Hepatol Res 2010

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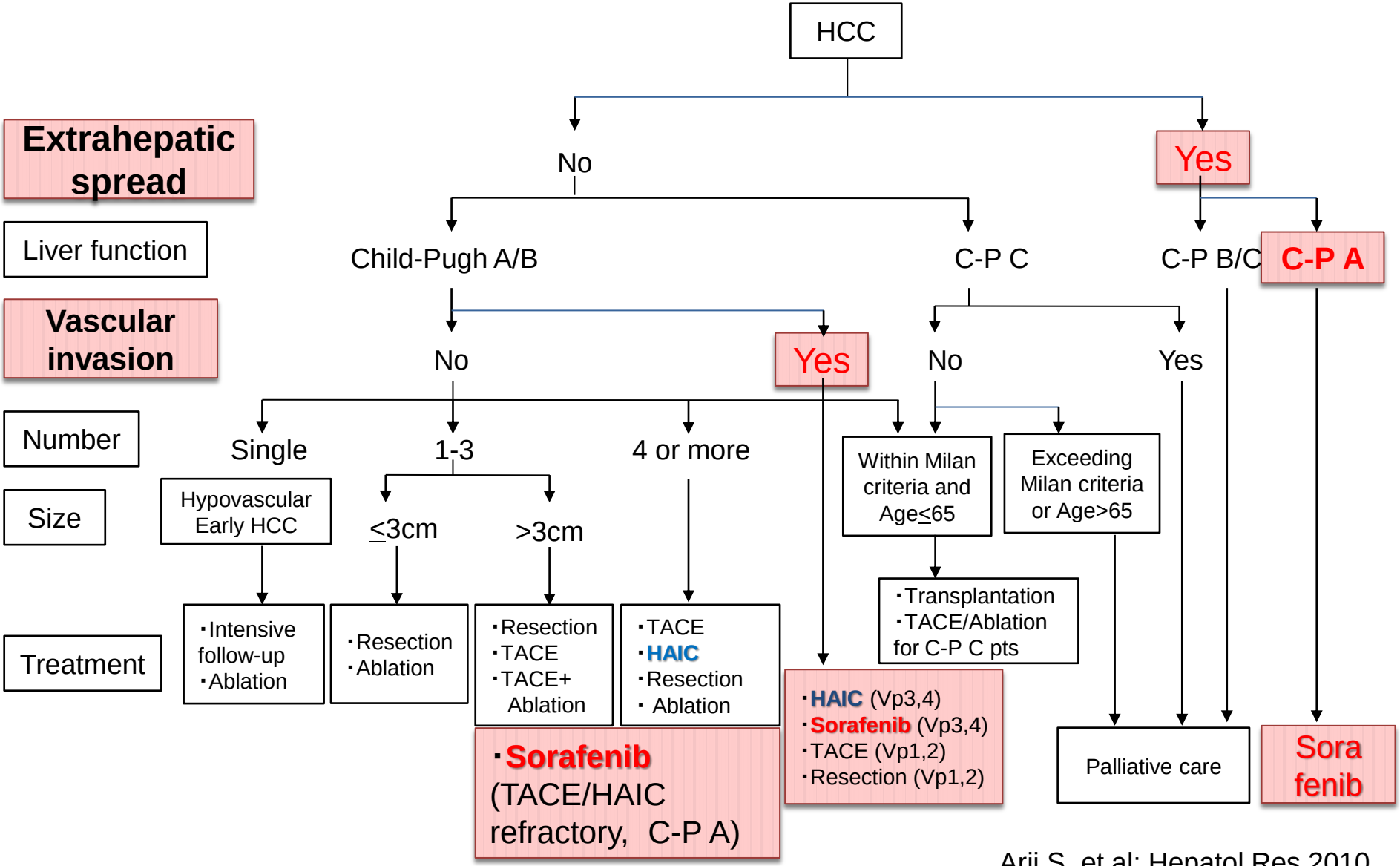


Arii S, et al: Hepatol Res 2010

Efficacy and safety of sorafenib in practice

The Study Group on New Liver Cancer Therapies

264 patients who received sorafenib were enrolled between June 2009 and December 2010

