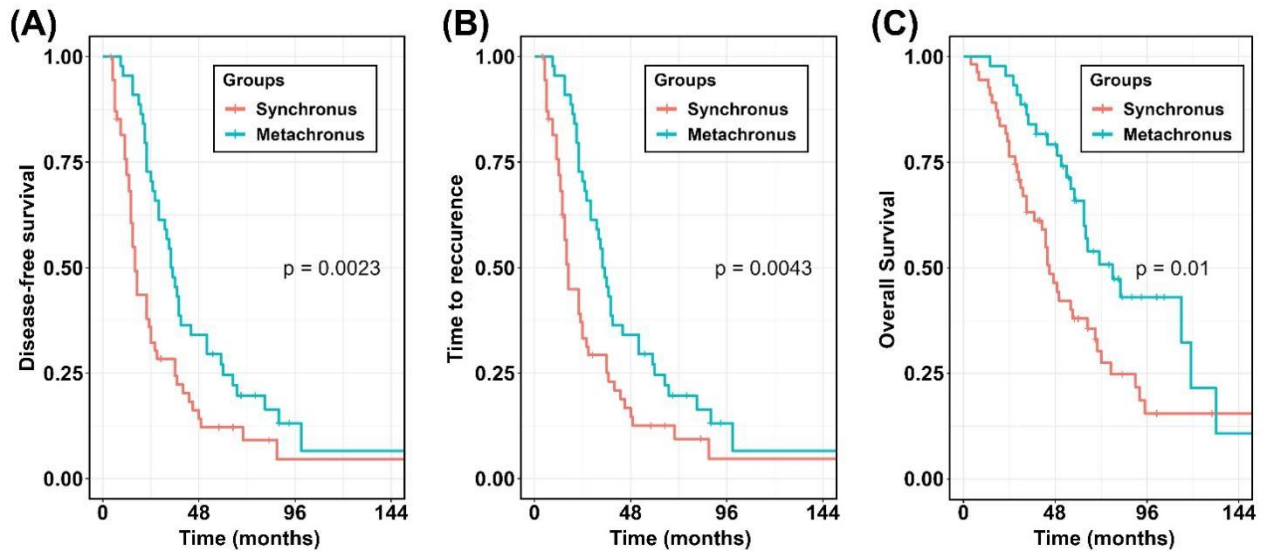
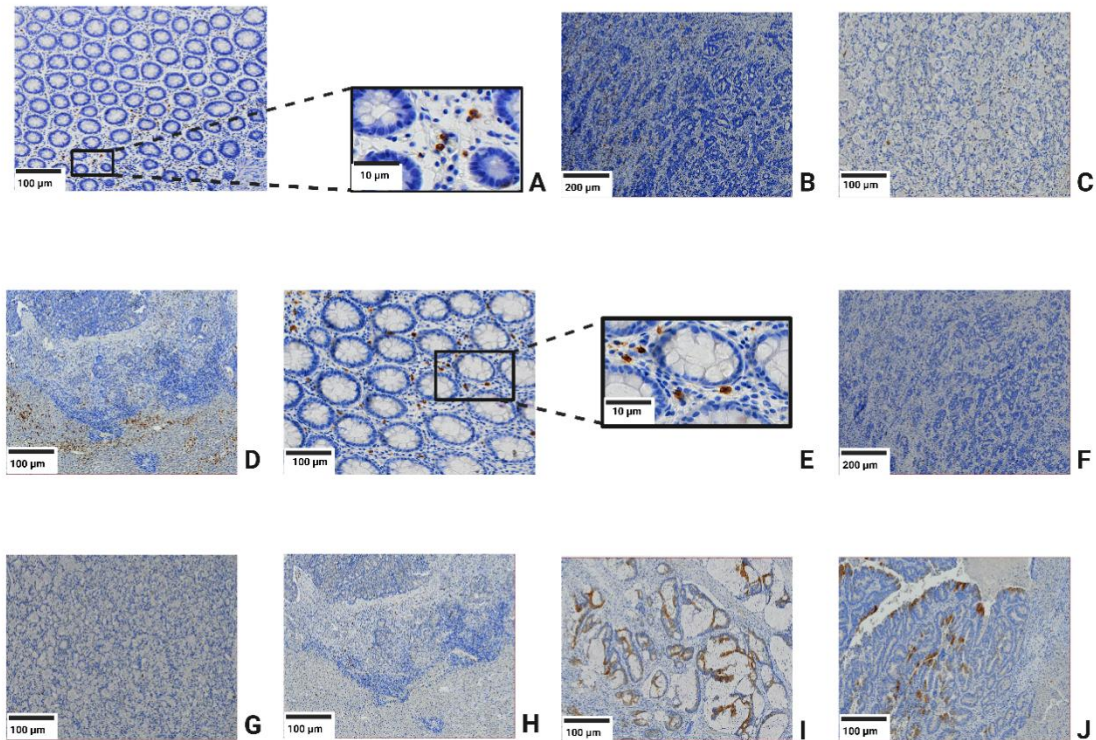
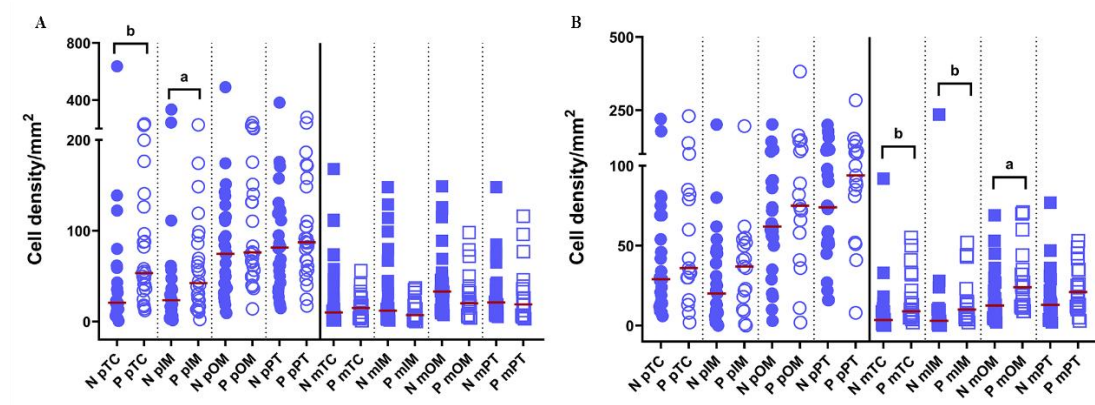




