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Efficacy of liver-directed combined radiotherapy in locally advanced hepatocellular carcinoma with portal vein tumor thrombosis

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Introduction and Objective

- **Portal vein tumor thrombosis (PVTT)** is a well-known **poor prognostic factor** for patients with HCC

- **Current guidelines only recommend the use of systemic treatment** for this locally advanced HCC patients presenting PVTT

- However, the **degree of PVTT can be heterogeneous** (from focal to spread to the main trunk), which is related to a wide range of prognoses

- We aimed to investigate the **clinical efficacy of liver-directed combined radiotherapy (LD-CRT) compared with that of sorafenib**, a recommended treatment until recently for locally advanced HCC presenting PVTT, using a multinational patient cohort

Materials and Methods

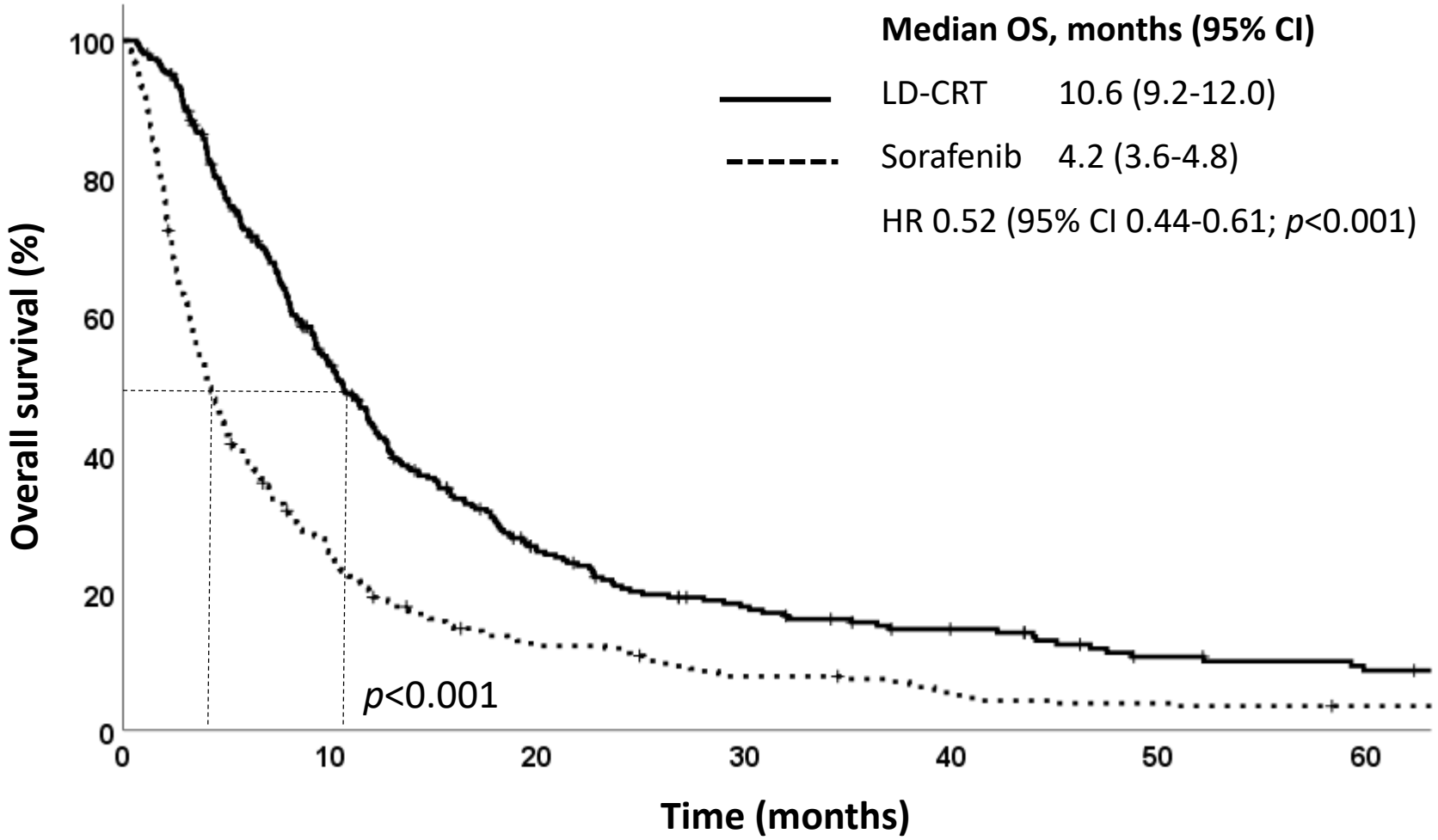
- **Patient selection**
  - 10 Tertiary hospitals in Asia
  - Clinically/pathologically diagnosed HCC patients with PVTT
  - Treated with sorafenib or LD-CRT (CCRT, TACE+RT, TACE+RFA+RT)
  - Patients with unknown PVTT extent or extrahepatic disease were excluded
  - Final cohort : Sorafenib n=360, LD-CRT n=675