Age(years)	
Median	70
Range	33-87
Gender	
Male	79%
Female	21%
Child-Pugh class	
A	81%
B	19%
HBs antigen (+)	10%
HCV antibody (+)	62%
Vascular invasion (+)	18%

Stage	
I	1%
II	9%
III	30%
IV a	17%
IV b	43%
Prior treatment (+)	91%
Resection	31%
Local ablation	47%
TACE	78%
Hepatic arterial infusion	29%

Kaneko S, et al: Hepatol Res 2012

Drug-related adverse events of sorafenib

The Study Group on New Liver Cancer Therapies in Japan

N=264

	Total	Grade 3/4
Hand-foot skin reaction	44%	10%
Rash/desquamation	31%	5%
Diarrhea	32%	5%
Anorexia	27%	4%
Hypertension	26%	8%
Fatigue	24%	2%
Alopecia	15%	0%
Nausea	10%	1%
Elevated AST or ALT	70%	25%
Elevated T-Bil	53%	11%
Elevated lipase	78%	37%

Kaneko S, et al: Hepatol Res 2012

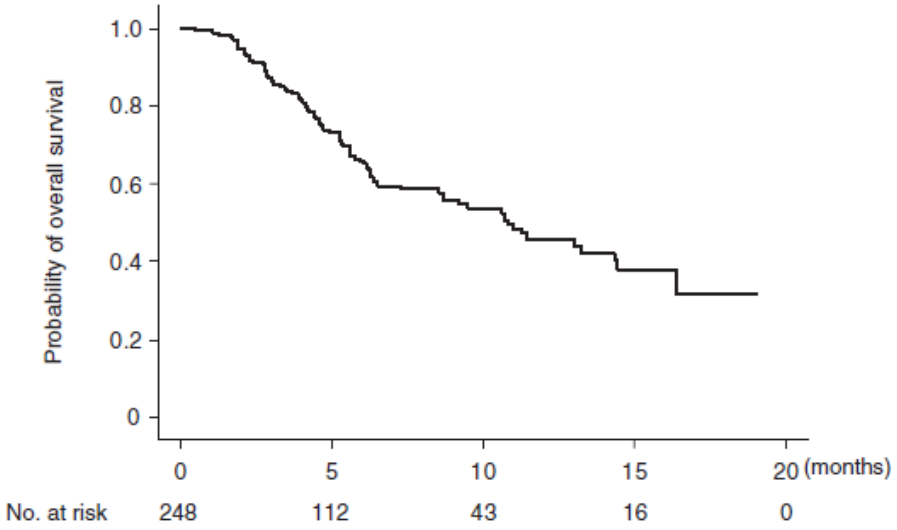
Efficacy data of sorafenib in practice

N=264

Response rate: 4%

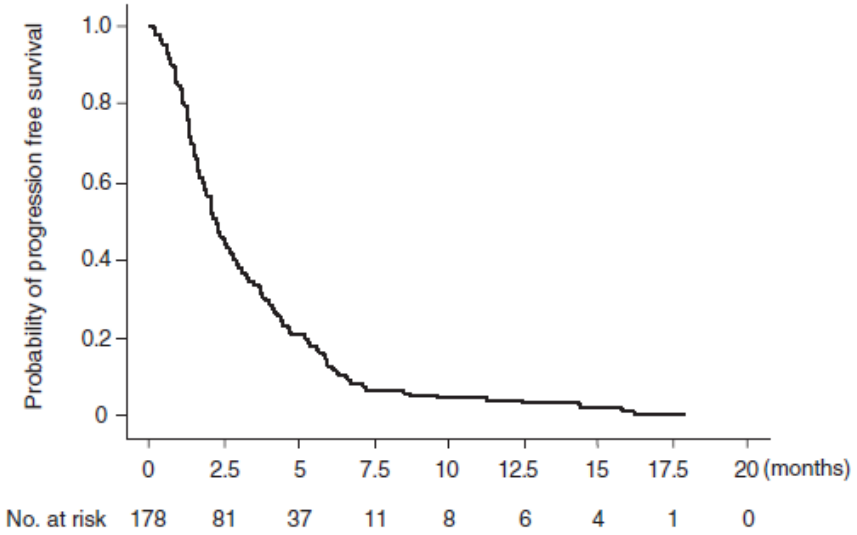
Tumor control rate: 49%

Overall survival



Median OS: 11.0 months

Progression-free survival



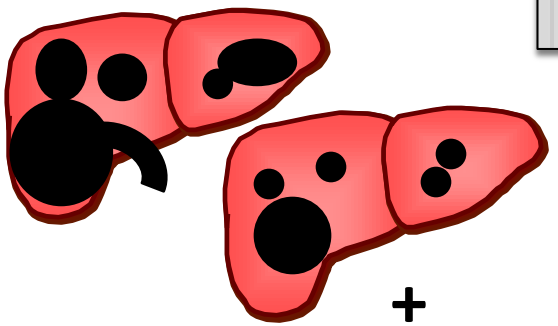
Median PFS: 2.1 months

Kaneko S, et al: Hepatol Res 2012

Clinical trials for HCC in Japan

Targets of clinical trials of systemic chemotherapy

Advanced



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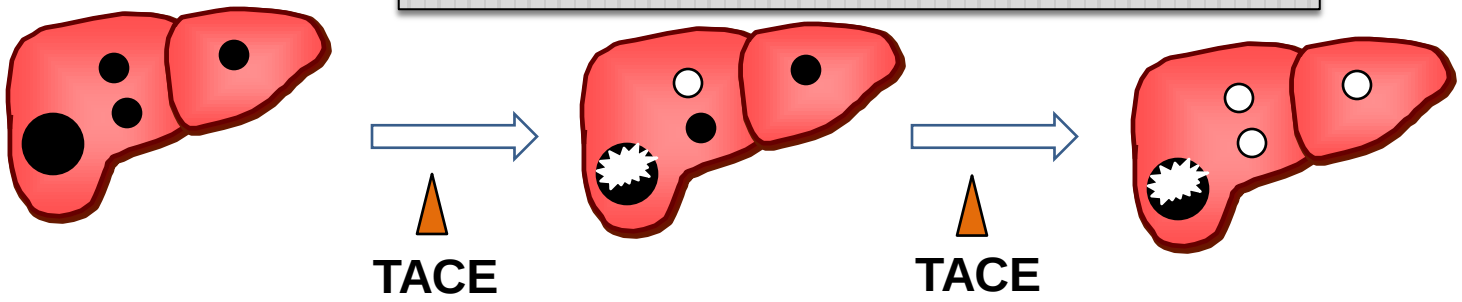
Extrahepatic spread

