Supplementary table 1. The detailed information of tumor numbers and treatment modalities in different tumor burden groups

|  |  |  |  |
| --- | --- | --- | --- |
| Low tumor burden (n=149) | Single (n=74) | SR | 57 |
| TACE | 17 |
| 2 or 3 (n=61) | SR | 19 |
| TACE | 42 |
| >3 (n=14) | SR | 0 |
| TACE | 14 |
| Intermediate tumor burden (n=203) | Single (n=119) | SR | 94 |
| TACE | 25 |
| 2 or 3 (n=57) | SR | 19 |
| TACE | 38 |
| >3 (n=27) | SR | 4 |
| TACE | 23 |
| High tumor burden (n=122) | Single (n=52) | SR | 35 |
| TACE | 17 |
| 2 or 3 (n=50) | SR | 15 |
| TACE | 35 |
| >3 (n=20) | SR | 4 |
| TACE | 16 |

Supplementary table 2. Characteristics of 474 patients with BCLC-A/B HCC beyond the Milan criteria according to the tumor number.

|  |  |  |  |
| --- | --- | --- | --- |
| Variables | Single large (n=245) | Multinodular (n=229) | P value |
| Age, years | 67 (55-75) | 65 (58-72) | 0.363 |
| Sex |  |  | 0.761 |
| male | 188 (77) | 173 (76) |  |
| female | 57 (23) | 56 (24) |  |
| FIB-4 index | 2.22 (1.54-3.58) | 3.54 (2.13-6.07) | <0.001 |
| ALBI score | -2.96 (-3.18--2.61) | -2.61 (-2.98--2.07) | <0.001 |
| AFP, ng/mL | 15.0 (4.1-819.4) | 42.4 (9.2-305.0) | 0.040 |
| HBV positive | 125 (49) | 123 (54) | 0.558 |
| HCV positive | 50 (20) | 77 (34) | 0.001 |
| Cirrhosis | 94 (38) | 171 (75) | <0.001 |
| Seven-eleven criteria |  |  | 0.017 |
| low (≤7) | 74 (30) | 75 (33) |  |
| intermediate (7-11) | 119 (49) | 84 (37) |  |
| high (>11) | 52 (21) | 70 (30) |  |
| Treatment |  |  | <0.001 |
| SR | 186 (76) | 61 (27) |  |
| TACE | 59 (24) | 168 (73) |  |
| Maximum tumor size, cm | 7.4 (6.0-10.0) | 5.0 (3.5-8.5) | <0.001 |
| Follow-up duration, years | 4.0 (1.8-5.3) | 2.5 (1.2-4.0) | <0.001 |
| Death | 89 (36) | 116 (51) | 0.002 |

BCLC, Barcelona clinic liver cancer classification; HCC, hepatocellular carcinoma; FIB-4 index, fibrosis-4 index; ALBI score, albumin-bilirubin score; AFP, α-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; SR, surgical resection; TACE, transarterial chemoembolization.

Data are expressed as median (interquartile range) or number (percentage).

Supplementary table 3. Cox regression analysis for prediction of overall survival in 176 patients with intermediate tumor burden with 1 to 3 nodule(s)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variables | Univariable analysis | | Multivariable analysis | |
|  | HR (95% CI) | P value | HR (95% CI) | P value |
| Age, 1 year increase | 1.03 (1.01-1.05) | 0.007 | 1.01 (0.99-1.03) | 0.503 |
| Male (vs. female) | 0.86 (0.49-1.51) | 0.598 | 1.10 (0.62-1.95) | 0.745 |
| FIB-4 index, 1 point increase | 1.06 (1.02-1.11) | 0.005 | 0.97 (0.91-1.03) | 0.335 |
| ALBI score, 1 point increase | 2.98 (2.01-4.42) | <0.001 | 2.47 (1.40-4.35) | 0.002 |
| AFP, 1 ng/mL increase | 1.00 (1.00-1.00) | 0.734 |  |  |
| HBV positive (vs. negative) | 0.90 (0.56-1.44) | 0.658 |  |  |
| HCV positive (vs. negative) | 1.23 (0.74-2.05) | 0.434 |  |  |
| Cirrhosis (vs. no) | 1.92 (1.17-3.15) | 0.010 |  |  |
| SR vs. TACE | 0.25 (0.16-0.41) | <0.001 | 0.36 (0.21-0.61) | <0.001 |

BCLC, Barcelona clinic liver cancer classification; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; FIB-4 index, fibrosis-4 index; ALBI score, albumin-bilirubin score; AFP, α-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; SR, surgical resection; TACE, transarterial chemoembolization.

Supplementary table 4. Cox regression analysis for prediction of overall survival in 27 patients with intermediate tumor burden with > 3 nodules

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variables | Univariable analysis | | Multivariable analysis | |
|  | HR (95% CI) | P value | HR (95% CI) | P value |
| Age, 1 year increase | 0.99 (0.94-1.05) | 0.848 | 1.01 (0.94-1.09) | 0.744 |
| Male (vs. female) | 0.57 (0.12-2.71) | 0.482 | 0.49 (0.08-2.95) | 0.438 |
| FIB-4 index, 1 point increase | 0.99 (0.81-1.21) | 0.896 | 0.94 (0.70-1.27) | 0.703 |
| ALBI score, 1 point increase | 1.40 (0.49-3.99) | 0.523 | 2.86 (0.47-17.31) | 0.252 |
| AFP, 1 ng/mL increase | 1.00 (1.00-1.00) | 0.110 |  |  |
| HBV positive (vs. negative) | 5.36 (1.14-25.28) | 0.034 |  |  |
| HCV positive (vs. negative) | 0.35 (0.08-1.64) | 0.184 |  |  |
| Cirrhosis (vs. no) | 1.21 (0.25-5.84) | 0.815 |  |  |
| SR vs. TACE | 1.38 (0.29-6.49) | 0.687 | 3.01 (0.35-25.66) | 0.313 |

BCLC, Barcelona clinic liver cancer classification; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; FIB-4 index, fibrosis-4 index; ALBI score, albumin-bilirubin score; AFP, α-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; SR, surgical resection; TACE, transarterial chemoembolization.

