Supplementary Material for Fako et al. Gene signature predictive of hepatocellular carcinoma patient response to transarterial chemoembolization

Supplementary Methods

Clinical Specimens

Test Cohort

The training/validation cohort was derived from the Liver Cancer Institute (LCI) cohort in which a total of 247 HCC patients were prospectively recruited and underwent radical resection at the Liver Cancer Institute and Zhongshan Hospital (Fudan University) between 2002 and 2003. Microarray profiling of LCI cohort patients was performed previously. Briefly, gene expression using RNA extracted from flash-frozen tumor tissue were previously profiled using Affymetrix Human Genome U133 2.0 microarray platform in two formats, Affymetrix GeneChip HG-U133A 2.0 or 96 HT HG-U133A 2.0 microarray platform, each containing the same probesets, as described (NCBI GEO accession number GSE14520). Data were processed by combining the CEL files from the two Affymetrix series using the matchprobes package in the R programming environment. Thereafter, the RMA method in the R affy package was used to obtain probe set expression summaries. Both raw and processed data are available in the GSE14520 at NCBI GEO. This dataset contains 488 samples: 247 tumor samples and 239 non-tumor samples, with expression information of the 13,101 genes in which signal could be measured. Of the 488 tumor and non-tumor samples contained in this data set, all 247 patients with tumor tissue available were considered for this study. Archived RNA extracted from the flash-frozen tumor tissue was stored at -80°C.

All TACE patients from the LCI cohort received a combination of cisplatin, fluorouracil and mitomycin C. Of the remaining patients, 86 received no additional therapy (Resection Only) and 51 received other forms of therapy (Other Therapy), not including TACE, following surgical resection. Patients who were administered TACE as adjuvant therapy following resection were those who were deemed to have a high probability of relapse (e.g. tumor size > 10 cm; >1 tumor nodules; or with vascular invasion, etc.). In this context, TACE is used for both diagnosis and treatment, in which digital subtraction angiography is performed to identify any tumor staining in the liver following resection. If tumor stains are noted, the size, location and number of stains are evaluated and TACE treatment is performed with superselective catheterization. If no tumor stains are noted, 1/3 of the standard dose of chemotherapy and lipiodol are injected into the hepatic artery. Patients designated as Other Therapy did not receive TACE during their treatment. Following surgical resection, Other Therapy patients received portal vein chemotherapy, interferon alfa therapy, radiofrequency ablation, percutaneous ethanol injection, or traditional Chinese medicine, or a combination thereof, and were treated outside usual clinical guidelines.

Validation

In the Hong Kong test cohort, patients who received TACE were those who were judged to have a high risk of recurrence following resection by the operating surgeons. The presence of tumor vs. non-tumor tissue was verified by H&E staining, and tumor tissue was collected by scraping five 5μm tumor sections for each patient. Total RNA was isolated using the Roche High Pure FFPET RNA Isolation Kit (Indianapolis, IN) according to manufacturer's instructions. All patients in the Hong Kong test cohort received cisplatin during the TACE procedure.

For the Shandong test cohort, patients who received TACE were those who were judged to have a high risk of recurrence following resection by the operating surgeons. The presence of tumor tissue was verified by H&E staining. Tumor tissue was collected by scraping five 10μm tumor sections for each patient. Total RNA was isolated using a MasterPure RNA Purification Kit (Epicenter, Madison, WI) according to manufacturer's instructions. For patients in the Shandong cohort, doxorubicin and cisplatin-based regimens were predominantly used.

For the Mainz test cohort, patients were treated with palliative TACE in accordance with BCLC guidelines. Total RNA was isolated using a peqGOLD Total RNA Kit (VWR, Darmstadt, Germany) according to manufacturer's instructions. For patients in the Mainz cohort, most patients received doxorubicin with drug-eluting beads (DEB TACE), while a minority of patients received TACE with Mitomycin C.

Signature Development and Patient Assignment

Bioinformatic analyses, including class comparison and survival risk prediction algorithms, were then used to identify genes that were predictive of overall survival in the group of 105 patients receiving TACE, but not in 86 other patients who received no additional therapy following resection. All bioinformatic analyses were performed using BRB-ArrayTools (Bethesda, MD).

