Gastrointestinal Tumours

Poster Discussion: Hepatocellular Carcinoma

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SGH – Surgery

ESMO Asia 2015 Congress

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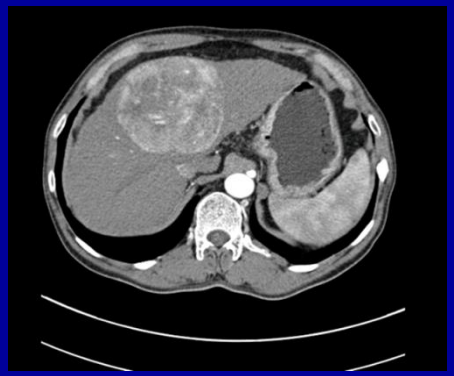
Disclosure slide

- Have received honorarium, research grants or consultancy fees from:
  - Sirtex Medical
  - Bayer Pharmaceutical
  - Ipsen
  - OncoSil
  - Glaxo-Smith-Kline
  - Merck Sharp and Dohme
  - Novartis

Most HCC presents locally Advanced

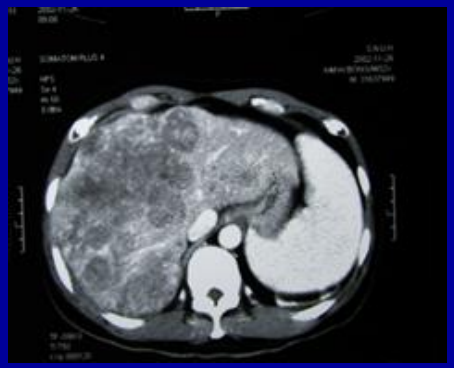
Early Stage HCC

- Lesions within the Milan Criteria
- criteria:
  - *Solitary tumour ≤ 5cm* OR *≤ 3 tumours, each < 3cm* AND *No invasion of blood vessels* and no distant spread



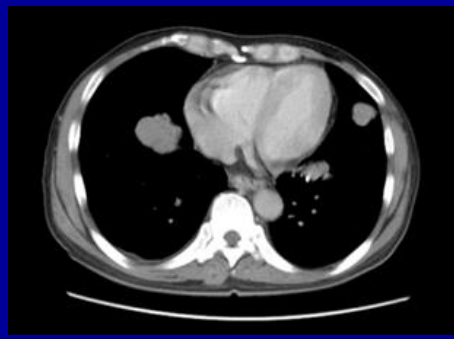
Locally Advanced HCC

- Lesions confined to the liver that are outside of the Milan criteria with or without vascular invasion



Metastatic HCC

- With good liver function (Child-Pugh A or early B)
- With poor liver function



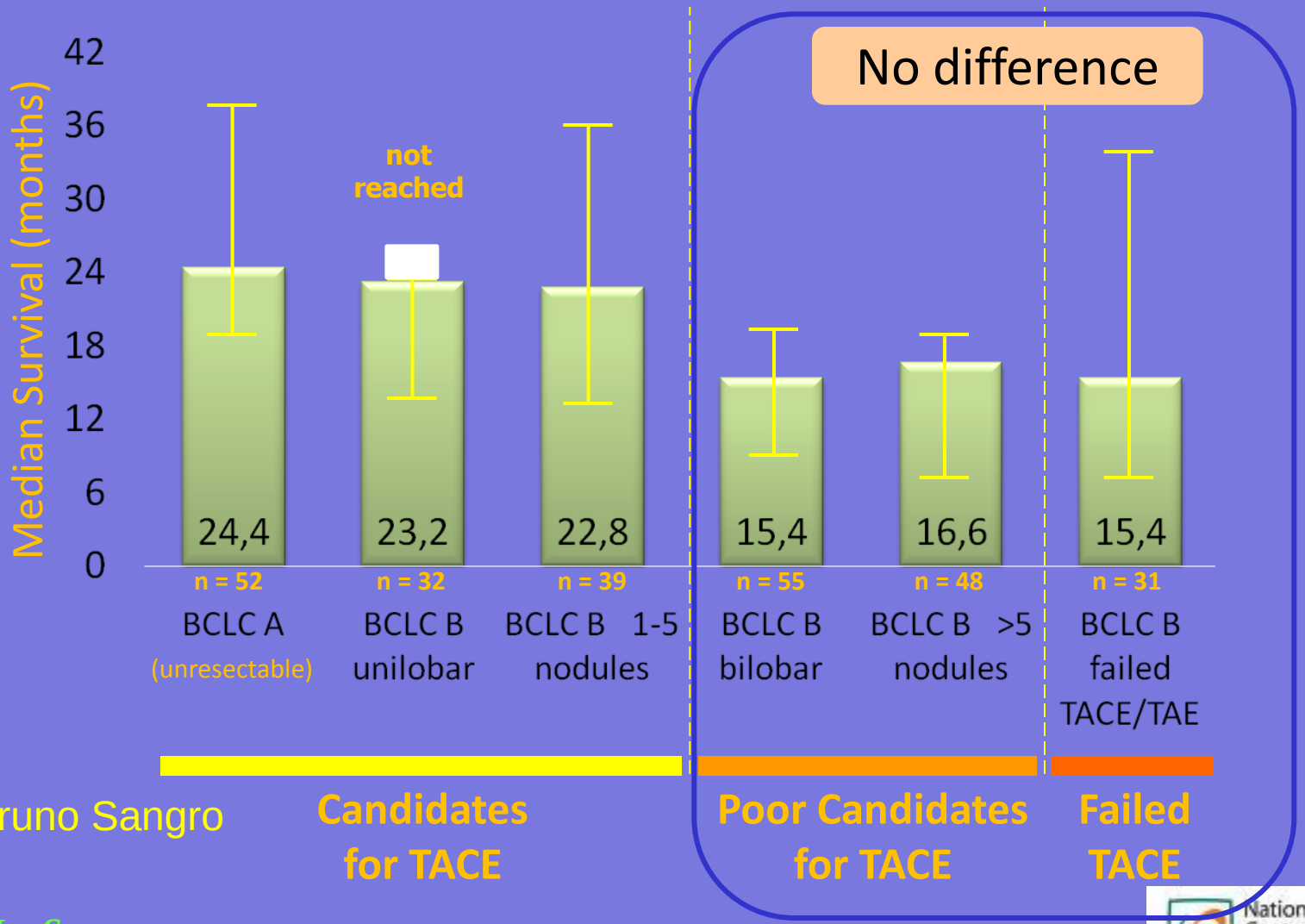
National Cancer Center Singapore Guidelines on Liver Cancer

http://www.nccs.com.sg/PatientCare/ComprehensiveLiverCancerClinic/Documents/CLCC guideline Final Ver to upload PDF 26092014.pdf

