Supplementary materials

Table S1. Clinicopathological characteristics of colorectal liver metastases undergoing liver resection followed by preoperative chemotherapy in the validation cohort

Variables	Overall (n=64)	TRG 1-3 (n=26)	TRG 4-5 (n=38)	P
Age, mean (SD), years	55.8 (8.9)	56.8 (8.5)	55.1 (9.3)	0.456[†]
Male gender				0.100[‡]
Male	39 (60.9 %)	19 (73.1 %)	20 (52.6 %)	
Female	25 (39.1 %)	7 (26.9 %)	18 (47.4 %)	
Location of primary tumor				0.217[‡]
Right-sided	20 (31.3 %)	11 (42.3 %)	9 (23.7 %)	
Left-sided	12 (18.7 %)	3 (11.5 %)	9 (23.7 %)	
Rectum	32 (50.0 %)	12 (46.2 %)	20 (52.6 %)	
Pathologic stage T_{3-4}	60 (93.8 %)	24 (92.3 %)	36 (94.7 %)	1.000[§]
Lymph nodes metastasis	50 (78.1 %)	18 (69.2 %)	32 (84.2 %)	0.155[‡]
Synchronous CRLMs	27 (42.2 %)	11 (42.3 %)	16 (42.1 %)	0.987[‡]
Maximum diameter of CRLMs, mean (SD), mm	36.7 (21.3)	35.9 (20.2)	37.9 (23.1)	0.720[†]
Number of CRLMs ≥ 2	38 (59.3 %)	13 (50.0 %)	25 (65.7 %)	0.207[‡]
Bilobar CRLMs	14 (21.9 %)	4 (15.4 %)	10 (26.3 %)	0.367[§]
Positive pre-operative CEA	43 (67.2 %)	12 (46.2 %)	31 (81.6 %)	0.003[‡]
Mutated *KRAS* [#]	8/43 (18.6 %)	5/19 (26.3 %)	3/24 (12.5 %)	0.362[§]
Extrahepatic disease	4 (6.2 %)	2 (7.7 %)	2 (5.3 %)	1.000[§]
Backbone of NACT				-[*]
Oxaliplatin	50 (78.1 %)	21 (80.8 %)	29 (76.3 %)	
Irinotecan	9 (14.1 %)	4 (15.4 %)	5 (13.2 %)	
Oxaliplatin+irinotecan	5 (7.8 %)	1 (3.8 %)	4 (10.5 %)	
Targeted therapy				-
Cetuximab	4 (6.3 %)	1 (3.8 %)	3 (7.9 %)	
Bevacizumab	3 (4.7 %)	2 (7.7 %)	1 (2.6 %)	
Without	57 (89.0 %)	23 (88.5 %)	34 (89.5 %)	
Preoperative chemotherapy > 1st line	10 (15.6 %)	3 (11.5 %)	7 (18.4 %)	0.514[§]
Number of cycles, median (IQR)	4 (2-6)	4 (2-6)	4 (2-5)	0.771[¶]
Radiological response				0.006[‡]
Response (CR+PR)	24 (37.5 %)	15 (57.7 %)	9 (23.7 %)	
No response (SD+PD)	40 (62.5 %)	11 (42.3 %)	29 (76.3 %)	
R1/2 margin	3 (4.7 %)	0 (0.0 %)	3 (7.9 %)	-[*]
Capsular invasion	40 (62.5 %)	12 (46.2 %)	28 (73.7 %)	0.025[‡]
Dense-TILs	26 (40.6 %)	17 (65.4 %)	10 (26.3 %)	0.002[‡]
Second-worst TRG [#]				-[*]
1-3	12/25 (48.0 %)	3/3 (100.0 %)	9/22 (40.9 %)	
4-5	13/25 (52.0 %)	0/3 (0.0 %)	13/22 (59.1 %)	

Variability of TRG[#]			-[*]
Decreased TRG	12/25 (48.0 %)	3/3 (100.0 %)	9/22 (40.9 %)
Stable TRG	13/25 (52.0 %)	0/3 (0.0 %)	13/22 (59.1 %)

Abbreviation: TRG, tumor regression grade; SD, standard deviation; CEA, carcinoembryonic antigen; NACT, neoadjuvant chemotherapy; IQR, interquartile range; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TILs, tumor infiltrating lymphocytes.

[#] There are 25 patients with multiple CRLMs receiving the evaluation of variability of TRG.

[†] Student's t test.

[‡] Pearson Chi-square test.

[§] Fisher's exact test.

[*] The sample size was too small for valid statistical analysis.
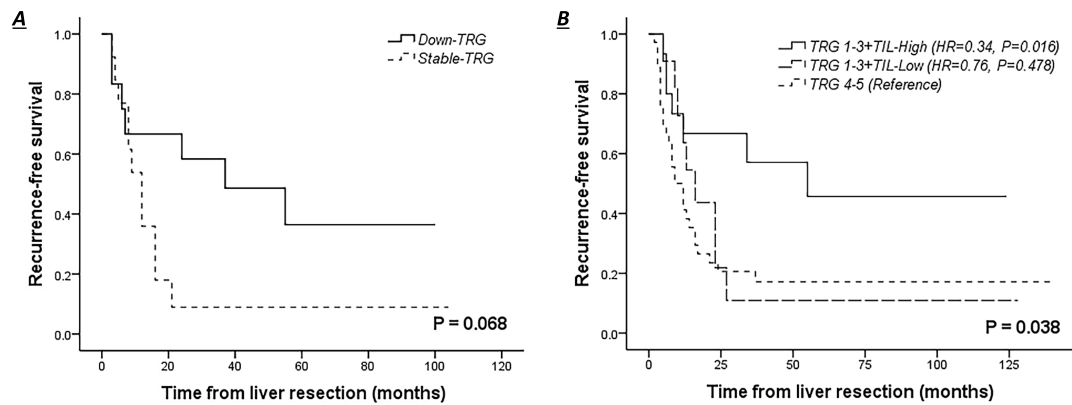
[¶] Wilcoxon rank-sum test.

Fig. S1 Comparison of recurrence-free survival curves in the validation cohort according to peritumoral lymphocytic infiltration and variation in TRG scores between metastases. *A.* Recurrence-free survival of patients presented with decreased or stable TRG scores of the second-worse metastases. *B.* Recurrence-free survival of patients presented with dense or weak TILs at the tumor–normal interface combining with histological tumor regression.