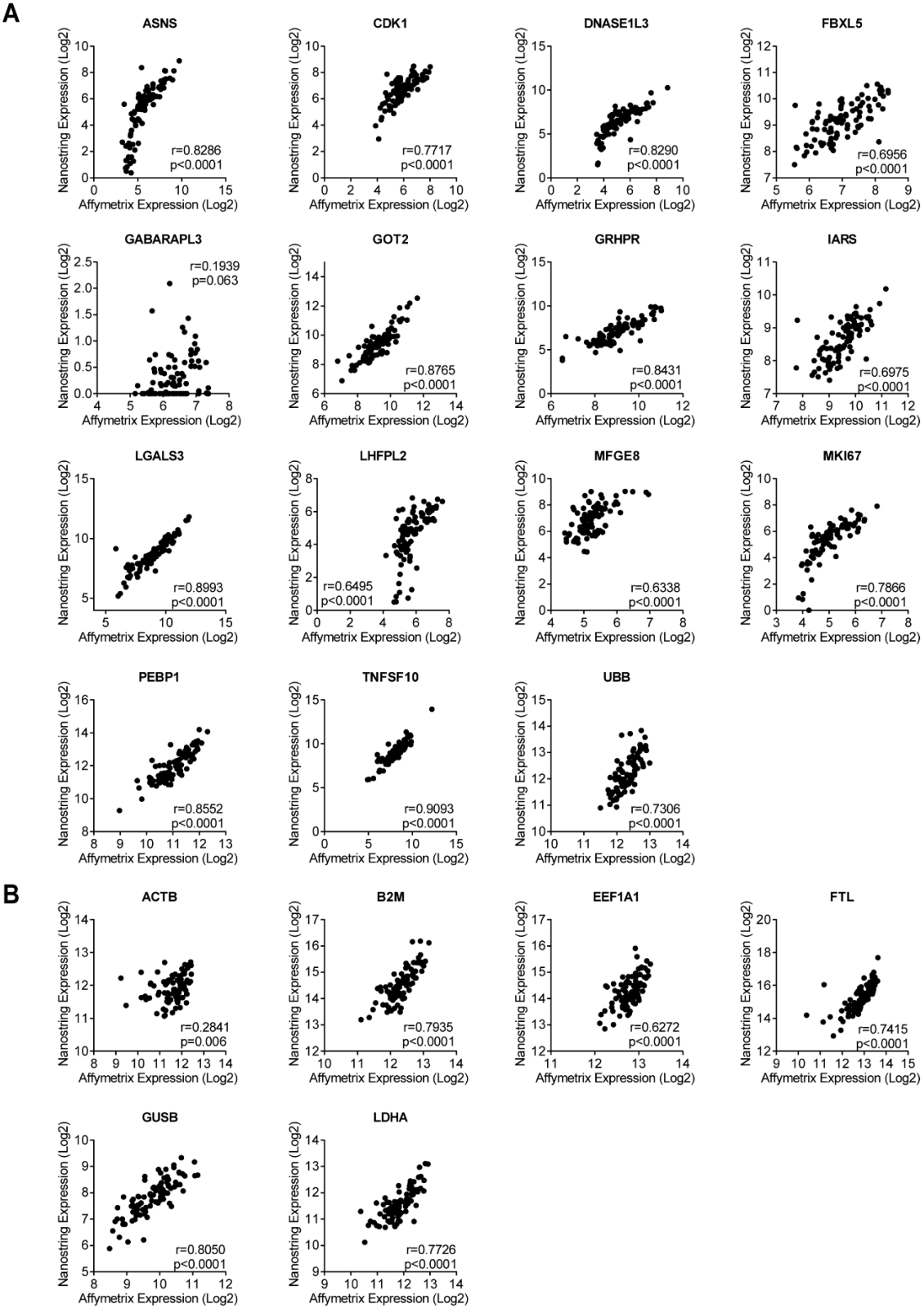
TACE Navigator was developed using a custom nCounter Gene Expression Codeset from NanoString (Seattle, Washington), consisting of 15-signature genes and six control genes. NanoString Digital Gene Expression Analysis was performed by the Center for Cancer Research Genomics Core in 93 TACE patients from the training/validation cohort. A prognostic index equation prediction module based on the expression of each signature gene was created using the survival risk prediction function in BRB-ArrayTools. Validation was performed using 10-fold cross validation.

NanoString analysis was then performed in a double-blind manner in the test and verification cohorts. Gene expression, measured by NanoString counts, was Log2 transformed and then converted to Z-score within each cohort. Patients were assigned into predicted Responders or Non-Responder groups using the prognostic index equation. Data were subsequently decoded and clinical data for each patient was obtained.