Main Loco-regional Therapies

- **Trans-arterial chemo-embolisation (TACE):**
  - widely used - disease control **approx 40%**
  - used mainly in *HCC*, *NETs* (includes DC Beads)
- **Selective Internal Radiation Therapy (SIRT):**
  - higher disease control **(approx 80%)**
  - SIR-Sphere®, Thera-Sphere®

Patient Outcomes According to Suitability for TACE in the ENRY Series



Courtesy Bruno Sangro

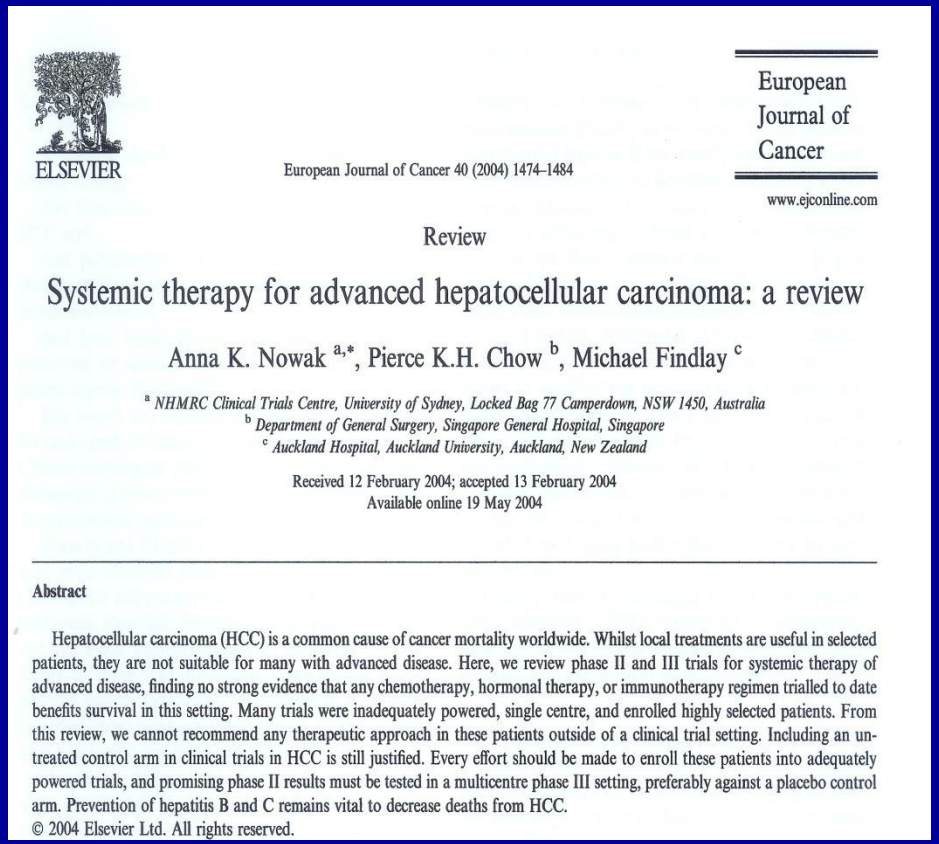
Sangro et al., Hepatology 2011;54:868-878

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National Cancer Centre Singapore
SingHealth

HCC is highly resistant to conventional systemic chemotherapy

- In spite of many phase III clinical trials, previously **no survival advantage** with any systemic therapy for advanced HCC
- 1st positive phase III trial: ***July 2007***, **Sorafenib** – an oral molecular targeted therapy



ELSEVIER

European Journal of Cancer 40 (2004) 1474–1484

European Journal of Cancer

www.ejconline.com

Review

Systemic therapy for advanced hepatocellular carcinoma: a review

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Abstract

Hepatocellular carcinoma (HCC) is a common cause of cancer mortality worldwide. Whilst local treatments are useful in selected patients, they are not suitable for many with advanced disease. Here, we review phase II and III trials for systemic therapy of advanced disease, finding no strong evidence that any chemotherapy, hormonal therapy, or immunotherapy regimen trialled to date benefits survival in this setting. Many trials were inadequately powered, single centre, and enrolled highly selected patients. From this review, we cannot recommend any therapeutic approach in these patients outside of a clinical trial setting. Including an untreated control arm in clinical trials in HCC is still justified. Every effort should be made to enroll these patients into adequately powered trials, and promising phase II results must be tested in a multicentre phase III setting, preferably against a placebo control arm. Prevention of hepatitis B and C remains vital to decrease deaths from HCC.

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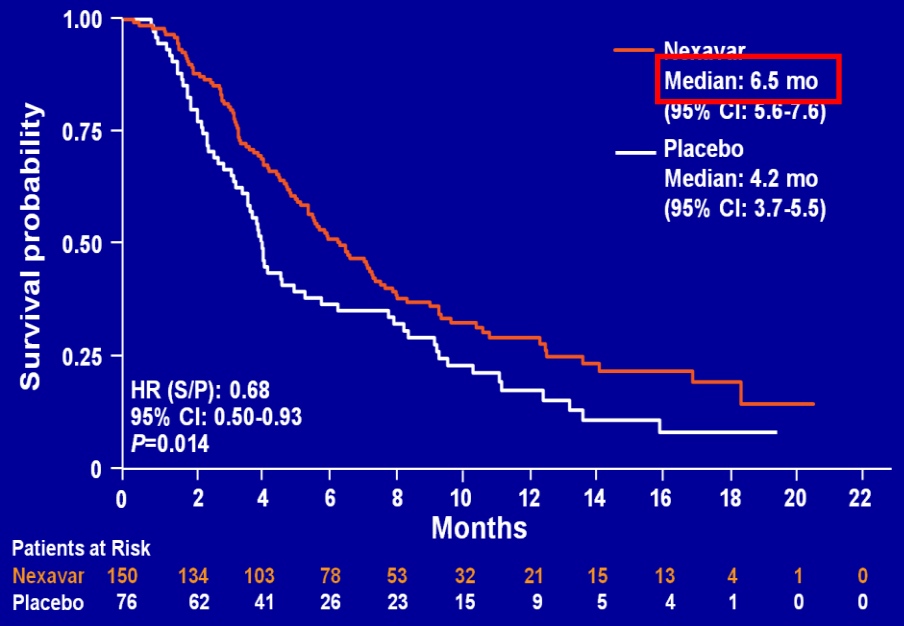
Novak, Chow, Findlay 2004