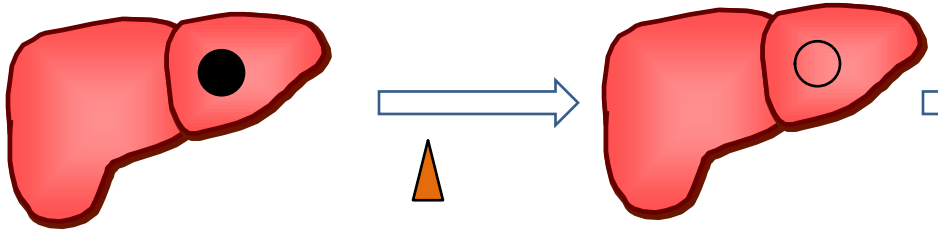
1st line → **2nd line**

Multiple

Combination with TACE



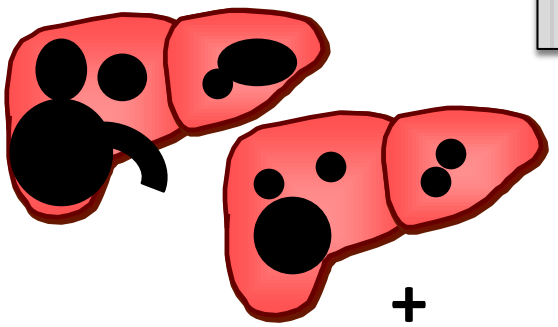
Solitary or a few tumors



Resection or RFA → **Adjuvant therapy**

Targets of clinical trials of systemic chemotherapy

Advanced



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Extrahepatic spread

1st line

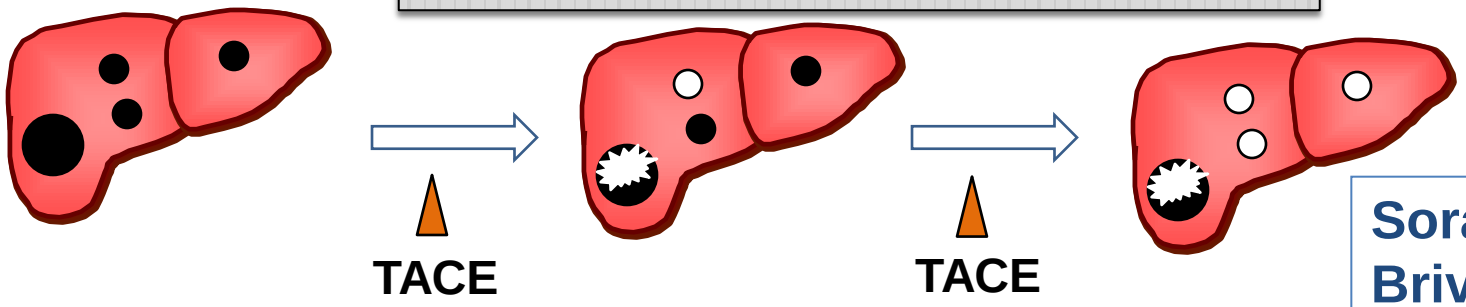
- Sunitinib
- Brivanib
- Linifanib
- Sor.+erolinib
- Sor.+HAIC

2nd line

- Brivanib
- Everolimus
- S-1
- Ramucirumab
- Axitinib, GC33, etc.

Multiple

Combination with TACE

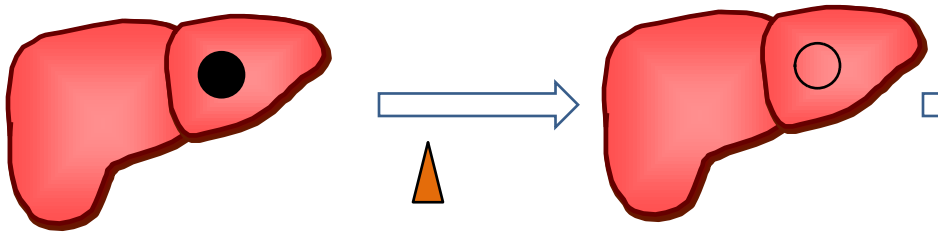


TACE

TACE

- Sorafenib
- Brivanib
- Orantinib

Solitary or a few tumors



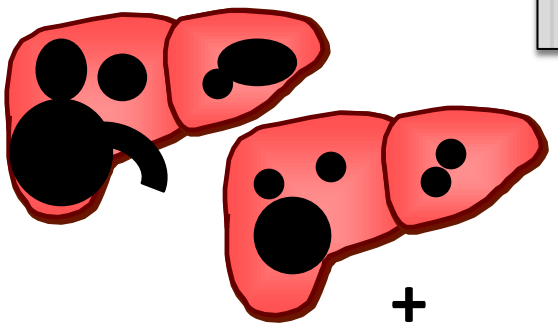
Resection or RFA

Adjuvant therapy

- Peretinoin
- Sorafenib

Targets of clinical trials of systemic chemotherapy

Advanced



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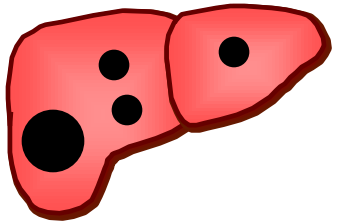
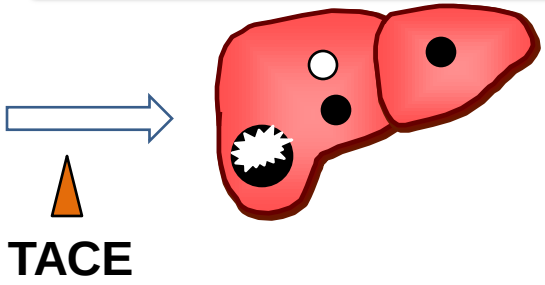
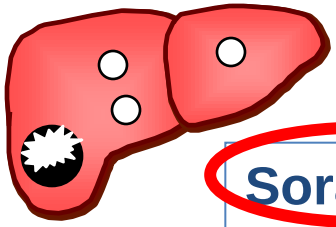