- **Statistical analysis**
  - 1:1 Propensity score matching with the nearest neighbor method
  - Factors for propensity score matching: Sex, Age, ECOG performance status, prior treatment history, tumor size, disease extent, PVTT type
  - Final cohort : Sorafenib n=305, LD-CRT n=305

Patient characteristics

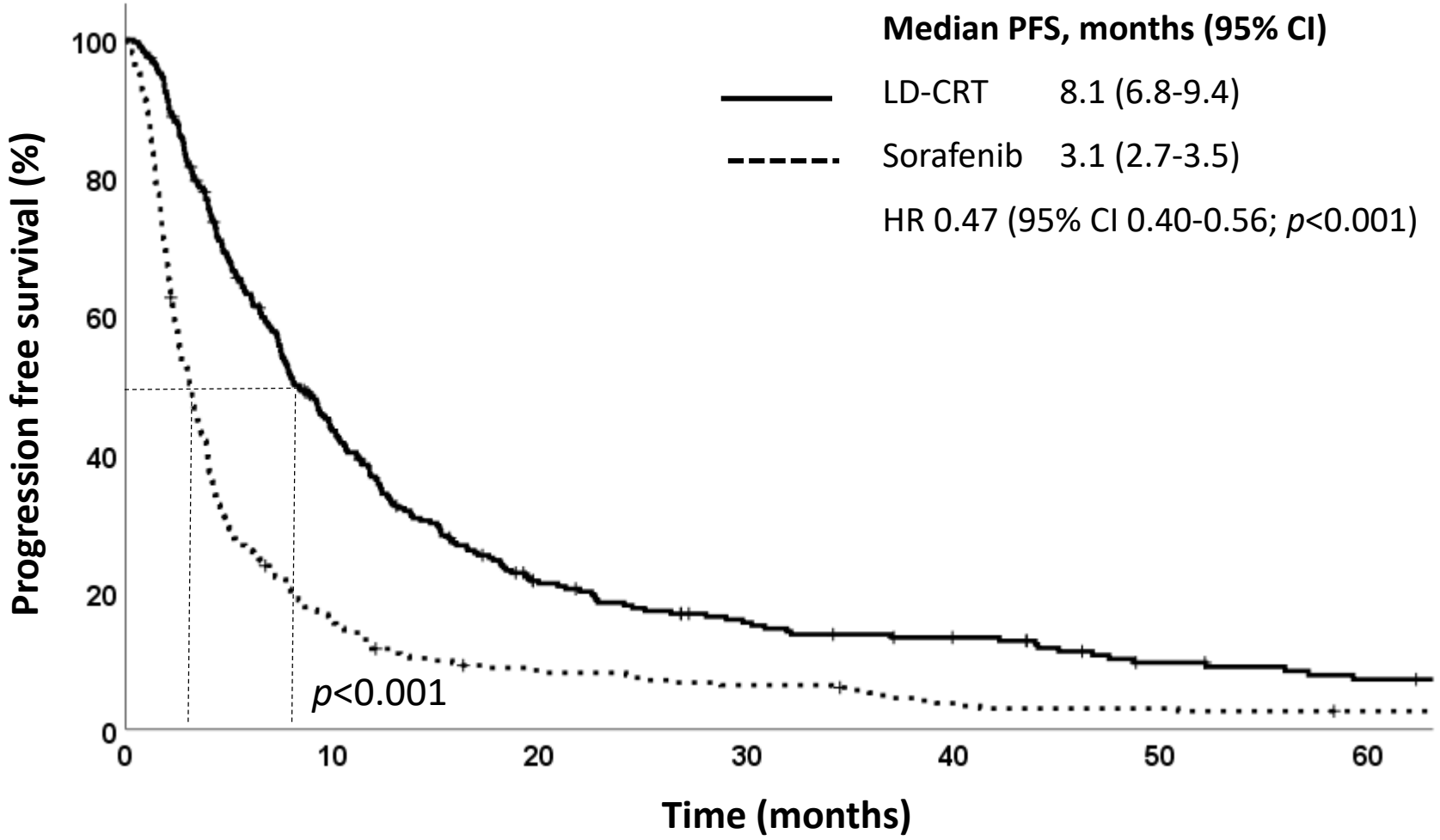
	After PSM		
	Sorafenib (N=305)	LD-CRT (N=305)	*p* value
Median age [IQR], years	59 [51-67]	57 [50-65]	0.090
Child-Pugh class, n (%)			0.777
A	230 (75.4)	233 (76.4)	
B-C	75 (24.6)	72 (23.6)	
Prior treatment history, n (%)			0.321
Yes	126 (41.3)	114 (37.4)	
Median AFP [IQR], ng/mL	962.3 [45.7-15769.0]	443.1 [26.7-9828.0]	0.602
Median tumor size [IQR], cm	8.4 [5.5-11.9]	8.4 [5.3-11.0]	0.907
Disease extent			0.257
Bilateral	170 (55.7)	156 (51.1)	
Lymph node status			0.257
Involved	40 (13.1)	31 (10.2)	
PVTT type (Cheng's criteria)			0.945
I	16 (5.2)	12 (3.9)	
II	164 (53.8)	168 (55.1)	
III	121 (39.7)	124 (40.7)	
IV	4 (1.3)	1 (0.3)	