Results of the phase III sorafenib Trial

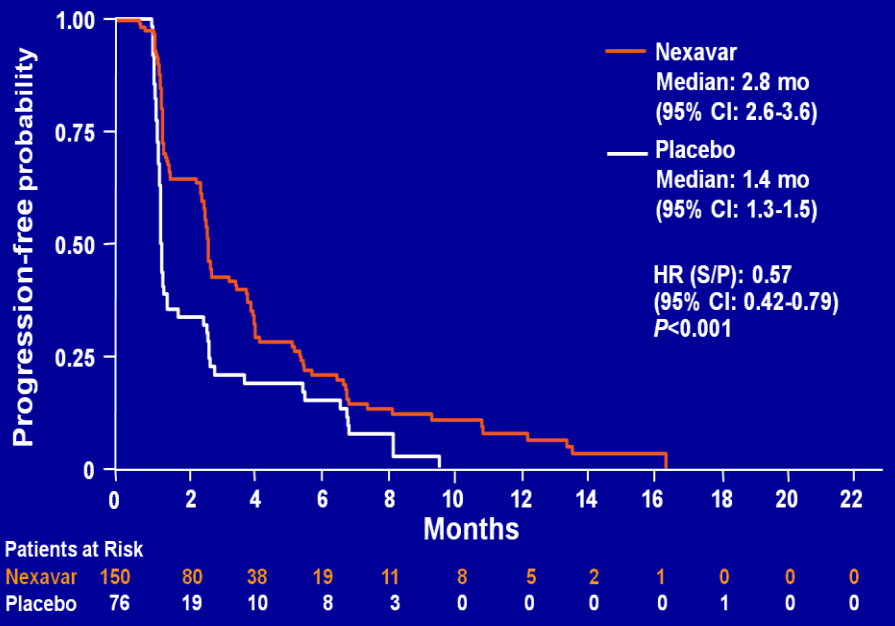
(Asia-Pacific patients) 2009

Child-Pugh A ECOG 0 -1

Overall Survival



Time to Progression



Improvement in survival of 2.3 months

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Cheng et al Lancet Oncol 2009

TACE-based phase III trials involving molecular targeted agents

Trial no	Sponsor	Size	Centers	Therapy 1	Therapy 2	PO	Start	End	Status	Protocol Chair
NCT00494299	Bayer	458	75 (Japan, Korea)	TACE + sorafenib	TACE + placebo	*TTP*	Apr-06	Nov-10	Completed (negative)	Bayer
Phase II NCT00855218	Bayer SPACE	307	107	DC-Beads + sorafenib	DC-BEADS + placebo	*TTP*	Mar-09	Mar-12	completed	Bayer
NCT01324076	Univ Coll, London	412	8 (UK)	DC-Beads + sorafenib	DC-BEADS + placebo	*PFS*	Nov-10	Nov-14	Recruiting	Tim Meyer
NCT01004978	ECOG	400	128 (US)	TACE + sorafenib	TACE + placebo	*PFS*	Oct-09	Sep-12	Recruiting	John Kauh
NCT01906216	Fourth Military Medical University	398	1 (China)	TACE + sorafenib	Sorafenib	*OS*	Sep-12	Mar-16	Recruiting	Guohong Han
NCT01829035	NCC, Korea	338	1 (Korea)	TACE + Sorafenib	TACE + Sorafenib	*OS*	Feb-13	Jul-16	Recruiting	Joong-Won Park
NCT01164202	Fed Francophone	190	3 (Frn)	TACE + Sunitinib	TACE + placebo	*OS*	Jul-10	Jul-13	Recruiting	M Hebbar
NCT01465464	Taiho	880	6 (Jap,Kor,Twn)	Orantinib and TACE	TACE + placebo	*OS*	Dec-10	May-17	Recruiting	Taiho
NCT00908752	BMS (BRISK TA)	870	102	TACE + Brivanib	TACE + placebo	*OS*	Aug-09	Mar-15	Recruiting	BMS