Univariable and Multivariable Analysis

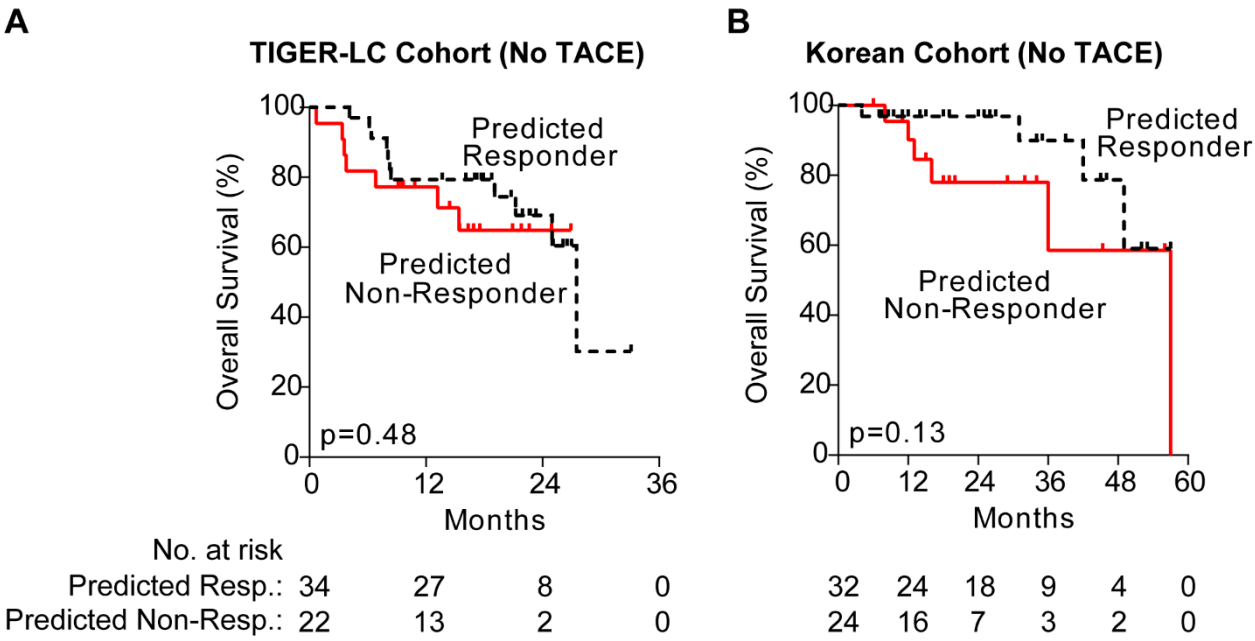
Univariable and multivariable analyses were performed with Cox proportional hazards regression analysis using STATA 14.0 (College Station, TX). The association of each clinical variable on survival was first evaluated with univariable analysis, followed by multivariable analysis, which included clinical variables that were significantly associated with survival in the univariable analysis. Age grouping was chosen by median age in the training/validation cohort. Alanine aminotransferase and alpha-fetoprotein groupings were chosen based on commonly used normal vs. abnormal clinical values. For TNM staging, stage I indicates a single tumor with no vascular invasion whereas stage II and greater indicates that multiple tumors or vascular invasion has taken place, thus groups II and III were grouped together. No multicollinearity of covariates was found, and the proportional hazards assumption was met in the final models.

Supplementary Figure 1. Affymetrix expression of TACE Navigator genes is correlated to NanoString expression