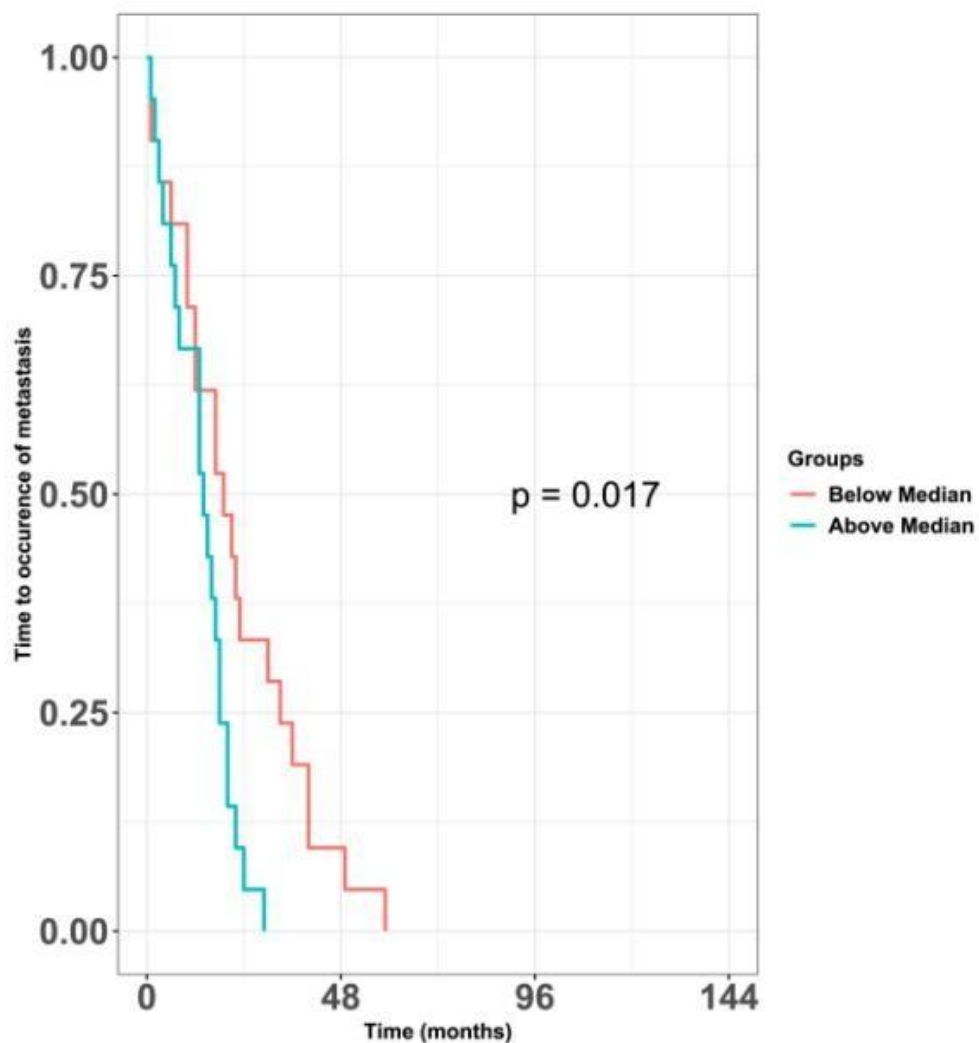
Supplementary Figure 1 Survival analysis since colon surgery. Up to December 2023, 47 (85.5%) and 42 (76.4%) patients experienced tumour recurrence and had died ($P=0.022$) in synchronous group, respectively. 38 (86.4%) and 24 (54.5%) patients experienced tumour recurrence and had died in metachronous group, respectively.



Supplementary Figure 2 Microscopic images for CD66b+ polymorphonuclear neutrophils and CD117+ mast cells. CD66b+ PMNs in NM (A), tumor center of pCRC (B), tumor center of LM (C), tumor invasive margin of LM (D). CD117+ MCs in NM (E), tumor center of pCRC (F), tumor center of LM (G); tumor invasive margin of LM (H). Expression of CD117 by tumor cells in pCRC (I) and LM (J). Abbreviations: NM: non-tumor mucosa; pCRC: primary colorectal cancer; LM: liver metastasis.



Supplementary Figure 3 Densities of CD117+ mast cells in groups of patients with (P) and without (N) expression of CD117 by tumor cells. (A) synchronous group; (B) metachronous group. Abbreviation: N: negative; P: positive; pTC: tumor center of pCRC; pIM: inner margin of pCRC; pOM: outer margin of pCRC; pPT: peritumor zone of pCRC; mTC: tumor center of LM; mIM: inner margin of LM; mOM: outer margin of LM; mPT: peritumor zone of LM; pCRC: primary colorectal cancer; LM: liver metastases. ^a $P < 0.05$, ^b $P < 0.01$.



Supplementary Figure 4 Association between ratio of CD66b+ polymorphonuclear neutrophils in IM/OM of primary colorectal cancer and TLM in metachronous group.
 Abbreviations: IM: inner margin; OM: outer margin; pCRC: primary tumor; LM: liver metastasis; TLM: time to the diagnosis of LM.

Supplementary Table 1 Clinical backgrounds of enrolled patients and histopathological features of primary colorectal cancer and liver metastasis

Parameter		Metachronous group, N=44	Synchronous group, N=55	<i>P</i> - value
Age at the diagnosis (years), median (min-max)		64 (46-73)	62 (29-78)	0.31
Gender	male	29 (65.9%)	34 (61.8%)	0.67
	female	15 (34.1%)	21 (38.2%)	
Primary tumor				
Location	Right colon	8 (18.2%)	12 (21.8%)	0.65
	Left colon	36 (81.8%)	43 (78.2%)	
Size (cm), median (min-max)		3.5 (0.8-8.3)	4.3 (1.0-7.5)	
Pathologic T stage	T1	1 (2.3%)	0 (0.0%)	0.25
	T2	6 (13.6%)	1 (1.8%)	
	T3	35 (79.5%)	48 (87.3%)	
	T4	2 (4.5%)	6 (10.9%)	
Histological type	NOS	39 (88.6%)	51 (92.7%)	
	Mucinous	4 (9.1%)	2 (3.6%)	
	Other	1 (2.3%)	2 (3.6%)	
Pathologic N stage	N0	13 (29.5%)	13 (23.6%)	0.51
	N1	16 (36.4%)	22 (40.0%)	
	N2	15 (34.1%)	20 (36.4%)	
AJCC 8th staging	Stage I	1 (2.3%)		
	Stage II	12 (27.3%)		
	Stage III	31 (70.4%)		
	Stage IV		55 (100%)	
Grade	1	14 (31.8%)	12 (21.8%)	0.77
	2	26 (59.1%)	37 (67.3%)	
	3	4 (9.1%)	6 (10.9%)	