Supplementary table 5. Cox regression analysis for prediction of overall survival in 102 patients with high tumor burden with 1 to 3 nodule(s)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variables | Univariable analysis | | Multivariable analysis | |
|  | HR (95% CI) | P value | HR (95% CI) | P value |
| Age, 1 year increase | 1.01 (0.99-1.03) | 0.505 | 1.00 (0.98-1.02) | 0.775 |
| Male (vs. female) | 0.79 (0.42-1.49) | 0.467 | 0.97 (0.50-1.87) | 0.919 |
| FIB-4 index, 1 point increase | 1.21 (1.10-1.32) | <0.001 | 1.13 (1.01-1.27) | 0.036 |
| ALBI score, 1 point increase | 2.22 (1.40-3.53) | 0.001 | 1.61 (0.95-2.74) | 0.080 |
| AFP, 1 ng/mL increase | 1.00 (1.00-1.00) | 0.416 |  |  |
| HBV positive (vs. negative) | 1.21 (0.73-2.00) | 0.466 |  |  |
| HCV positive (vs. negative) | 1.45 (0.77-2.75) | 0.253 |  |  |
| Cirrhosis (vs. no) | 0.87 (0.51-1.47) | 0.598 |  |  |
| SR vs. TACE | 0.44 (0.26-0.74) | 0.002 | 0.58 (0.33-1.01) | 0.056 |

BCLC, Barcelona clinic liver cancer classification; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; FIB-4 index, fibrosis-4 index; ALBI score, albumin-bilirubin score; AFP, α-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; SR, surgical resection; TACE, transarterial chemoembolization.

Supplementary table 6. Cox regression analysis for prediction of overall survival in 20 patients with high tumor burden with > 3 nodules

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variables | Univariable analysis | | Multivariable analysis | |
|  | HR (95% CI) | P value | HR (95% CI) | P value |
| Age, 1 year increase | 1.03 (0.98-1.07) | 0.236 | 1.03 (0.98-1.09) | 0.234 |
| Male (vs. female) | 1.10 (0.23-5.23) | 0.900 | 1.73 (0.31-9.67) | 0.535 |
| FIB-4 index, 1 point increase | 1.04 (0.90-1.21) | 0.590 | 1.01 (0.84-1.22) | 0.917 |
| ALBI score, 1 point increase | 0.96 (0.38-2.44) | 0.936 | 1.06 (0.33-3.46) | 0.922 |
| AFP, 1 ng/mL increase | 1.00 (1.00-1.00) | 0.106 |  |  |
| HBV positive (vs. negative) | 1.91 (0.54-6.70) | 0.315 |  |  |
| HCV positive (vs. negative) | 3.30 (0.92-11.82) | 0.066 |  |  |
| Cirrhosis (vs. no) | 3.32 (0.42-26.48) | 0.257 |  |  |
| SR vs. TACE | 0.36 (0.05-2.85) | 0.331 | 0.30 (0.03-2.66) | 0.283 |

BCLC, Barcelona clinic liver cancer classification; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; FIB-4 index, fibrosis-4 index; ALBI score, albumin-bilirubin score; AFP, α-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; SR, surgical resection; TACE, transarterial chemoembolization.

Supplementary table 7. Cox regression analysis for prediction of overall survival in 74 patients with low tumor burden with single nodule

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variables | Univariable analysis | | Multivariable analysis | |
|  | HR (95% CI) | P value | HR (95% CI) | P value |
| Age, 1 year increase | 0.99 (0.96-1.02) | 0.399 | 0.96 (0.93-0.99) | 0.008 |
| Male (vs. female) | 0.63 (0.25-1.62) | 0.340 | 0.49 (0.17-1.39) | 0.181 |
| FIB-4 index, 1 point increase | 1.09 (0.94-1.27) | 0.245 | 0.85 (0.69-1.03) | 0.100 |
| ALBI score, 1 point increase | 3.91 (1.53-9.97) | 0.004 | 5.56 (1.44-21.50) | 0.013 |
| AFP, 1 ng/mL increase | 1.00 (1.00-1.00) | 0.333 |  |  |
| HBV positive (vs. negative) | 0.80 (0.44-1.44) | 0.454 |  |  |
| HCV positive (vs. negative) | 1.37 (0.56-3.38) | 0.493 |  |  |
| Cirrhosis (vs. no) | 1.42 (0.61-3.29) | 0.413 |  |  |
| SR vs. TACE | 0.31 (0.13-0.74) | 0.008 | 0.24 (0.07-0.78) | 0.018 |

BCLC, Barcelona clinic liver cancer classification; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; FIB-4 index, fibrosis-4 index; ALBI score, albumin-bilirubin score; AFP, α-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; SR, surgical resection; TACE, transarterial chemoembolization.