Results



LD-CRT	305	149	64	40	28	17	13
Sorafenib	305	76	35	21	14	10	8

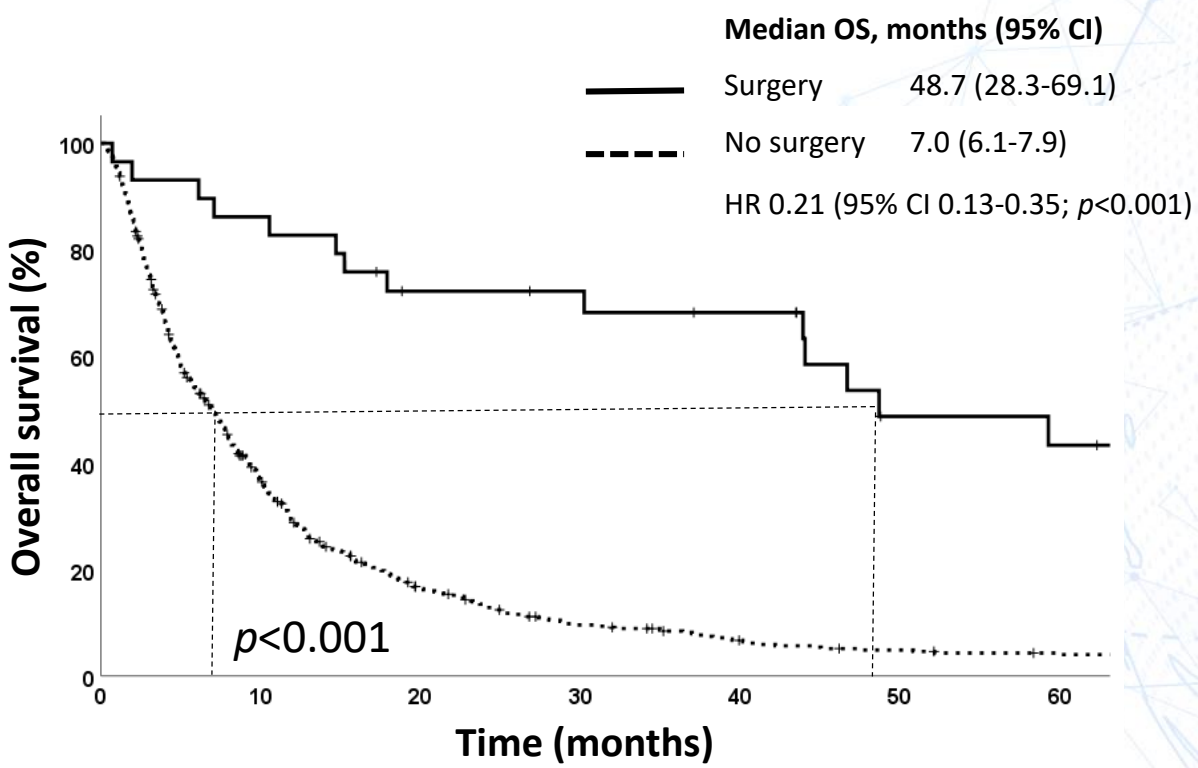