<i>KRAS</i> status	mutated	11 (25.0%)	20 (36.4%)	0.26
	WT	25 (56.8%)	27 (49.1%)	
	not tested	8 (18.2%)	8 (14.5%)	
<i>BRAF</i> status	mutated	1 (2.3%)	0 (0.0%)	0.27
	WT	35 (79.5%)	44 (80.0%)	
	not tested	8 (18.2%)	11 (20.0%)	
MSI status	high	1 (2.3%)	1 (1.8%)	0.90
	low	35 (79.5%)	42 (76.4%)	
	not tested	8 (2.3%)	12 (21.8%)	
CEA ng/ml		8.9 (0.8-1649.0)	6.8 (1.0-945.0)	0.90
CEA	<5ng/mL	13 (46.4%)	18 (46.2%)	0.98
	>5ng/mL	15 (53.6%)	21 (53.8%)	
Number of examined lymph nodes		11 (0-43)	13 (1-34)	0.38
Lymph node ratio, median (25-75perc)		0.13 (0-0.32)	0.22 (0-0.57)	0.14
Number, median (min-max)		1 (1-7)	2 (1-24)	0.08
Size (cm), median (min-max)		2.7 (0.6-7.1)	2.0 (0.4-26.0)	0.02
Grade	1	18 (42.9%)	21 (39.6%)	0.75
	2	24 (57.1%)	32 (60.4%)	
Metastasis resection	R0	29 (69.0%)	40 (76.9%)	0.39
R status	R1	13 (31.0%)	12 (23.1%)	
Chemotherapy	± CHT alone	30 (68.2%)	28 (50.9%)	0.07
targeted therapy	CHT + anti-VEGF	4 (9.1%)	11 (20.0%)	
	CHT + anti-EGFR	5 (11.4%)	9 (16.4%)	
	no treatment	2 (4.5%)	4 (7.3%)	
	not known	3 (6.8%)	3 (5.4%)	
Chemotherapy regimens	FOLFOX	16 (36.4%)	31 (56.4%)	0.05
	de Gramont	9 (20.5%)	7 (12.7%)	
	FOLFIRI	2 (4.5%)	4 (7.3%)	
	other	12 (27.3%)	6 (10.9%)	

Notes: Bold values indicate statistical significance at the $P < 0.05$ level.

Abbreviations: NOS: not otherwise specified; AJCC: the American joint committee on cancer; WT: wild type; MSI: microsatellite instability; CEA: the carcinoembryonic antigen; R0: No tumor cells detected at the resection margin; R1: tumor cells present at the microscopic resection margin; CHT: chemotherapy.

Supplementary Table 2 The estimated probability of outcomes for patients in synchronous and metachronous groups in Kaplan-Meier analysis

		Metachronous group, N=44		Synchronous group, N=55	
OS	1y	93.2%	(85.7%-100.0%) [§]	87.2%	(78.3%-96.1%)
	3y	62.6%	(47.7%-77.5%)	51.9%	(38.3%-65.5%)
	5y	34.8%	(17.0%-52.7%)	31.3%	(17.9%-44.8%)
DFS	1y	50.0%	(35.2%-64.8%)	35.4%	(22.7%-48.2%)
	3y	17.6%	(5.8%-29.3%)	11.4%	(2.7%-20.1%)
	5y	Not applicable ¹		7.0%	(0%-14.8%)
RFP	1y	50.0%	(35.2%-64.8%)	37.0%	(23.9%-50.2%)
	3y	17.6%	(5.8%-29.3%)	11.9%	(2.9%-21.0%)
	5y	Not applicable ¹		7.3%	(0%-15.5%)

Notes: ¹there were no complete observations after 5 years.

Abbreviations: CRC: colorectal cancer; RFP: recurrence-free proportion; DFS: disease-free survival; OS: overall survival. [§]estimated probability of outcomes (95% confidence interval).

Supplementary Table 3 Correlation between primary colorectal cancer and liver metastasis in synchronous and metachronous groups as for densities of CD66b+ polymorphonuclear neutrophils and CD117+ mast cells

Synchronous				Metachronous			
CD66b	CD66	CD66	CD66b	CD66b	CD66b	CD66b	CD66b

	pTC	b	pIM	b	pPT	pTC	pIM	pOM	pPT
	pOM								
CD66b									
mTC	0.25 ¹				0.04				
CD66b									
mIM		0.22				0.18			
CD66b									
mOM			0.06					0.19	
CD66b									0.15
mPT				-0.02					
	Synchronous				Metachronous				
	CD117	CD117	CD117	CD117	CD117	CD117	CD117	CD117	CD117
	pTC	pIM	pOM	pPT	pTC	pIM	pOM	pPT	
CD117									
mTC	0.17				0.25				
CD117									
mIM		-0.03				0.19			
CD117									
mOM			0.18					0.10	
CD117									
mPT				0.13					0.14

Notes: ¹ Spearman rho.

Abbreviations: pCRC: primary colorectal cancer; LM: liver metastasis; PMNs: Polymorphonuclear neutrophils; MCs: mast cells; pTC: tumor center of pCRC; pIM: inner margin of pCRC; pOM: outer margin of pCRC; pPT: peritumor area of pCRC; mTC: tumor center of LM; mIM: inner margin of LM; mOM: outer margin of LM; mPT: peritumor area of LM.

Supplementary Table 4 Hazard ratios for time to the diagnosis of liver metastases

between high vs low densities of CD66b+ polymorphonuclear neutrophils of nontumor mucosa and per individual regions of interests of primary colorectal cancer in colorectal cancer patients with metachronous metastases

Metachronous		
	N (%)	HR (95% CI), <i>P</i> - value
NM	33 (75.0)	0.86 (0.43-1.72), <i>P</i> = 0.67
pTC	31 (73.8)	0.77 (0.38-1.55), <i>P</i> = 0.46
pIM	31 (73.8)	1.83 (0.85-3.92), <i>P</i> = 0.12
pOM	31 (73.8)	1.14 (0.56-2.34), <i>P</i> = 0.72
pIM/pOM	21 (50.0)	2.29 (1.14-4.61), <i>P</i> = 0.02
pPT	31 (73.8)	1.14 (0.56-2.34), <i>P</i> = 0.72

Notes: Bold values indicate statistical significance at the *P* < 0.05 level.

Abbreviations: PMNs: polymorphonuclear neutrophils; NM: adjacent non-tumor mucosa; ROIs: regions of interest; pCRC: primary colorectal cancer. CRC: colorectal cancer; pTC: tumor center of pCRC; pIM: inner margin of pCRC; pOM: outer margin of pCRC; pPT: peritumor region of pCRC. N: number of patients in “high” group. HR (95% CI): Hazard ratio (95% confidence interval) shows the relative risk compared with 1.00 for the “low” group.