Impact of TACE-based phase III trials on Practice

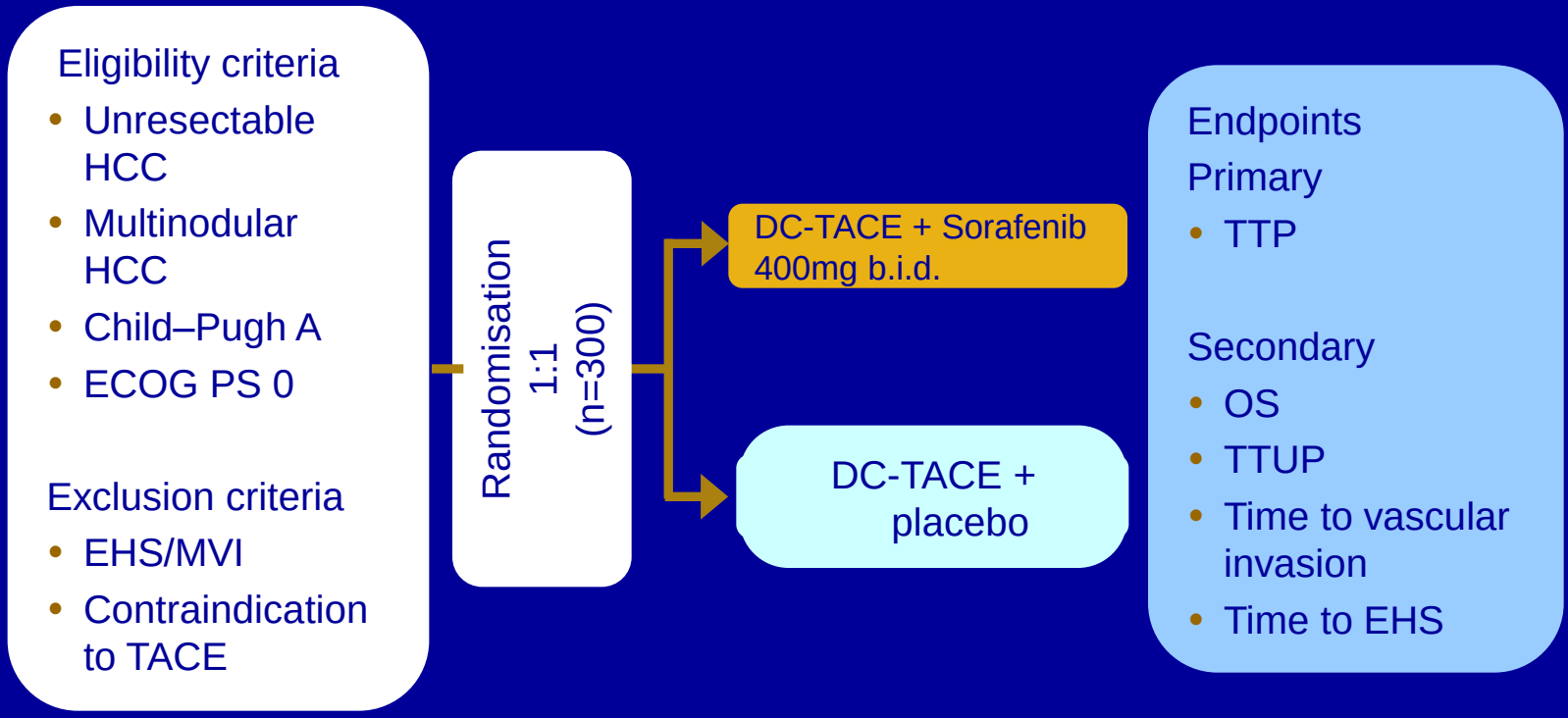
- Any positive phase III trial with OS as primary end-point will be likely to establish that combination as being superior to TACE alone in locally advanced disease

- TACE has little efficacy in HCC with PVT

SPACE
Sorafenib or Placebo in combination with TACE in hepatocellular carcinoma

Sorafenib or Placebo in combination with TACE for intermediate stage HCC

- International (Europe, Americas, Asia–Pacific), Phase II, randomised, double-blind study of Sorafenib® or placebo with TACE with DC Bead and doxorubicin



ECOG PS = Eastern Cooperative Oncology Group Performance Status
MVI = macrovascular invasion; TTUP = time to untreatable progression

- 2011 Kudo et al
- **Phase III**
- Patients ≥ 25% response to TACE after 1 – 2 sessions
- PVT excluded
- **Placebo controlled**
- Maximum target lesion 70 mm
- 73.4% ≤ 3 lesions

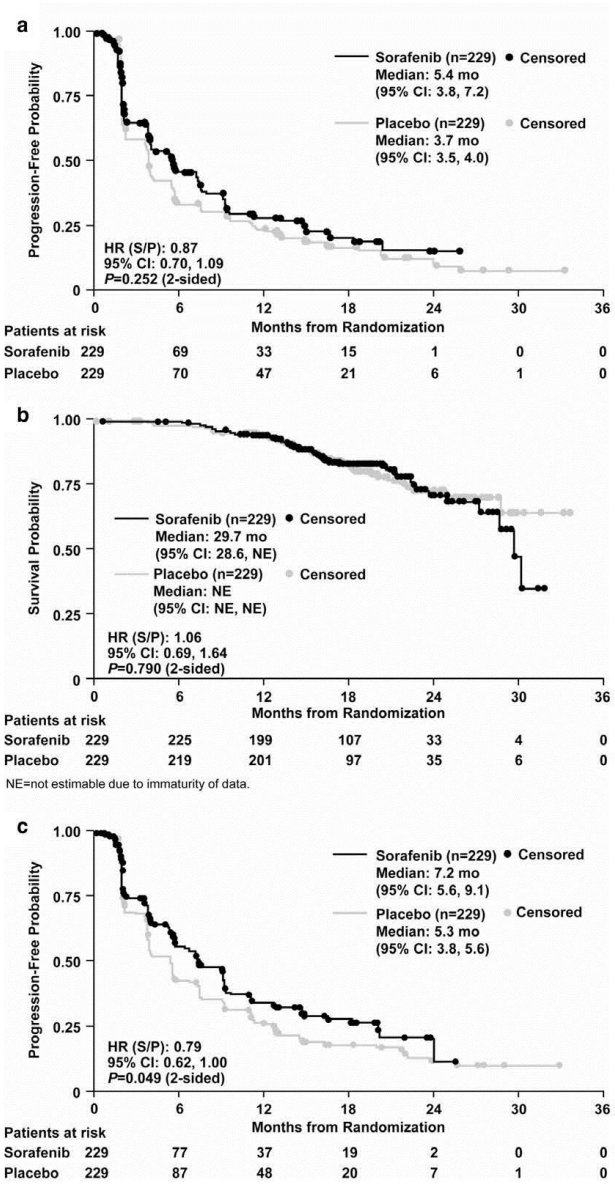


Fig. 2 – Kaplan–Meier analysis of time to progression (TTP) and overall survival (OS). (a) TTP by central review (primary intention-to-treat (ITT) analysis); (b) OS (secondary ITT analysis) and (c) TTP by investigator assessment (exploratory ITT analysis).