Results



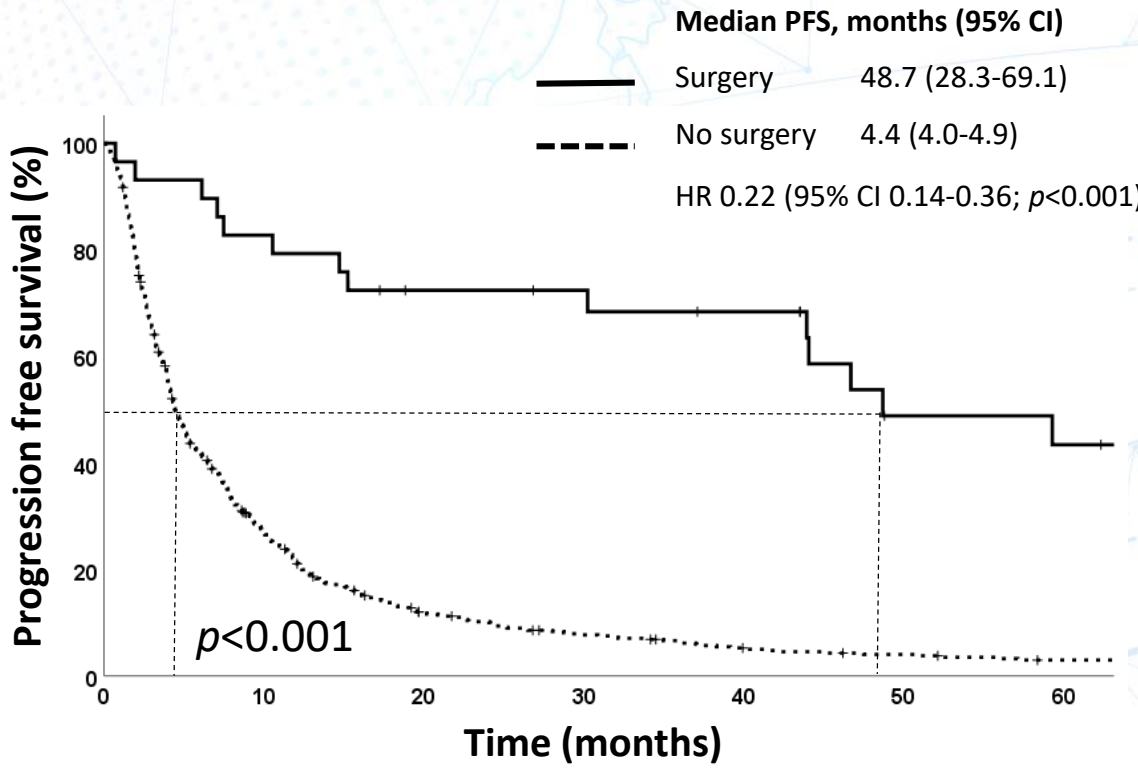
LD-CRT	305	124	54	36	28	17	12
Sorafenib	305	48	24	18	10	8	6