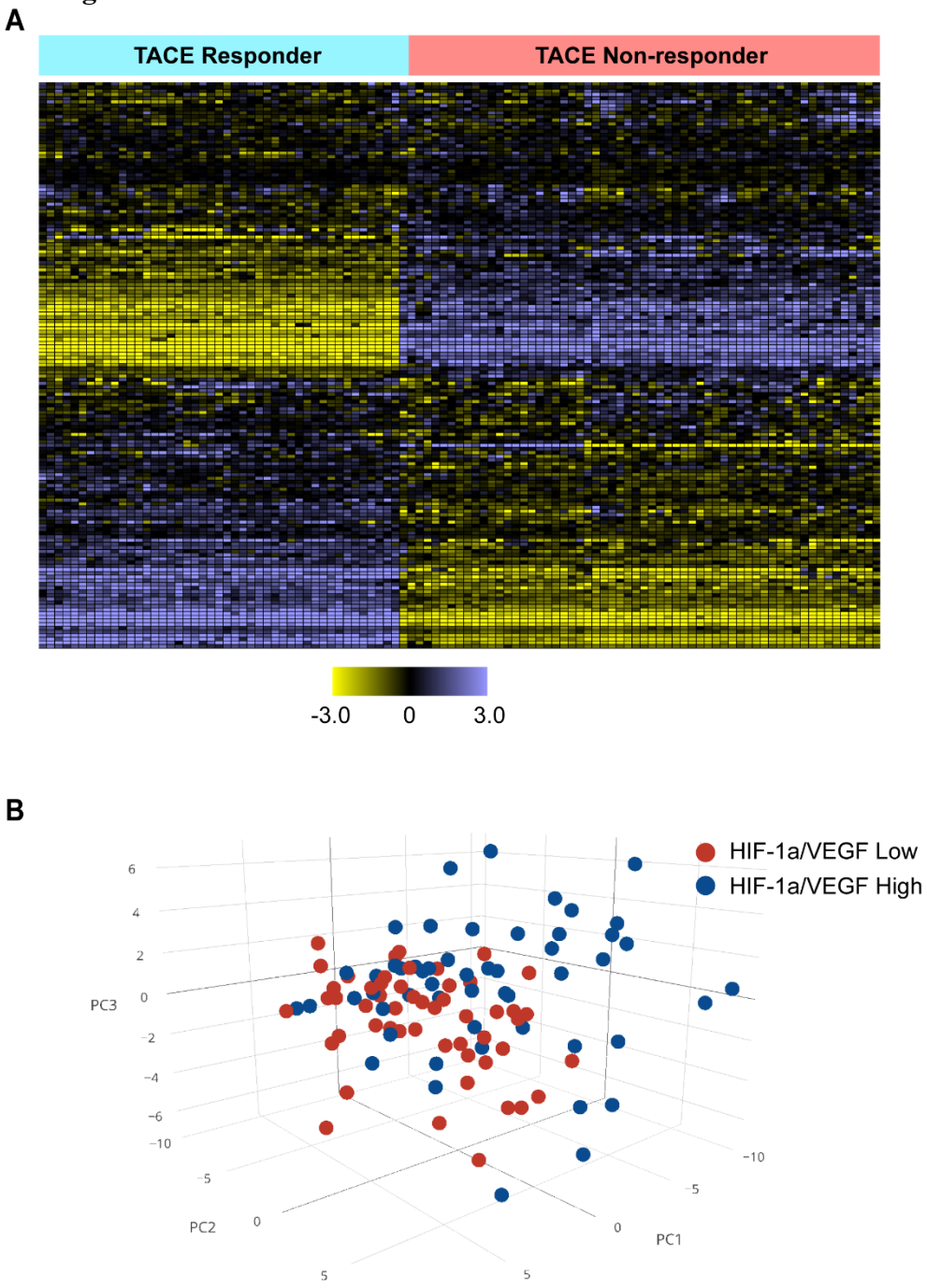
Correlation between gene expression (Log2), as measured by Affymetrix chip and NanoString, is shown for (A) TACE Navigator signature genes and (B) accompanying housekeeping genes. P and R values shown in each panel were calculated by Pearson Correlation, with a P value of less than 0.05 indicating statistical significance.

Supplementary Figure 2. The TACE Navigator gene signature does not predict overall survival in patients who did not receive TACE



HCC patients from two independent cohorts who did not receive TACE: (A) TIGER-LC and (B) Korean Cohort were assigned into predicted Responder or Non-Responder groups using our developed prognostic index equation and prognostic threshold. In both cohorts, no significant difference in overall survival was seen in patients assigned to the two groups, as shown by Kaplan-Meier curve.

Supplementary Figure 3. Responders and Non-Responders exhibit differential expression of hypoxia-related genes



Heat map of 155 hypoxia target genes in TACE Responders and Non-Responders with columns representing individual patients and rows representing expression of each variable gene (A). Both patients and genes were clustered using Pearson Correlation distance and average linkage using the Genesis program. 100% concordance of TACE Responder and Non-Responder groups were observed following clustering. Expression values are Log2, and yellow indicates relative under-expression and purple indicates relative over-expression of each gene.

Supplementary Table 1. Inclusion of patients from LCI cohort (GSE14520) and assignment into each therapy group