Ginsenoside Rg3 Improves Transarterial Chemoembolization Treatment in Chinese Patients with Advanced Hepatocellular Carcinoma

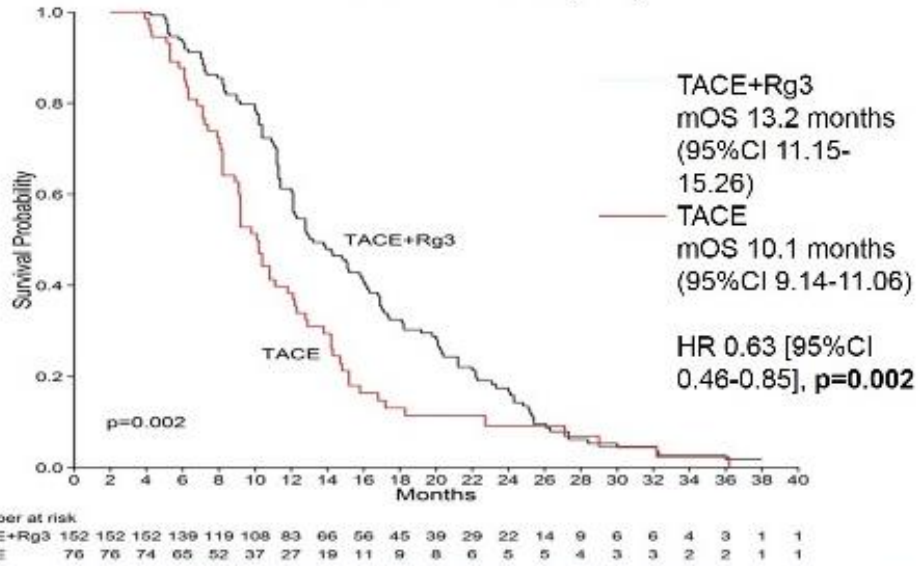
Bo Zhou, Jianhua Wang, Zhiping Yan

Department of Interventional Radiology, Fudan University Zhongshan Hospital, Shanghai, China

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- Ginseng Saponin
- Open labelled
- RCT
- 152 vs 76
- No prior systemic therapy

Overall survival (OS)



TACE+Rg3
mOS 13.2 months
(95%CI 11.15-15.26)
TACE
mOS 10.1 months
(95%CI 9.14-11.06)

HR 0.63 [95%CI 0.46-0.85], **p=0.002**

6-month OS rate were 92.8% in TACE+Rg3 vs 85.5% in TACE groups (p=0.081), 12-month OS rate of 54.6 % vs 35.5% (p=0.008)

Table 2 Response Rate

	TACE+Rg3 (n=152)	TACE (n=76)	P
Complete response	0(0)	0(0)	
Partial response	30(19.7)	5(6.6)	0.009
Stable disease	76(50.0)	34(44.7)	0.453
Progressive disease	42(27.7)	29(38.2)	0.106
Not accessible	4(2.6)	8(10.5)	
DCR %	106(69.7)	39(51.3)	0.012
95%CI	63.1-77.7	41.4-63.8	

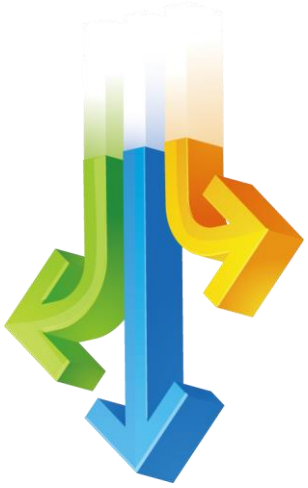
There was no significant difference in median TTP and TTUP between the two groups (4.3m vs 3.2m p=0.151). TTUP (8.3 m vs 7.3 m, p=0.063).

Concurrent sorafenib and TACE therapy improved survival of patients with unresectable hepatocellular carcinoma compared to TACE alone

Wan XY et al

Aim

- We tested the hypothesis in this study that **combined therapy may improve patient survival**