Results

Conversion rate to surgery: LD-CRT 8.5% vs. sorafenib 1.0% (p<0.001)



Surgery	29	25	19	18	16	9	8
No Surgery	581	200	80	43	26	18	13



Surgery	29	24	19	18	16	9	8
No Surgery	581	148	59	36	22	16	10

Prognostic factors for OS

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Treatment (LD-CRT vs Sorafenib)	0.52	0.44-0.61	<0.001	0.46	0.39-0.55	<0.001
Sex (Female vs Male)	0.98	0.77-1.26	0.887	N.S.		
Age	1.00	0.99-1.01	0.425	N.S.		
ECOG PS (2-3 vs 0-1)	1.60	1.19-2.14	0.002	N.S.		
Child-Pugh class (B-C vs A)	1.88	1.55-2.28	<0.001	1.69	1.38-2.07	<0.001
Prior treatment history (Yes vs No)	0.91	0.77-1.09	0.308	N.S.		
Log(Pretreatment AFP)	1.27	1.19-1.35	<0.001	1.23	1.15-1.31	<0.001
Tumor size	1.05	1.04-1.07	<0.001	1.05	1.03-1.07	<0.001
Disease extent (Bilateral vs Unilateral)	1.35	1.14-1.61	<0.001	N.S.		
LN status (Involved vs Not involved)	1.39	1.08-1.79	0.011	N.S.		
PVTT type (III, IV vs I, II)	1.28	1.08-1.52	0.004	N.S.		

Treatment related toxicity

	Sorafenib (N=360)			LD-CRT (N=675)		
	Grade 1-2	Grade 3-4	Total	Grade 1-2	Grade 3-4	Total
Acute toxicity (within 3 months)						
Fatigue	21 (5.8%)	0 (0.0%)	21 (5.8%)	13 (1.9%)	2 (0.3%)	15 (2.2%)
Nausea	9 (2.5%)	1 (0.3%)	10 (2.8%)	18 (2.7%)	3 (0.4%)	21 (3.1%)
Vomiting	9 (2.5%)	0 (0.0%)	9 (2.5%)	19 (2.8%)	0 (0.0%)	19 (2.8%)
Anorexia	22 (6.1%)	0 (0.0%)	22 (6.1%)	25 (3.7%)	2 (0.3%)	27 (4.0%)
Fever	4 (1.1%)	2 (0.6%)	6 (1.7%)	14 (2.1%)	0 (0.0%)	14 (2.1%)
Hand-foot syndrome	26 (7.2%)	2 (0.6%)	28 (7.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Skin rash	35 (9.7%)	4 (1.1%)	39 (10.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Leukopenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (0.7%)	0 (0.0%)	5 (0.7%)
Diarrhea	61 (16.9%)	4 (1.1%)	65 (18.1%)	7 (1.0%)	0 (0.0%)	7 (1.0%)
AST/ALT elevation	31 (8.6%)	16 (4.4%)	47 (13.0%)	52 (7.7%)	21 (3.1%)	73 (10.8%)
Bilirubin elevation	27 (7.5%)	15 (4.2%)	42 (11.7%)	38 (5.6%)	26 (3.9%)	64 (9.5%)
Abdominal pain	25 (6.9%)	2 (0.6%)	27 (7.5%)	38 (5.6%)	1 (0.2%)	39 (5.8%)
Late toxicity (after 3 months)						
Fatigue	2 (0.6%)	1 (0.3%)	3 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypertension	2 (0.6%)	0 (0.0%)	2 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GI bleeding	13 (3.6%)	10 (2.8%)	23 (6.4%)	0 (0.0%)	5 (0.7%)	5 (0.7%)
Duodenal ulcer	0 (0.0%)	1 (0.3%)	1 (0.3%)	6 (0.9%)	0 (0.0%)	6 (0.9%)

Conclusions

- Analysis of a multinational patient cohort revealed that **LD-CRT improved survival outcomes with a higher conversion rate to curative surgery** in patients with locally advanced HCC presenting PVTT

- Although further prospective studies are warranted, **active multimodal local treatment involving radiotherapy** is suggested for locally advanced HCC presenting PVTT