Adjuvant TACE subset (Included)	Post-Recurrence TACE subset (Included)	Resection Only (Included)	Other Therapy (Excluded)	Missing Survival Data (Excluded)
LCS_007A	LCS_008A	LCS_010A	LCS_002A	LCS_204A
LCS_009A	LCS_012A	LCS_014A	LCS_004A	LCS_283A
LCS_019A	LCS_023A	LCS_015A	LCS_005A	LCS_347A
LCS_020A	LCS_024A	LCS_016A	LCS_011A	X02_342A
LCS_025A	LCS_032A	LCS_018A	LCS_021A	X02_262A
LCS_027A	LCS_035A	LCS_022A	LCS_036A	
LCS_028A	LCS_067A	LCS_040A	LCS_039A	
LCS_029A	LCS_072A	LCS_041A	LCS_042A	
LCS_031A	LCS_088A	LCS_044A	LCS_054A	
LCS_033A	LCS_096A	LCS_045A	LCS_066A	
LCS_034A	LCS_120A	LCS_046A	LCS_074A	
LCS_038A	LCS_138A	LCS_048A	LCS_083A	
LCS_043A	LCS_139A	LCS_051A	LCS_089A	
LCS_047A	LCS_145A	LCS_056A	LCS_093A	
LCS_049A	LCS_178A	LCS_057A	LCS_095A	
LCS_050A	LCS_190A	LCS_061A	LCS_103A	
LCS_062A	LCS_194A	LCS_063A	LCS_107A	
LCS_065A	LCS_198A	LCS_064A	LCS_123A	
LCS_068A	LCS_200A	LCS_069A	LCS_125A	
LCS_071A	LCS_207A	LCS_073A	LCS_126A	
LCS_075A	LCS_224A	LCS_076A	LCS_129A	
LCS_079A	LCS_227A	LCS_078A	LCS_135A	
LCS_085A	LCS_234A	LCS_084A	LCS_143A	
LCS_086A	LCS_238A	LCS_090A	LCS_148A	
LCS_092A	LCS_267A	LCS_091A	LCS_149A	
LCS_097A	LCS_273A	LCS_094A	LCS_152A	
LCS_100A	LCS_274A	LCS_099A	LCS_153A	
LCS_104A	LCS_281A	LCS_101A	LCS_157A	
LCS_110A	LCS_333A	LCS_102A	LCS_162A	
LCS_116A	LCS_403A	LCS_105A	LCS_164A	
LCS_117A		LCS_106A	LCS_173A	
LCS_118A		LCS_108A	LCS_175A	
LCS_121A		LCS_109A	LCS_182A	
LCS_127A		LCS_119A	LCS_183A	
LCS_134A		LCS_122A	LCS_188A	
LCS_136A		LCS_130A	LCS_193A	
LCS_140A		LCS_131A	LCS_195A	
LCS_142A		LCS_132A	LCS_199A	
LCS_146A		LCS_137A	LCS_201A	
LCS_154A		LCS_144A	LCS_203A	
LCS_158A		LCS_147A	LCS_206A	
LCS_159A		LCS_150A	LCS_219A	
LCS_161A		LCS_151A	LCS_230A	
LCS_166A		LCS_156A	LCS_248A	
LCS_167A		LCS_160A	LCS_250A	
LCS_170A		LCS_163A	LCS_256A	
LCS_171A		LCS_165A	LCS_277A	
LCS_177A		LCS_169A	LCS_290A	
LCS_185A		LCS_172A	LCS_339A	
LCS_191A		LCS_174A	LCS_341A	
LCS_192A		LCS_179A	LCS_401A	
LCS_196A		LCS_180A		
LCS_197A		LCS_184A		
LCS_208A		LCS_189A		
LCS_209A		LCS_205A		
LCS_212A		LCS_210A		
LCS_213A		LCS_211A		
LCS_223A		LCS_215A		
LCS_228A		LCS_216A		
LCS_231A		LCS_222A		
LCS_240A		LCS_236A		
LCS_241A		LCS_237A		
LCS_245A		LCS_243A		

LCS_251A LCS_259A LCS_260A LCS_263A LCS_264A LCS_265A LCS_266A LCS_270A LCS_272A LCS_284A LCS_289A LCS_393A		LCS_247A LCS_249A LCS_253A LCS_254A LCS_261A LCS_262A LCS_268A LCS_269A LCS_275A LCS_278A LCS_279A LCS_282A LCS_285A LCS_286A LCS_291A LCS_343A LCS_344A LCS_346A LCS_400A LCS_406A LCS_415A LCS_424A LCS_426A		

Supplementary Table 2. Clinical characteristics of LCI test cohort treatment groups

Variable	TACE (N=105)	Resection Only (N=86)	P Value*
Age—year			
Median	50	50	0.71
Range	27-73	21-77	
Sex—no. (%)			
Female	8 (7.6)	12 (14.0)	0.16
Male	97 (92.4)	74 (86.0)	
HBV—no. (%)			
Chronic carrier	71 (67.6)	63 (73.3)	0.74
Active virus	28 (26.7)	21 (24.4)	
Negative	6 (5.7)	2 (2.3)	
/Missing data			
Cirrhosis—no. (%)			0.06
No	12 (11.4)	3 (3.5)	
Yes	93 (88.6)	83 (96.5)	
Alanine aminotransferase—no. (%)			0.14
Normal (≤50 U/L)	56 (53.3)	55 (64.0)	
Elevated (>50 U/L)	49 (46.7)	31 (36.0)	
Alpha-fetoprotein—no. (%)			0.99
≤200 ng/mL	52 (49.5)	43 (50.0)	
>200 ng/mL	52 (49.5)	42 (48.8)	
Missing Data	1 (1.0)	1 (1.2)	
Tumor Size—no. (%)			0.99
≤3 cm	30 (28.6)	24 (27.9)	
>3 cm	75 (71.4)	62 (72.1)	
Microvascular Invasion—no. (%)			0.23
No	68 (64.8)	48 (55.8)	
Yes	37 (35.2)	38 (44.2)	
Multinodular Tumor—no. (%)			0.60
No	84 (80.0)	66	
Yes	21 (20.0)	20	
TNM Stage—no. (%)			0.44
I	44 (41.9)	29 (33.7)	
II+III	56 (53.3)	49 (57.0)	
Missing Data	5 (4.8)	8 (9.3)	
BCLC State—no. (%)			0.86
0+A	76 (72.4)	58 (67.4)	
B+C	24 (22.8)	20 (23.3)	
Missing Data	5 (4.8)	8 (9.3)	
Survival (mo)			0.22
Median	>66.3	54.8	
Range	1.8->67	2.5->67	