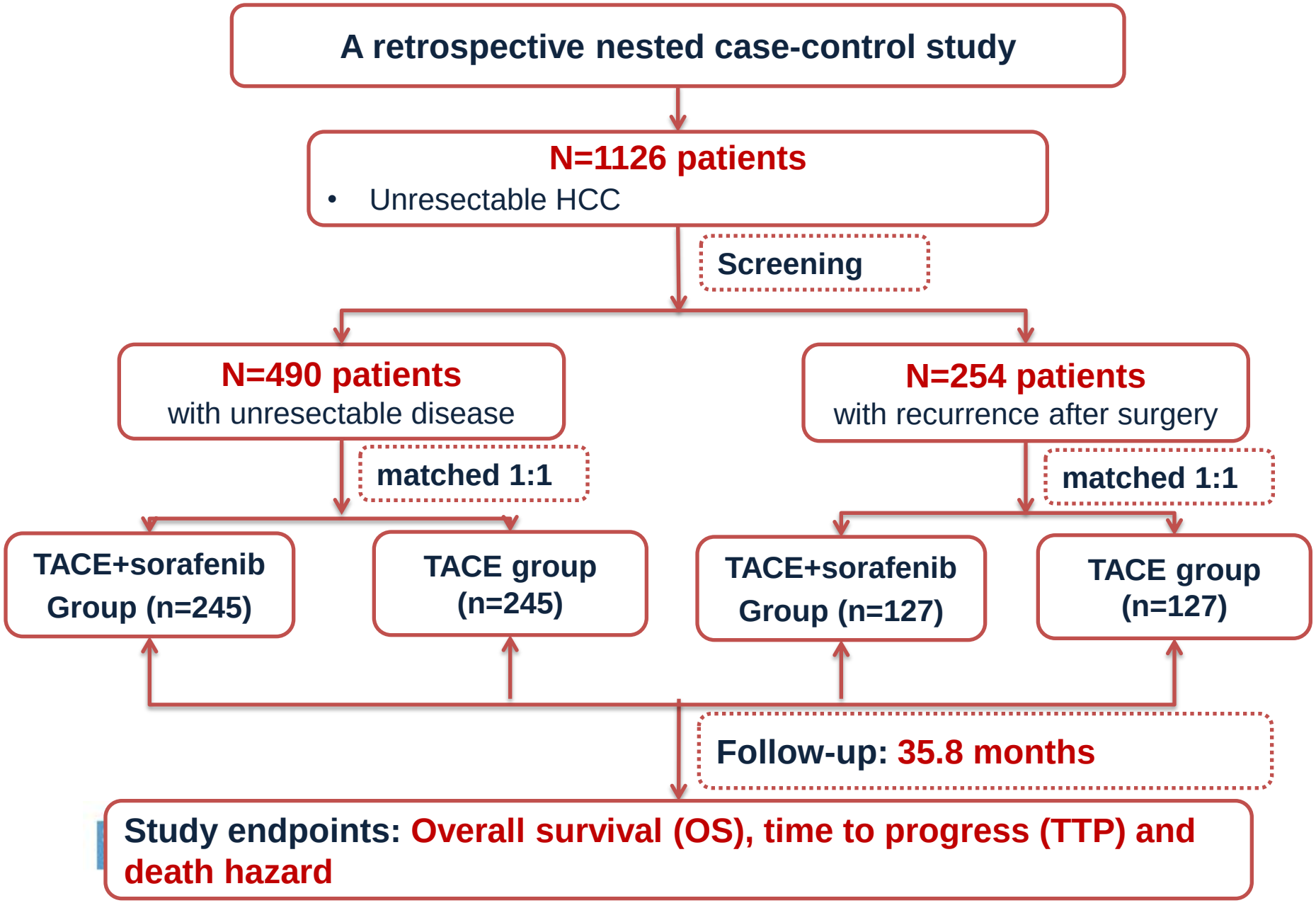


Methods

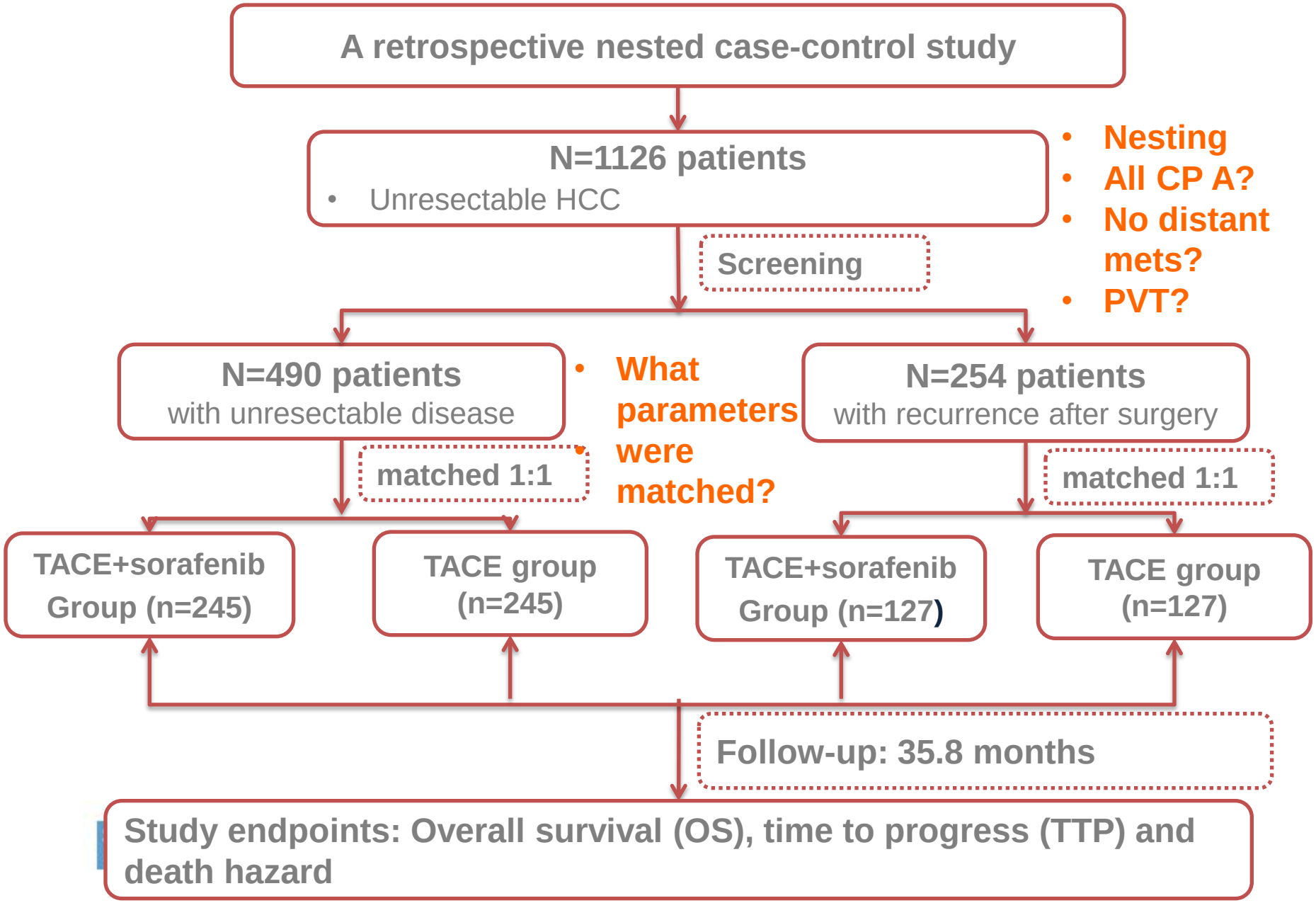
- A retrospective nested case-control study

Retrospective **Nested** Case Control Study - **all incident cases** in the cohort are matched against some number of controls selected for each case from that case's matched risk set.

Methods


A retrospective nested case-control study
N=1126 patients
• Unresectable HCC
Screening
N=490 patients
with unresectable disease
N=254 patients
with recurrence after surgery
matched 1:1
matched 1:1
TACE+sorafenib Group (n=245)
TACE group (n=245)
TACE+sorafenib Group (n=127)
TACE group (n=127)
Follow-up: 35.8 months
Study endpoints: Overall survival (OS), time to progress (TTP) and death hazard

Methods


A retrospective nested case-control study
N=1126 patients
• Unresectable HCC
Screening
• Nesting
• All CP A?
• No distant mets?
• PVT?
N=490 patients
with unresectable disease
N=254 patients
with recurrence after surgery
• What parameters were matched?
matched 1:1
matched 1:1
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Child-Pugh ?
Metastases?
PVT?