Supplementary Table 5 Hazard ratios for DFS and time to the diagnosis of liver metastases between high vs low densities of CD66b+ polymorphonuclear neutrophils and CD117+ mast cells per individual regions of interests of nontumor mucosa, primary colorectal cancer and liver metastasis in colorectal cancer patients who developed metachronous liver metastasis 3-59 months after surgery of primary colorectal cancer

polymorphonuclear neutrophils		mast cells	
DFS			
N (%)	HR (95% CI), <i>P</i> - value	N (%)	HR (95% CI), <i>P</i> - value

NM	1.61 (0.72-3.62, $P = 29$	0.85 (0.39-1.85, $P =$
	30 (75.0) 0.245) (74.4)	0.686)
pTC	1.00 (0.43-2.35, $P = 27$	2.17 (0.96-4.91, $P =$
	29 (76.3) 0.999) (71.1)	0.064)
pIM	1.41 (0.58-3.44, $P = 27$	0.86 (0.42-1.76, $P =$
	30 (78.9) 0.447) (67.5)	0.682)
pOM	3.31 (1.24-8.80, $P = 29$	0.65 (0.29-1.45, $P =$
	29 (76.3) 0.016) (76.3)	0.296)
pIM/pO	1.32 (0.66-2.67, $P = 19$	1.76 (0.87-3.56, $P =$
M	19 (50.0) 0.433) (50.0)	0.114)
pPT	1.94 (0.83-4.55, $P = 29$	0.89 (0.40-1.99, $P =$
	28 (73.7) 0.125) (76.3)	0.775)
mTC	0.56 (0.25-1.26, $P = 29$	1.10 (0.52-2.33, $P =$
	32 (80.0) 0.161) (72.5)	0.798)
mIM	0.79 (0.34-1.84, $P = 29$	0.86 (0.40-1.87, $P =$
	31 (79.5) 0.586) (74.4)	0.710)
mOM	0.85 (0.38-1.90, $P = 29$	1.76 (0.75-4.13, $P =$
	30 (76.9) 0.689) (74.4)	0.190)
mIM/mO	1.35 (0.67-2.69, $P = 21$	0.99 (0.50-1.97, $P =$
M	20 (51.3) 0.402) (53.8)	0.982)
mPT	1.09 (0.47-2.53, $P = 29$	1.43 (0.64-3.20, $P =$
	30 (76.9) 0.847) (74.4)	0.380)
TLM		
NM	0.85 (0.41-1.76, $P = 29$	0.68 (0.32-1.42, $P =$
	30 (75.0) 0.659) (74.4)	0.304)
pTC	0.86 (0.40-1.85, $P = 27$	1.31 (0.63-2.70, $P =$
	29 (76.3) 0.708) (71.1)	0.468)
pIM	2.84 (1.16-6.97, $P = 27$	1.28 (0.65-2.49, $P =$
	30 (78.9) 0.023) (67.5)	0.475)

pOM	1.35 (0.61-2.96, $P = 29$	0.81 (0.37-1.74, $P =$
	29 (76.3) 0.460)	(76.3) 0.584)
pIM/pO	2.57 (1.22-5.43, $P = 19$	1.05 (0.55-2.02, $P =$
M	19 (50.0) 0.013)	(50.0) 0.876)
pPT	1.14 (0.54-2.43, $P = 29$	0.80 (0.37-1.73, $P =$
	28 (73.7) 0.730)	(76.3) 0.579)

Abbreviations: PMNs: polymorphonuclear neutrophils; MCs: mast cells; DFS: disease free survival; NM: adjacent non-tumor mucosa; ROIs: regions of interest; pCRC: primary colorectal cancer. LM: liver metastasis. pTC: tumor center of pCRC; pIM: inner margin of pCRC; pOM: outer margin of pCRC; pPT: peritumor zone of pCRC; mTC: tumor center of metastasis; mIM: inner margin of LM; mOM: outer margin of LM; mPT: peritumor zone of LM. N: number of patients in “high” group. HR (95% CI): Hazard ratio (95% confidence interval) shows the relative risk compared with 1.00 for the “low” group.

Supplementary Table 6 Hazard ratios for time to recurrence between high vs low densities of CD66b+ polymorphonuclear neutrophils in the nontumor mucosa and per individual regions of interests of primary colorectal cancer and liver metastasis in colorectal cancer patients with synchronous and metachronous metastases

	Synchronous		Metachronous	
	N (%)	HR (95% CI), P - value	N (%)	HR (95% CI), P - value
NM	40 (74.1)	1.60 (0.81-3.16), $P = 0.18$	33 (75.0)	1.56 (0.73-3.35), $P = 0.25$
pTC	40 (75.5)	0.60 (0.31-1.16), $P = 0.13$	31 (73.8)	0.89 (0.41-1.93), $P = 0.77$
pIM	40 (75.5)	0.80 (0.42-1.54), $P = 0.51$	31 (73.8)	1.15 (0.54-2.46), $P = 0.71$
pOM	39 (75.0)	0.99 (0.51-1.92), $P = 0.97$	31 (73.8)	2.59 (1.11-6.02), $P = 0.027$

pIM/pOM	27 (51.9)	0.50 (0.27-0.92), P = 0.027	21 (50.0)	1.30 (0.67-2.51), P = 0.44
pPT	39 (75.0)	0.63 (0.32-1.27), P = 0.20	31 (73.8)	1.92 (0.87-4.25), P = 0.11
mTC	38 (74.5)	0.89 (0.46-1.75), P = 0.75	33 (75.0)	0.48 (0.24-0.99), P = 0.048
mIM	39 (75.0)	1.62 (0.79-3.30), P = 0.19	32 (74.4)	0.65 (0.31-1.36), P = 0.25
mOM	40 (75.5)	2.36 (1.12-4.98), P = 0.024	32 (74.4)	0.76 (0.36-1.58), P = 0.46
mIM/mOM	26 (49.1)	0.80 (0.44-1.45), P = 0.46	21 (48.8)	1.23 (0.64-2.36), P = 0.53
mPT	40 (75.5)	2.54 (1.20-5.40), P = 0.015	32 (74.4)	0.93 (0.44-1.99), P = 0.85

Notes: Bold values indicate statistical significance at the $P < 0.05$ level.

Abbreviations: TTR: time to recurrence; PMNs: polymorphonuclear neutrophils; NM: adjacent non-tumor mucosa; ROIs: regions of interest; pCRC: primary colorectal cancer. LM: liver metastasis. CRC: colorectal cancer; pTC: tumor center of pCRC; pIM: inner margin of pCRC; pOM: outer margin of pCRC; pPT: peritumor area of pCRC; mTC: tumor center of metastasis; mIM: inner margin of LM; mOM: outer margin of LM; mPT: peritumor area of LM. N: number of patients in “high” group. HR (95% CI): Hazard ratio (95% confidence interval) shows the relative risk compared with 1.00 for the “low” group.