*A P value of less than 0.05 was considered to indicate statistical significance. P values were calculated with the use of Fisher's exact tests, except for age, which was calculated with 2-tailed Student's t-test, and survival, which was calculated with the log-rank test.

Supplementary Table 3. Clinical characteristics of test cohort TACE patients and test cohorts TACE patients

Variable	LCI Training/Validation Cohort (N=105)	Hong Kong Test Cohort (N=49)	Shandong Test Cohort (N=50)	Mainz Test Cohort (N=31)
Age—year				
Median	50	54	51	70
Range	27-73	24-74	31-71	57-91
Sex—no. (%)				
Female	8 (7.6)	7 (14.3)	5 (10.0)	26 (83.9)
Male	97 (92.4)	42 (85.7)	45 (90.0)	5 (16.1)
HBV—no. (%)				
Chronic carrier	71 (67.6)	34 (69.4)	42 (84.0)	5 (16.1)
Active virus	28 (26.7)	9 (18.4)	1 (2.0)	0 (0.0)
Negative/Missing data	6 (5.7)	6 (12.2)	7 (14.0)	26 (83.9)
Cirrhosis—no. (%)				
No	12 (11.4)	19 (38.8)	n.a.	8 (25.8)
Yes	93 (88.6)	30 (61.2)	n.a.	23 (74.2)
Alpha-fetoprotein—no. (%)				
Negative (≤200 ng/mL)	52 (49.5)	24 (49.0)	24 (48.0)	14 (45.2)
Positive (>200 ng/mL)	52 (49.5)	24 (49.0)	19 (38.0)	9 (29.0)
Missing Data	1 (1.0)	1 (2.0)	7 (14.0)	7 (22.6)
Tumor Size—no. (%)				
≤3 cm	30 (28.6)	8 (16.3)	19 (38.0)	4 (12.9)
>3 cm	75 (71.4)	41 (83.7)	29 (58.0)	25 (80.6)
Missing Data	0 (0.0)	0 (0.0)	2 (4.0)	2 (0.05)
Microvascular Invasion—no. (%)				
No	68 (64.8)	22 (44.9)	n.a.	20 (64.5)
Yes	37 (35.2)	27 (55.1)	n.a.	11 (35.5)
TNM Stage—no. (%)				
I	44 (41.9)	11 (22.4)	27 (54.0)	16 (51.6)
II+III+IV	56 (53.3)	38 (77.6)	23 (46.0)	11 (35.5)
Missing Data	5 (4.8)	0 (0.0)	0 (0.0)	4 (12.9)
BCLC Stage—no (%)				
0+A	24 (22.9)	n.a.	32 (64.0)	19 (61.3)
B+C	75 (72.4)	n.a.	18 (36.0)	12 (38.7)
Missing Data	5 (4.7)	n.a	0 (0.0)	0 (0.0)
Survival (mo)				
Median	>67	44.1	>60	59.1
Range	2.5->67.3	4.8->60	3.7->60	5.5->60

n.a. denotes data not available

Supplementary Table 4. Hazard ratios for death among TACE Cluster 1 and Resection Only patients, according to univariable and multivariable analysis