Table 1. Demographic distribution of the study participants

	TACE+sorafenib (n=245)	TACE (n=245)	p-value
Age (y)			1.000
<50	115 (46.9%)	115 (46.9%)	
≥50	130 (53.1%)	130 (53.1%)	
Gender			1.000
Male	218 (89%)	218 (89%)	
Female	27 (11%)	27 (11%)	
Tumor size (cm)			1.000
<5	153 (62.4%)	153 (62.4%)	
≥5	92 (37.6%)	92 (37.6%)	
Tumor number			1.000
Single	107 (43.7%)	107 (43.7%)	
Multiple	138 (56.3%)	138 (56.3%)	

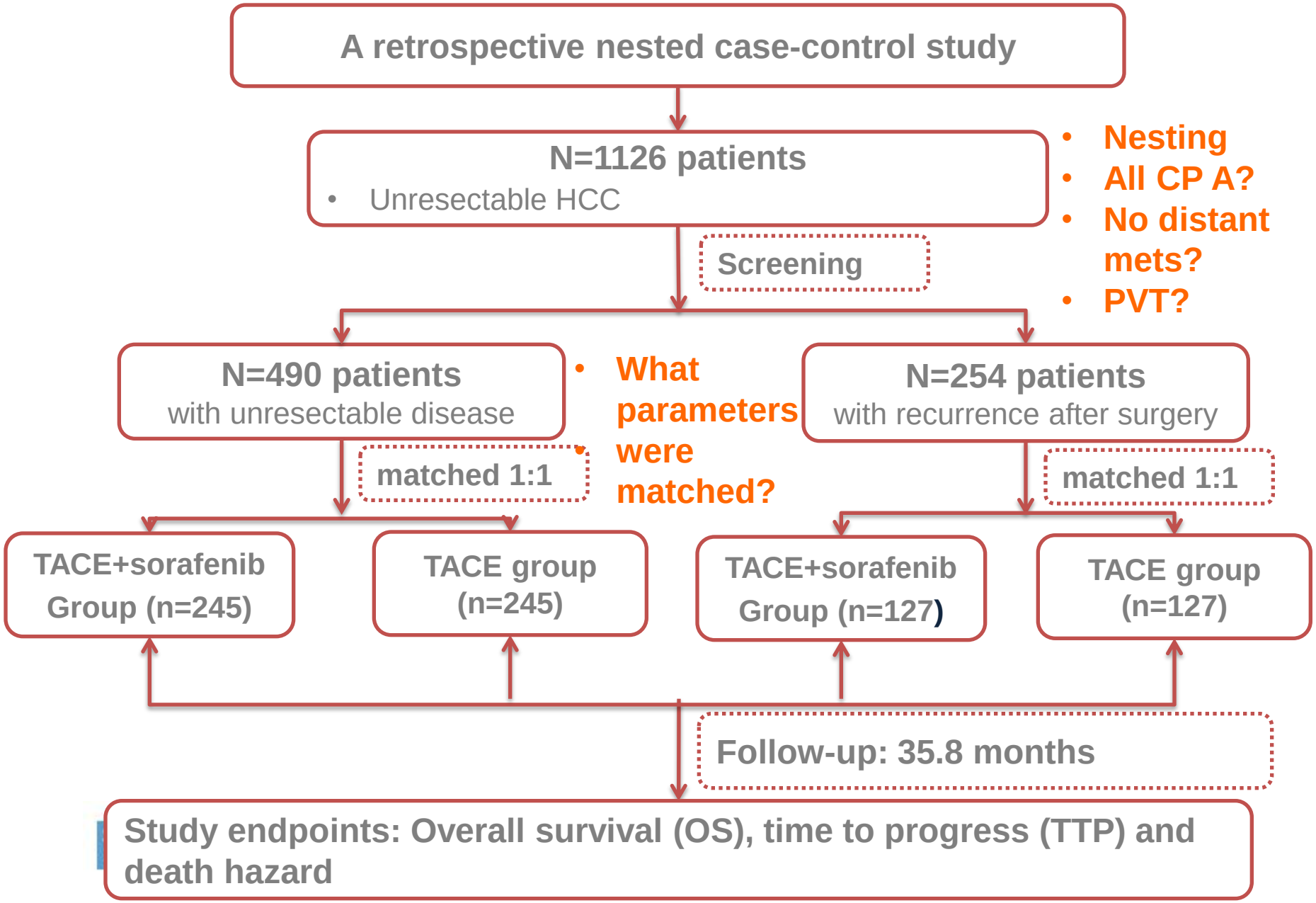
TACE, transarterial chemoembolization

Table 2. Demographic distribution of the patients with disease recurrence

	TACE+sorafenib (n=127)	TACE (n=127)	p-value
Age (y)			1.000
<50	69 (54.3%)	69 (54.3%)	
≥50	58 (45.7%)	58 (45.7%)	
Gender			1.000
Male	116 (91.3%)	116 (91.3%)	
Female	11 (8.7%)	11 (8.7%)	
Tumor size (cm)			1.000
<5	99 (78%)	99 (78%)	
≥5	28 (22%)	28 (22%)	
Tumor number			1.000
Single	54 (42.5%)	54 (42.5%)	
Multiple	73 (57.5%)	73 (57.5%)	

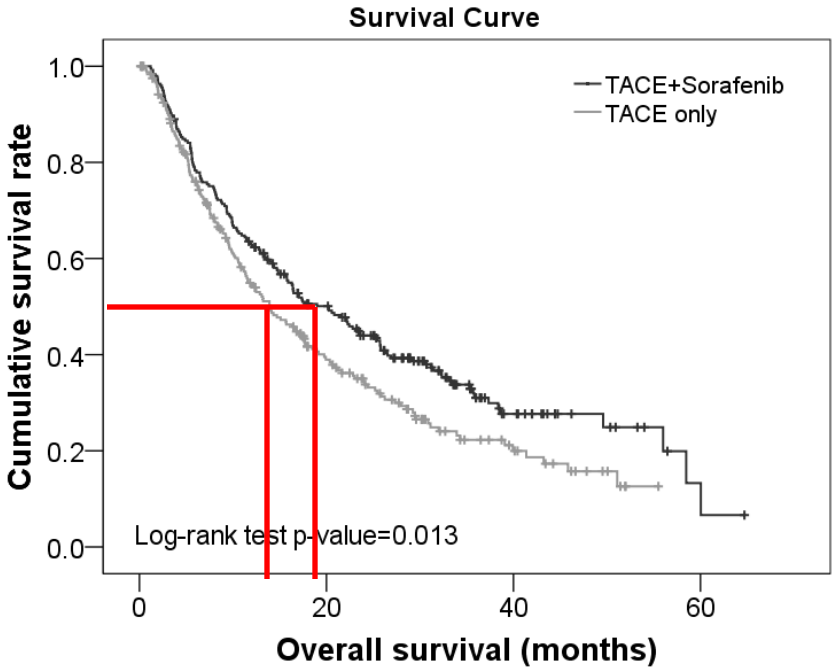
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Methods