Supplementary Table 7 Hazard ratios for time to recurrence between high vs low densities of CD117+ mast cells in the nontumor mucosa and per individual regions of interests of primary colorectal cancer and liver metastasis in colorectal cancer patients with synchronous and metachronous metastases

Synchronous	Metachronous
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	N (%)	HR (95% CI), P - value	N (%)	HR (95% CI), P - value
NM	40 (74.1)	1.36 (0.68-2.74), P = 0.39	32 (74.4)	0.85 (0.41-1.77), P = 0.67
pTC	40 (74.1)	0.60 (0.31-1.14), P = 0.12	31 (73.8)	2.34 (1.05-5.23), P = 0.038
pIM	40 (74.1)	0.94 (0.48-1.83), P = 0.85	31 (70.5)	0.96 (0.48-1.92), P = 0.92
pOM	40 (74.1)	0.90 (0.47-1.71), P = 0.74	31 (73.8)	0.67 (0.32-1.40), P = 0.28
pIM/pOM	27 (50.0)	1.57 (0.87-2.83), P = 0.14	21 (50.0)	1.66 (0.86-3.22), P = 0.13
pPT	40 (74.1)	0.93 (0.49-1.78), P = 0.83	31 (73.8)	0.86 (0.41-1.80), P = 0.69
mTC	39 (75.0)	0.67 (0.34-1.32), P = 0.25	33 (75.0)	1.20 (0.57-2.49), P = 0.63
mIM	39 (75.0)	0.90 (0.45-1.78), P = 0.75	32 (74.4)	0.83 (0.40-1.72), p= 0.62
mOM	40 (75.5)	1.29 (0.62-2.68), P = 0.50	32 (74.4)	1.61 (0.73-3.58), P = 0.24
mIM/mOM	27 (50.9)	0.63 (0.35-1.14), P = 0.12	22 (51.2)	0.93 (0.48-1.78), P = 0.82
mPT	40 (75.5)	0.78 (0.39-1.55), P = 0.47	32 (74.4)	1.35 (0.63-2.88), P = 0.44

Notes: Bold values indicate statistical significance at the $P < 0.05$ level.

Abbreviations: TTR: time to recurrence; MCs: mast cells; NM: adjacent non-tumor mucosa; ROIs: regions of interest; pCRC: primary colorectal cancer. LM: liver metastasis; CRC: colorectal cancer; pTC: tumor center of pCRC; pIM: inner margin of pCRC; pOM: outer margin of pCRC; pPT: peritumor area of pCRC; mTC: tumor center of metastasis; mIM:

inner margin of LM; mOM: outer margin of LM; mPT: peritumor area of LM. N: number of patients in “high” group. HR (95% CI): Hazard ratio (95% confidence interval) shows the relative risk compared with 1.00 for the “low” group.

Supplementary Table 8 Hazard ratios for overall survival between high vs low densities of CD66b+ polymorphonuclear neutrophils in the nontumor mucosa and per individual regions of interests of primary colorectal cancer and liver metastasis in colorectal cancer patients with synchronous and metachronous metastases

	Synchronous		Metachronous	
	N (%)	HR (95% CI), P - value	N (%)	HR (95% CI), P - value
NM	40 (74.1)	1.24 (0.61-2.54), P = 0.56	33 (75.0)	1.48 (0.55-3.99), P = 0.44
pTC	40 (75.5)	1.36 (0.64-2.90), P = 0.43	31 (73.8)	0.68 (0.28-1.68), P = 0.41
pIM	40 (75.5)	1.48 (0.72-3.07), P = 0.29	31 (73.8)	0.98 (0.38-2.51), P = 0.97
pOM	39 (75.0)	0.74 (0.36-1.51), P = 0.40	31 (73.8)	1.15 (0.45-2.95), P = 0.77
pIM/pOM	27 (51.9)	0.91 (0.48-1.71), P = 0.77	21 (50.0)	0.60 (0.25-1.40), P = 0.24
pPT	39 (75.0)	1.00 (0.49-2.07), P = 0.99	31 (73.8)	1.13 (0.44-2.90), P = 0.80
mTC	38 (74.5)	1.55 (0.73-3.30), P = 0.25	33 (75.0)	0.63 (0.27-1.49), P = 0.30
mIM	39 (75.0)	1.85 (0.85-4.04), P = 0.12	32 (74.4)	0.79 (0.32-1.92), P = 0.60
mOM	40 (75.5)	2.24 (0.93-5.37), P = 0.07	32 (74.4)	0.85 (0.35-2.10), P = 0.73

mIM/mOM	26	1.28 (0.69-2.39), <i>P</i> =	21	2.37 (0.99-5.67), <i>P</i> =
	(49.1)	0.44	(48.8)	0.05
mPT	40	1.89 (0.83-4.30), <i>P</i> =	32	0.77 (0.31-1.87), <i>P</i> =
	(75.5)	0.13	(74.4)	0.56

Abbreviations: OS: overall survival; PMNs: polymorphonuclear neutrophils; NM: adjacent non-tumor mucosa; ROIs: regions of interest; pCRC: primary colorectal cancer. LM: liver metastasis. CRC: primary colorectal cancer; pTC: tumor center of pCRC; pIM: inner margin of pCRC; pOM: outer margin of pCRC; pPT: peritumor area of pCRC; mTC: tumor center of metastasis; mIM: inner margin of LM; mOM: outer margin of LM; mPT: peritumor area of LM. N: number of patients in “high” group. HR (95% CI): Hazard ratio (95% confidence interval) shows the relative risk compared with 1.00 for the “low” group.

Supplementary Table 9 Hazard ratios for overall survival between high vs low densities of CD117+ mast cells in the nontumor mucosa and per individual regions of interests of primary colorectal cancer and liver metastasis in colorectal cancer patients with synchronous and metachronous metastases

		Synchronous		Metachronous	
	N (%)	HR (95% CI), <i>P</i> - value	N (%)	HR (95% CI), <i>P</i> - value	
NM	40	1.10 (0.51-2.37), <i>P</i> =	32	0.61 (0.25-1.51), <i>P</i> =	
	(74.1)	0.80	(74.4)	0.29	
pTC	40	0.82 (0.40-1.69), <i>P</i> =	31	1.80 (0.69-4.70), <i>P</i> =	
	(74.1)	0.59	(73.8)	0.23	
pIM	40	0.91 (0.45-1.85), <i>P</i> =	31	1.89 (0.74-4.83), <i>P</i> =	
	(74.1)	0.80	(70.5)	0.18	
pOM	40	0.73 (0.36-1.47), <i>P</i> =	31	1.09 (0.43-2.79), <i>P</i> =	
	(74.1)	0.38	(73.8)	0.86	
pIM/pOM	27	0.97 (0.52-1.80), <i>P</i> =	21	2.34 (0.98-5.60), <i>P</i> =	

	(50.0)	0.92		(50.0)	0.06
pPT	40	0.93 (0.46-1.87), <i>P</i> =	31	0.67 (0.26-1.75), <i>P</i> =	
	(74.1)	0.84	(73.8)	0.42	
mTC	39	0.82 (0.41-1.67), <i>P</i> =	33	0.88 (0.37-2.07), <i>P</i> =	
	(75.0)	0.59	(75.0)	0.77	
mIM	39	0.72 (0.34-1.54), <i>P</i> =	32	0.87 (0.36-2.14), <i>P</i> =	
	(75.0)	0.40	(74.4)	0.77	
mOM	40	0.68 (0.31-1.47), <i>P</i> =	32	1.10 (0.43-2.82), <i>P</i> =	
	(75.5)	0.33	(74.4)	0.84	
mIM/mOM	27	1.14 (0.60-2.15), <i>P</i> =	22	0.87 (0.38-1.99), <i>P</i> =	
	(50.9)	0.70	(51.2)	0.74	
mPT	40	0.56 (0.27-1.15), <i>P</i> =	32	0.95 (0.37-2.42), <i>P</i> =	
	(75.5)	0.12	(74.4)	0.91	

Abbreviations: OS: overall survival; MCs: mast cells; NM: adjacent non-tumor mucosa; ROIs: regions of interest; pCRC: primary colorectal cancer. LM: liver metastasis. CRC: primary colorectal cancer; pTC: tumor center of pCRC; pIM: inner margin of pCRC; pOM: outer margin of pCRC; pPT: peritumor area of pCRC; mTC: tumor center of metastasis; mIM: inner margin of LM; mOM: outer margin of LM; mPT: peritumor area of LM. N: number of patients in “high” group. HR (95% CI): Hazard ratio (95% confidence interval) shows the relative risk compared with 1.00 for the “low” group.