Clinical Variable	Univariable Analysis Hazard Ratio (95 % CI)	P Value	Multivariable Analysis Hazard Ratio (95 % CI)	P Value
Treatment Group (TACE Cluster 1 vs. Resection Only) TACE Cluster 1: 39 (31.2%) Resection Only: 86 (68.8%)	0.45 (0.23-0.88)	**0.019**	0.66 (0.33-1.35)	0.260
Age (≤50 yr vs. >50 yr) ≤50 yr: 56 (44.8%) >50 yr: 69 (55.2%)	0.59 (0.35-1.02)	0.058	n.a.	
Sex (male vs. female) Male: 111 (88.8%) Female: 14 (11.2%)	1.41 (0.56-3.56)	0.453	n.a.	
HBV (active virus vs. chronic carrier) Active virus: 31 (24.8%) Chronic carrier: 91 (72.8%) Missing data/no virus: 3 (2.4%)	1.82 (1.02-3.26)	**0.044**	1.63 (0.85-3.13)	0.143
Cirrhosis (yes vs. no) Yes: 118 (94.4%) No: 7 (5.6%)	1.65 (0.40-6.78)	0.488	n.a.	
Alanine aminotransferase (>50 U/L vs. ≤50 U/L) Elevated (>50 U/L): 50 (40.0%) Normal (≤50 U/L): 75 (60.0%)	1.32 (0.77-2.28)	0.309	n.a.	
Alpha-fetoprotein (>200 ng/mL vs. ≤200 ng/mL) >200 ng/mL: 53 (42.4%) ≤200 ng/mL: 71 (56.8%) Missing data: 1 (0.8%)	1.79 (1.04-3.10)	**0.036**	1.09 (0.58-2.02)	0.812
Tumor size (>3 cm vs. ≤3 cm) >3 cm: 84 (67.2%) ≤3 cm: 41 (32.8%)	1.51 (0.84-2.72)	0.170	n.a.	
Microvascular invasion (yes vs. no) Yes: 50 (40.0%) No: 75 (60.0%)	1.92 (1.12-3.29)	**0.018**	2.38 (1.30-4.33)	**0.005**
Multinodular tumor (yes vs. no) Yes: 25 (20.0%) No: 100 (80.0%)	1.79 (0.97-3.29)	0.064	n.a.	
TNM Stage (II+III vs. I) II+III: 67 (61.6%) I: 49 (39.2%) Missing data: 9 (7.2%)	2.69 (1.41-5.10)	**0.003**	n.a.	
BCLC Stage (B+C vs. 0+A) B+C: 24 (19.2%) 0+A: 92 (73.6%) Missing data: 9 (7.2%)	3.44 (1.84-6.45)	**<0.001**	2.77 (1.35-5.69)	**0.005**

Supplementary Table 5. 15 TACE Navigator genes

Gene Symbol	Description	Fold Change Responders vs. Non-Responders	Parametric p-value
ASNS	Asparagine synthetase	0.33	$<1x10^{-7}$
CDK1*	Cyclin-dependent kinase 1	0.54	$3.4x10^{-6}$
DNASE1L3	Deoxyribonuclease I-like 3 (DNase)	2.91	$<1x10^{-7}$
FBXL5	F-box and leucine-rick repeat protein 5	1.52	$1.8x10^{-6}$
GABARAPL3	GABA(A) receptors associated protein like 3	1.41	$8.5x10^{-6}$
GOT2	Glutamic-oxaloacetic transaminase 2, mitochondrial	1.92	$1x10^{-7}$
GRHPR	Glyoxylate reductase/hydroxypyruvate reductase	2.20	$<1x10^{-7}$
IARS	Isoleucyl-tRNA synthetase	0.64	$4x10^{-7}$
LGALS3	Lectin, galactoside-binding, soluble 3	0.35	$<1x10^{-7}$
LHFPL2	Lipoma HMGIC fusion partner-like 2 protein	0.57	$<1x10^{-7}$
MFGE8	Milk fat globule-EGF factor 8 protein	0.80	$8.16x10^{-5}$
MKI67	Antigen Ki-67	0.63	$<1x10^{-7}$
PEBP1	Phosphatidylethanolamine binding protein 1	1.74	$<1x10^{-7}$
TNFSF10	Tumor necrosis factor superfamily, member 10 (TRAIL)	2.05	$1.7x10^{-6}$
UBB	Ubiquitin B	1.23	$6.8x10^{-6}$

*Note: CDK1 is abbreviated as CDC2 in the training/validation cohort dataset.

Supplementary Table 6. Hazard ratios for death among TACE Responders and Resection Only patients, according to univariable and multivariable analysis