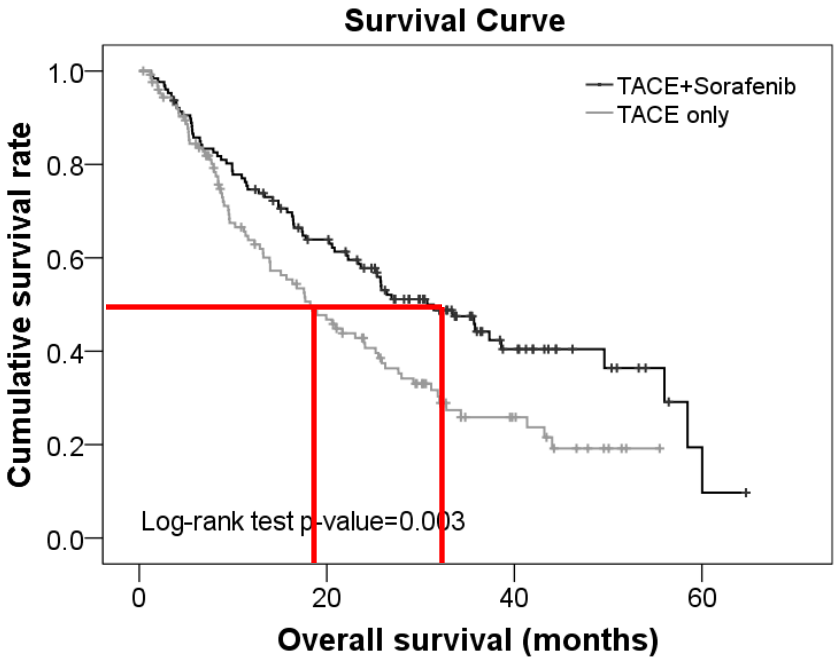

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Result

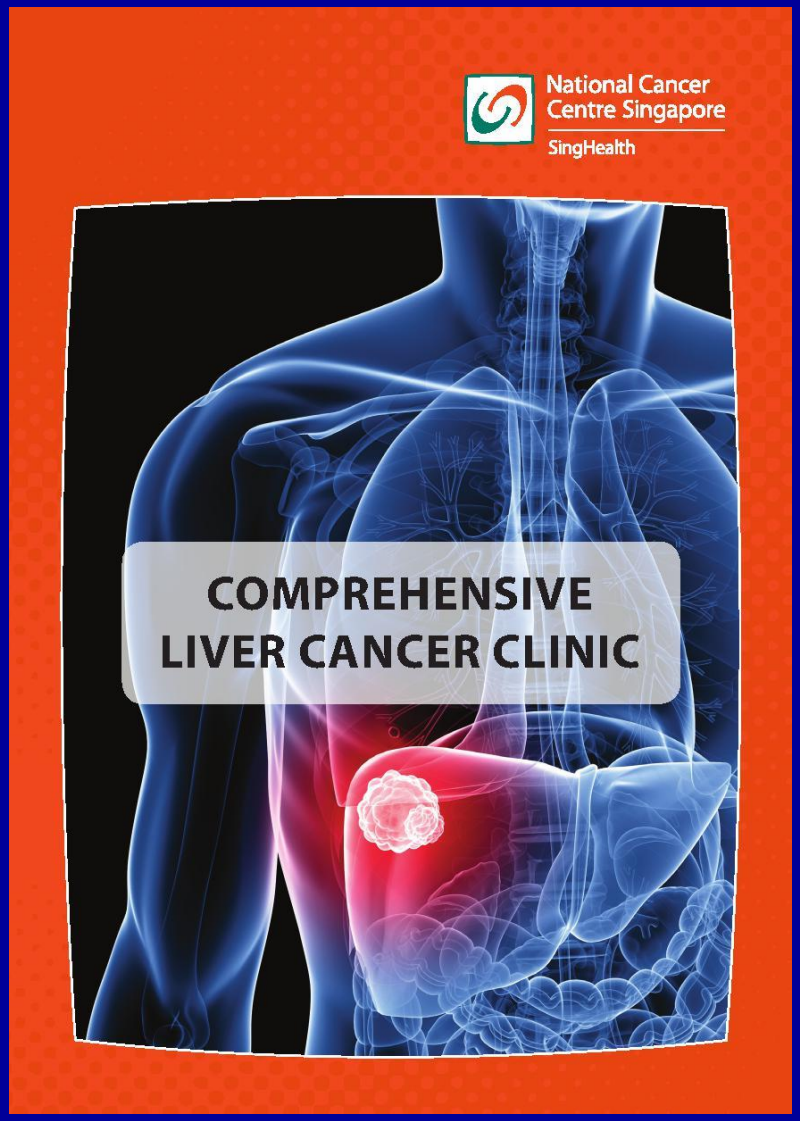
- For patients with unresectable disease, **the survival rate was significantly higher in the TACE+sorafenib group** compared with TACE alone group



- For patients with recurrence after surgery, **the survival rate was significantly higher in the TACE+sorafenib group** compared with TACE alone group



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Thank You!

National Cancer Center Singapore Guidelines on Liver Cancer

http://www.nccs.com.sg/PatientCare/ComprehensiveLiverCancerClinic/Documents/CLCC guideline Final Ver to upload PDF 26092014.pdf