Supplementary Table 10 Hazard ratios for time to the diagnosis of liver metastases between high vs low densities of CD117+ mast cells in the nontumor mucosa and per individual regions of interests of primary colorectal cancer in colorectal cancer patients with metachronous metastases

Metachronous		
	N (%)	HR (95% CI), <i>P</i> - value
NM	32 (74.4)	0.71 (0.35-1.43), <i>P</i> = 0.34

pTC	31 (73.8)	1.47 (0.72-2.98), $P = 0.29$
pIM	31 (70.5)	1.43 (0.74-2.74), $P = 0.29$
pOM	31 (73.8)	0.73 (0.36-1.47), $P = 0.38$
pIM/pOM	21 (50.0)	1.05 (0.56-1.94), $P = 0.89$
pPT	31 (73.8)	0.72 (0.36-1.47), $P = 0.37$

Abbreviations: MCs: mast cells; NM: adjacent non-tumor mucosa; ROIs: regions of interest; pCRC: primary colorectal cancer: pTC: tumor center of pCRC; pIM: inner margin of pCRC; pOM: outer margin of pCRC; pPT: peritumor area of pCRC; N: number of patients in “high” group; HR (95% CI): Hazard ratio (95% confidence interval) shows the relative risk compared with 1.00 for the “low” group.

Supplementary Table 11 Hazard ratios for DFS between high vs low densities of CD117+ mast cells per individual regions of interests in the subset of patients with CD117-negative tumor cells

ROI	Synchronous		Metachronous	
	N (%)	HR (95% CI), P - value	N (%)	HR (95% CI), P - value
NM		1.37 (0.55-4.15), $P =$	27	
	29 (62)	0.50	(70.3)	0.90 (0.36-2.53), $P = 0.83$
pTC		1.10 (0.49-2.62), $P =$	27	
	29 (62)	0.80	(59.3)	2.3 (0.88-7.12), $P = 0.09$
pIM		1.46 (0.65-3.60), $P =$		
	29 (62)	0.36	27 (63)	0.97 (0.42-2.28), $P = 0.94$
pOM		1.83 (0.80-4.51), $P =$	27	
	29 (62)	0.14	(59.2)	0.73 (0.3-1.95), $P = 0.51$
pPT		1.63 (0.70-4.24), $P =$	27	
	29 (62)	0.25	(66.7)	0.85 (0.34-2.42), $P = 0.75$

mTC	36	0.71 (0.31-1.84), <i>P</i> =	24	
	(69.4)	0.46	(58.3)	1.35 (0.57-3.31), <i>P</i> = 0.48
mIM	36	0.88 (0.37-2.43), <i>P</i> =	24	
	(72.2)	0.79	(58.3)	0.89 (0.38-2.08), <i>P</i> = 0.81
mOM	36	1.06 (0.46-2.88), <i>P</i> =	24	
	(72.2)	0.89	(62.5)	1.16 (0.49-2.95), <i>P</i> = 0.73
mPT		0.58 (0.22-1.38), <i>P</i> =	24	
	36 (75)	0.18	(70.8)	0.90 (0.36-2.54), <i>P</i> = 0.83

Abbreviations: MCs: mast cells; DFS: disease free survival. NM: adjacent non-tumor mucosa; ROIs: regions of interest. pTC: tumor center of pCRC; pIM: inner margin of pCRC; pOM: outer margin of pCRC; pPT: peritumor zone of pCRC; mTC: tumor center of metastasis; mIM: inner margin of LM; mOM: outer margin of LM; mPT: peritumor zone of LM. N: number of patients in “high” group. HR (95% CI): Hazard ratio (95% confidence interval) shows the relative risk compared with 1.00 for the “low” group.

Supplementary Table 12 Validation of highlighted significant associations of densities of polymorphonuclear neutrophils and mast cells with outcomes colorectal cancer patients with synchronous and metachronous liver metastasis

Variable	Categorical cell densities		cell	Continuous cell densities		Cox-Mantel test
	HR	(95 %CI),	<i>P</i>	HR (95 %CI),	<i>P</i> value	<i>P</i> value/cut-off ¹
	value					
Synchronous group, DFS						
CD66b+ PMNs	2.40 (1.14-5.04),			1.0003 (0.9995-1.0012),		<i>P</i> = 0.0068
mOM	<i>P</i> = 0.021			<i>P</i> = 0.2467		at 68 cells/mm ²
CD66b+ PMNs	2.58 (1.22-5.46),					
mPT	<i>P</i> = 0.013			1.0006 (0.9999-1.0013),		<i>P</i> = 0.0040

		$P = 0.0511$	at 49 cells/mm ²
Metachronous group, DFS			
CD66b+ PMNs	2.59 (1.11-6.02),	1.0003 (0.9995-1.0012),	$P = 0.0082$
pOM	$P = 0.027$	$P = 0.1957$	at 58 cells/mm ²
CD66b+ PMNs	0.48 (0.24-0.99),	1.0000 (0.9991-1.0009),	$P = 0.0440$
mTC	$P = 0.048$	$P = 0.2602$	at 43 cells/mm ²
CD117+ MCs	2.34 (1.05-5.23),	1.0001 (0.9997-1.0016),	$P = 0.0320$
pTC	$P = 0.038$	$P = 0.3455$	at 15 cells/mm ²
Metachronous group, TLM			
CD66b+ PMNs	2.29 (1.14-4.61),	1.1414 (1.0033-1.2986),	$P = 0.0060$
pIM/pOM	$P = 0.02$	$P = 0.0487$	at 1.32

¹: Cox-Mantel test P value at a cut-off selected using a minimum P-value approach.