Clinical Variable	Univariable Analysis Hazard Ratio (95 % CI)	P Value	Multivariable Analysis Hazard Ratio (95 % CI)	P Value
Treatment Group (TACE Responders vs. Resection Only) Resection Only: 86 (65.7%) TACE Responders: 45 (34.3%)	0.16 (0.06-0.41)	**<0.001**	0.21 (0.08-0.55)	**0.001**
Age (≤50 yr vs. >50 yr) ≤50 yr: 57 (43.5%) >50 yr: 74 (56.5%)	0.64 (0.37-1.15)	0.137	n.a.	
Sex (male vs. female) Male: 116 (88.6%) Female: 15 (11.4%)	1.24 (0.49-3.14)	0.650	n.a.	
HBV (active virus vs. chronic carrier) Active virus: 29 (22.1%) Chronic carrier: 99 (75.6%) Missing data/no virus: 3 (2.3%)	1.88 (1.00-3.54)	**0.049**	1.59 (0.79-3.23)	0.196
Cirrhosis (yes vs. no) Yes: 122 (93.1%) No: 9 (6.9%)	1.90 (0.46-7.83)	0.375	n.a.	
Alanine aminotransferase (>50 U/L vs. ≤50 U/L) Elevated (>50 U/L): 52 (39.7%) Normal (≤50 U/L): 79 (60.3%)	1.45 (0.82-2.57)	0.205	n.a.	
Alpha-fetoprotein (>200 ng/mL vs. ≤200 ng/mL) >200 ng/mL: 60 (45.8%) ≤200 ng/mL: 69 (52.7%) Missing data: 2 (1.5%)	2.03 (1.12-3.65)	**0.019**	1.23 (0.64-2.37)	0.532
Tumor size (>3 cm vs. ≤3 cm) >3 cm: 86 (65.7%) ≤3 cm: 45 (34.3%)	1.45 (0.78-2.68)	0.237	n.a.	
Microvascular invasion (yes vs. no) Yes: 30 (22.9%) No: 101 (77.1%)	0.75 (0.37-1.57)	0.456	n.a.	
Multinodular tumor (yes vs. no) Yes: 26 (19.8%) No: 105 (80.2%)	2.14 (1.14-4.00)	**0.018**	0.64 (0.26-1.61)	0.348
TNM Stage (II+III vs. I) II+III: 67 (51.1%) I: 56 (42.7%) Missing data: 8 (6.2%)	2.68 (1.37-5.27)	**0.004**	n.a.	
BCLC Stage (B+C vs. 0+A) B+C: 24 (18.3%) 0+A: 98 (74.8%) Missing data: 9 (6.9%)	4.65 (2.41-9.00)	**<0.001**	3.99 (1.70-9.37)	**0.001**

Supplementary Table 7. Known and predicted HIF-1α targets used for TACE Responder and Non-Responder patient clustering

Known HIF-1α Targets: Expression Data Available	Known HIF-1α Targets: Expression Data Unavailable	Predicted Core Hypoxia Response Genes: Expression Data Available*	Predicted Core Hypoxia Response Genes: Expression Data Unavailable
ABCB1	CYP2S1	ABCF2	ANKRD37
ABCG2	PROK1	ACTR1A	GOPC
ADM		ALDOC	LOC162073
ADRA1B		ANKRD37	
AK3		ASCC1	
ALDOA		ASPH	
BHLHB2		ATF3	
BHLHB3		ATF7IP	
BNIP3		BNIP3*	
BNIP3L		C14orf169	
CA9		C3orf28	
CCNG2		CAD	
CD99		CCNB1	
CDKN1A		CLK3	
CITED2		CRKL	
COL5A1		CXCR4*	
CP		CYCS	
CTGF		DDIT4*	
CTSD		DHX40	
CXCL12		EDEM3	
CXCR4		EFNA1	
DDIT4		EIF1	
DEC1		EIF2B3	
EDN1		ERO1L	
EGLN1		FH	
EGLN3		GADD45B	
ENG		GAPDH*	
ENO1		GOPC	
EPO		GOSR2	
ETS1		GRK6	
FECH		GYS1	
FN1		HIG2	
FURIN		ILF3	
GAPDH		INSIG2	
GPI		JMJD1A	
GPX3		JMJD2B	
HK1		JMJD2C	
HK2		KLF10	
HMOX1		LDHA*	
HSP90B1		LOC162073	
ID2		LOX*	
IGF2		MIF	
IGFBP1		MRPL4	
IGFBP2		MRPS12	
IGFBP3		MXI1*	
ITGB2		NARF	
KRT14		NDRG1	
KRT18		NF2	
KRT19		NR3C1	
LDHA		NXF1	
LEP		OXSR1	
LOX		P4HA1	
LRP1		P4HA2	
MCL1		PBEF1	
MET		PER2	
MMP14		PGAM1	
MMP2		PGK1*	
MXI1		PHLDA1	
NOS2A		PIM1	
NOS3		PJA2	
NPM1		PLOD1	
NR4A1		PPME1	
NT5E		R3HDM1	

PDGFA PDK1 PFKFB3 PFKL PGK1 PH-4 PKM2 PLAUR PMAIP1 PPP5C SERPINE1 SLC2A1 TERT TF TFF3 TFRC TGFA TGFB3 TGM2 TPI1 VEGFA VIM		RAB8B RARA RBPJ RRAGD RSBN1 SEC61G SFRS7 SLC16A1 SLC7A6 SNRPD1 SPAG4 STC2 TGFBR1 TMEM45A TPCN1 TUBG1 VDAC1 WSB1	

*Genes denoted with an asterisk indicate genes from the core hypoxia response that are previously known HIF-1α targets. Other genes in this column are predicted hypoxia response genes.