Combination with TACE



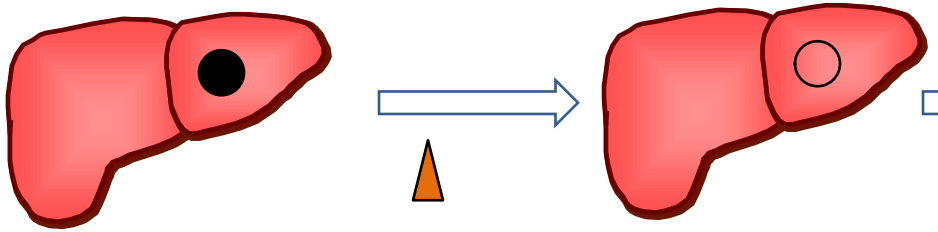
TACE

TACE



- Sorafenib
- Brivanib
- Orantinib

Solitary or a few tumors



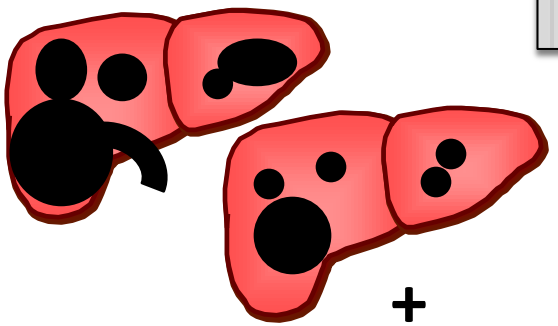
Resection or RFA

Adjuvant therapy

- Peretinoin
- Sorafenib

Targets of clinical trials of systemic chemotherapy

Advanced



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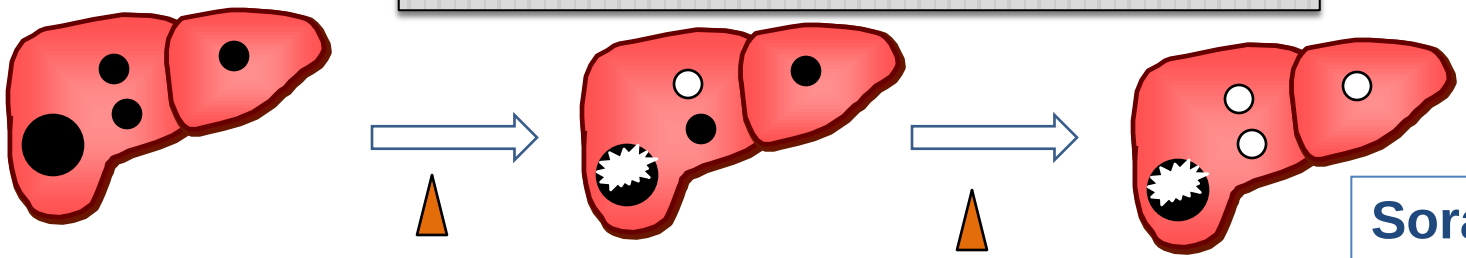
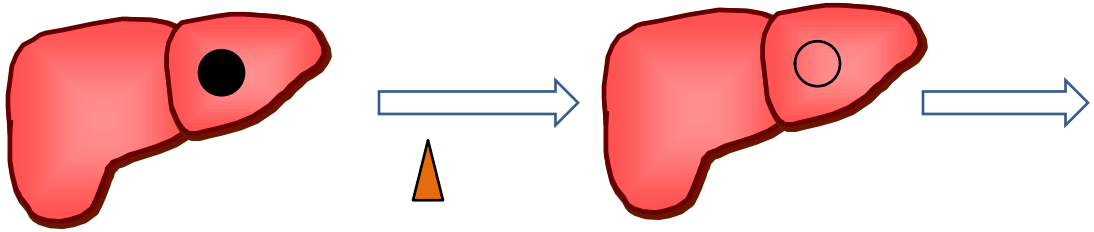