Abbreviations: PMNs: polymorphonuclear neutrophils; MCs: mast cells; DFS: disease-free survival, TLM: time to the diagnosis of liver metastases, LM: liver metastases; CRC: colorectal cancer; HR: hazard ratio; CI: confidence interval; pTC: tumor center of pCRC; pIM: inner margin of pCRC; pOM: outer margin of pCRC; mTC: tumor center of metastasis; mOM: outer margin of LM; mPT: peritumor area of LM. Hazard ratio (95% confidence interval) shows the relative risk compared with 1.00 for the low categorical density and the change in risk for a one-cell/mm² increase for continuous cell densities.

Supplementary Table 13 Densities of CD66b+ polymorphonuclear neutrophils and CD117+ mast cells in primary colorectal cancer and liver metastasis associated with DFS (multivariable analysis) in colorectal cancer patients

Cell type and location		N (%)	HR (95%CI), P value
Synchronous			
Model 1			
CD66b mOM	Low	13 (24.5)	-
	High	40 (75.5)	2.98 (1.30-6.84), $P = 0.01$

Age	Under		-
	med	25 (45.5)	
	Above		
	med	30 (54.5)	2.47 (1.20-5.08), <i>P</i> = 0.014
N stage	0	13 (23.6)	-
	1	22 (40.0)	1.54 (0.60-3.97), <i>P</i> = 0.37
	2	20 (36.4)	1.48 (0.57-3.87), <i>P</i> = 0.43
Grade of pCRC	1	9 (19.1)	-
	2	32 (68.1)	0.75 (0.29-1.97), <i>P</i> = 0.56
	3	6 (12.8)	0.52 (0.16-1.72), <i>P</i> = 0.29
Model 2			
CD66b mOM	Low	13 (24.5)	-
	High	40 (75.5)	3.25 (1.42-7.43), <i>P</i> = 0.005
Number of LM	1	25 (46.3)	-
	>1	29 (53.7)	1.04 (0.55-1.98), <i>P</i> = 0.90
Size of LM	Under		-
	med	27 (49.1)	
	Above		
	med	28 (50.9)	0.54 (0.29-1.02), <i>P</i> = 0.058
Grade of LM	1	21 (39.6)	-
	2	32 (60.4)	0.69 (0.36-1.35), <i>P</i> = 0.28
Model 3			
CD66b mOM	Low	13 (24.5)	-
	High	40 (75.5)	3.73 (1.62-8.57), <i>P</i> = 0.002
Targeted therapy	No	29 (59.2)	-
	Yes	20 (40.8)	1.86 (0.86-4.04), <i>P</i> = 0.12
Regimen	Other	24 (43.6)	-
	FOLFOX	31 (56.4)	1.39 (0.67-2.88), <i>P</i> = 0.37
Model 4			

CD66b mPT	Low	13 (24.5)	-
	High	40 (75.5)	3.07 (1.33-7.08), <i>P</i> = 0.008
Age	Under med25 (45.5)		-
	Above med30 (54.5)		2.17 (1.08-4.37), <i>P</i> = 0.03
N stage	0	13 (23.6)	-
	1	22 (40.0)	1.72 (0.67-4.43), <i>P</i> = 0.26
	2	20 (36.4)	1.61 (0.62-4.19), <i>P</i> = 0.33
Grade of pCRC	1	9 (19.1)	-
	2	32 (68.1)	0.73 (0.28-1.88), <i>P</i> = 0.52
	3	6 (12.8)	0.53 (0.16-1.76), <i>P</i> = 0.30

Model 5

CD66b mPT	Low	13 (24.5)	-
	High	40 (75.5)	3.14 (1.43-6.93), <i>P</i> = 0.005
Number of LM	1	25 (46.3)	-
	>1	29 (53.7)	1.08 (0.57-2.06), <i>P</i> = 0.80
Size of LM	Under med	27 (49.1)	-
	Above med	28 (50.9)	0.54 (0.29-1.02), <i>P</i> = 0.057
Grade of LM	1	21 (39.6)	-
	2	32 (60.4)	0.74 (0.38-1.44), <i>P</i> = 0.38

Model 6

CD66b mPT	Low	13 (24.5)	-
	High	40 (75.5)	4.09 (1.75-9.52), <i>P</i> = 0.001
Targeted therapy	No	29 (59.2)	-
	Yes	20 (40.8)	1.99 (0.95-4.17), <i>P</i> = 0.07
Regimen	Other	24 (43.6)	-
	FOLFOX	31 (56.4)	1.32 (0.67-2.62), <i>P</i> = 0.43

Metachronous			
Model 7			
CD66b pOM	Low	11 (26.2)	-
	High	31 (73.8)	2.64 (0.93-7.54), <i>P</i> = 0.07
Age	Under med25	56.8	-
	Above med19	43.2	1.81 (0.89-3.64), <i>P</i> = 1.00
N stage	0	13 (29.5)	-
	1	16 (36.4)	2.25 (0.87-5.79), <i>P</i> = 0.09
	2	15 (34.1)	1.26 (0.43-3.69), <i>P</i> = 0.68
Grade of pCRC	1	14 (31.8)	-
	2	26 (59.1)	0.99 (0.35-2.77), <i>P</i> = 0.98
	3	4 (9.1)	0.45 (0.09-2.16), <i>P</i> = 0.32
Model 8			
CD66b pOM	Low	11 (26.2)	-
	High	31 (73.8)	2.24 (0.94-5.34), <i>P</i> = 0.07
Number of LM	1	25 (58.1)	-
	>1	18 (41.9)	1.47 (0.69-3.15), <i>P</i> = 0.32
Size of LM	Under		
	med	22 (50.0)	-
	Above		
	med	22 (50.0)	1.01 (0.48-2.15), <i>P</i> = 0.97
Grade of LM	1	18 (42.9)	-
	2	24 (57.1)	1.19 (0.60-2.36), <i>P</i> = 0.63
Model 9			
CD66b pOM	Low	11 (26.2)	-
	High	31 (73.8)	2.54 (1.08-5.94), <i>P</i> = 0.032
Targeted therapy	No	30 (75.0)	-
	Yes	10 (25.0)	1.68 (0.75-3.79), <i>P</i> = 0.21
Regimen	Other	28 (63.6)	-

	FOLFOX	16 (36.4)	0.65 (0.31-1.39), <i>P</i> = 0.27
Model 10			
CD66b mTC	Low	11 (25.0)	
	High	33 (75.0)	0.46 (0.21-1.03), <i>P</i> = 0.059
Age	Under med25	(56.8)	
	Above med19	(43.2)	2.36 (1.15-4.85), <i>P</i> = 0.019
N stage	0	13 (29.5)	-
	1	16 (36.4)	1.80 (0.79-4.07), <i>P</i> = 0.16
	2	15 (34.1)	1.00 (0.39-2.55), <i>P</i> = 1.00
Grade of pCRC	1	14 (31.8)	-
	2	26 (59.1)	1.50 (0.66-3.42), <i>P</i> = 0.33
	3	4 (9.1)	0.58 (0.12-2.75), <i>P</i> = 0.49
Model 11			
CD66b mTC	Low	11 (25.0)	
	High	33 (75.0)	0.51 (0.24-1.07), <i>P</i> = 0.08
Number of LM	1	25 (58.1)	-
	>1	18 (41.9)	1.41 (0.69-2.87), <i>P</i> = 0.35
Size of LM	Under		
	med	22 (50.0)	-
	Above		
	med	22 (50.0)	1.21 (0.61-2.43), <i>P</i> = 0.58
Grade of LM	1	18 (42.9)	-
	2	24 (57.1)	1.43 (0.72-2.84), <i>P</i> = 0.31
Model 12			
CD66b mTC	Low	11 (25.0)	
	High	33 (75.0)	0.51 (0.24-1.07), <i>P</i> = 0.08
Targeted therapy	No	30 (75.0)	-
	Yes	10 (25.0)	1.52 (0.70-3.32), <i>P</i> = 0.29
Regimen	Other	28 (63.6)	-