Sorafenib
Brivanib
Orantinib

Solitary or a few tumors



Adjuvant therapy

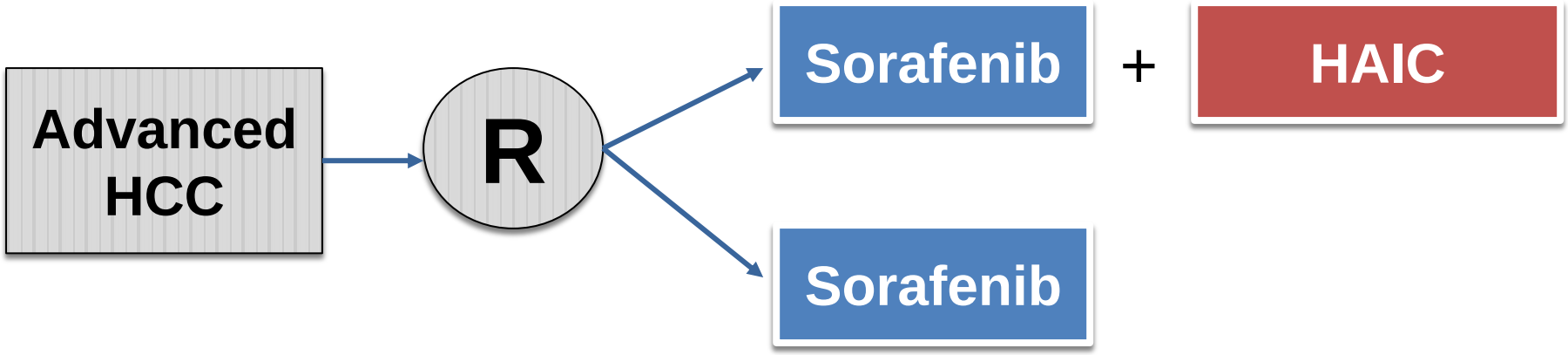
Peretinoin
Sorafenib

Hepatic arterial infusion chemotherapy

- **Indication: highly extended portal invasion and/or unresectable huge tumor**
- **Various regimens of HAIC are used**
- **No evidence of the survival benefits**

	n	RR (%)	mTTP (mo)	mOS (mo)	Author	Year
5-FU/cisplatin	48	48	NA	10.2	Ando	2002
5-FU/IFN	55	43.6	5.2	11.8	Ota	2005
	116	52.6	NA	6.9	Obi	2006
Cisplatin	25	28	3.6	7.1	Okusaka	2008

Comparison studies between sorafenib vs. sorafenib+HAIC to confirm the survival benefits of HAIC



Randomized phase II study of sorafenib + CDDP HAIC

Phase III study of sorafenib + 5-FU/CDDP HAIC

Randomized phase II study Sorafenib+CDDP HAIC vs. sorafenib

- Cisplatin arterial infusion is promising anti-tumor effect; response rate is 28%
- Simple methods
  - One shot infusion repeated every 4-6 months
  - Port system replacement is not necessary
- Primary endpoint: overall survival
- Assumption
  - Median OS: 7 mo in Sor→ 9.5 mo in Sor+CDDP HAIC
  - HR 0.74; go to phase III study
  - Patient number: 105

http://www.umin.ac.jp/ctr/index-j.htm: UMIN000005703

Summary

- **90% patients with HCC undergo local treatments, hepatectomy, RFA and TACE as the first line treatment.**
- **Sorafenib is indicated in patients with advanced HCC who are not suitable candidates for local treatments.**
- **Safety and efficacy of sorafenib in practice are comparable with the SHARP trial.**
- **Many new agents are developing in every stage of treatment for HCC.**
- **Hepatic arterial infusion chemotherapy (HAIC) shows high response rate, but no survival benefits has been confirmed. RCTs of sorafenib+HAIC are currently ongoing in Japan.**

Thank you for your kind attention.