	FOLFOX	16 (36.4)	0.81 (0.40-1.64), <i>P</i> = 0.56
Model 13			
CD117 pTC	Low	11 (26.2)	-
	High	31 (73.8)	2.39 (0.98-5.80), <i>P</i> = 0.054
Age	Under med25	(56.8)	
	Above med19	(43.2)	1.93 (0.95-3.93), <i>P</i> = 0.07
N stage	0	13 (29.5)	-
	1	16 (36.4)	2.09 (0.85-5.13), <i>P</i> = 0.11
	2	15 (34.1)	1.27 (0.45-3.54), <i>P</i> = 0.65
Grade of pCRC	1	14 (31.8)	-
	2	26 (59.1)	1.32 (0.56-3.10), <i>P</i> = 0.53
	3	4 (9.1)	0.50 (0.11-2.34), <i>P</i> = 0.38
Model 14			
CD117 pTC	Low	11 (26.2)	-
	High	31 (73.8)	1.93 (0.83-4.49), <i>P</i> = 0.13
Number of LM	1	25 (58.1)	-
	>1	18 (41.9)	1.17 (0.56-2.47), <i>P</i> = 0.67
Size of LM	Under		
	med	22 (50.0)	-
	Above		
	med	22 (50.0)	1.03 (0.50-2.12), <i>P</i> = 0.94
Grade of LM	1	18 (42.9)	-
	2	24 (57.1)	1.20 (0.60-2.38), <i>P</i> = 0.61
Model 15			
CD117 pTC	Low	11 (26.2)	-
	High	31 (73.8)	2.57 (1.13-5.82), <i>P</i> = 0.024
Targeted therapy	No	30 (75.0)	-
	Yes	10 (25.0)	1.69 (0.77-3.74), <i>P</i> = 0.19
Regimen	Other	28 (63.6)	-

	FOLFOX	16 (36.4)	0.64 (0.31-1.34), <i>P</i> = 0.24
Model 16			
CD117 pTC	Low	11 (26.2)	-
	High	31 (73.8)	0.40 (0.18-0.92, <i>P</i> = 0.031)
Cytoplasmic staining of CD117 in pCRC TC	Negative	27 (61.4)	-
	Positive	17 (38.6)	0.80 (0.40-1.58, <i>P</i> = 0.516)

Notes: Models 1, 4, 7, 10, 13: adjusted for Age, N stage and grade of primary tumor; models 2, 5, 8, 11, 14: adjusted for number, size and grade of liver metastases; models 3, 6, 9, 12, 15: adjusted for chemotherapy regimen (FOLFOX vs other and use of targeted therapy); model 16: adjusted for cytoplasmic staining of CD117. Bold values indicate statistical significance at the *P* < 0.05 level. Abbreviations: DFS: disease-free survival; PMNs: polymorphonuclear neutrophils; MCs: mast cells; pCRC: primary colorectal cancer; LM: liver metastases; pTC: tumor center of pCRC; pIM: inner margin of pCRC; pOM: outer margin of pCRC; pPT: peritumor area of pCRC; mTC: tumor center of metastasis; mIM: inner margin of LM; mOM: outer margin of LM; mPT: peritumor area of LM.

Supplementary Table 14 Hazard ratios for DFS between CD117+ mast cells and CD66b+ polymorphonuclear neutrophils high/low, low/high and high/high vs. low/low density in the nontumor mucosa and per individual regions of interests of primary colorectal cancer and liver metastasis in colorectal cancer patients with synchronous and metachronous metastases

Cell type and location	Group	Synchronous			Metachronous		
		N (%)	HR (95% CI), <i>P</i> - value		N (%)	HR (95% CI), <i>P</i> - value	
NM	High/Lo	11 (20.4)	4.36 (0.55-34.52), <i>P</i> = 0.16		10 (23.3)	0.84 (0.10-6.85), <i>P</i> = 0.87	

7&CD	Low/Hig	11	4.92 (0.62-39.06), $P =$	10	1.34 (0.17-10.83), $P =$
66b	h	(20.4)	0.13	(23.3)	0.78
	High/Hi	29	5.97 (0.80-44.69), $P =$	22	1.30 (0.17-9.73), $P =$
	gh	(53.7)	0.08	(51.2)	0.80
pTC	High/Lo		1.14 (0.38-3.38), $P =$	7	7.70 (1.47-40.43), $P =$
CD11	w	7 (13.2)	0.82	(16.7)	0.02
7&CD	Low/Hig		1.04 (0.33-3.25), $P =$	7	1.93 (0.38-9.77), $P =$
66b	h	8 (15.1)	0.94	(16.7)	0.43
	High/Hi	32	0.64 (0.26-1.57), $P =$	24	3.26 (0.74-14.37), $P =$
	gh	(60.4)	0.33	(57.1)	0.12
pIM	High/Lo		0.32 (0.10-1.08), $P =$	8	0.48 (0.13-1.75), $P =$
CD11	w	9 (17.0)	0.07	(18.6)	0.27
7&CD	Low/Hig	10	0.26 (0.07-0.90), $P =$	8	0.56 (0.16-1.95), $P =$
66b	h	(18.9)	0.034	(18.6)	0.37
	High/Hi	30	0.38 (0.13-1.13), $P =$	23	0.77 (0.26-2.30), $P =$
	gh	(56.6)	0.08	(53.5)	0.64
pOM	High/Lo		1.08 (0.33-3.56), $P =$	7	0.22 (0.05-0.98), $P =$
CD11	w	7 (13.5)	0.89	(16.7)	0.05
7&CD	Low/Hig		1.33 (0.42-4.19), $P =$	7	1.15 (0.33-4.05), $P =$
66b	h	8 (15.4)	0.63	(16.7)	0.82
	High/Hi	31	1.15 (0.44-2.99), $P =$	24	1.00 (0.34-2.93), $P =$
	gh	(59.6)	0.78	(57.1)	0.10
pPT	High/Lo		0.54 (0.17-1.73), $P =$	7	0.54 (0.13-2.17), $P =$
CD11	w	8 (14.8)	0.30	(16.7)	0.39
7&CD	Low/Hig		0.29 (0.09-0.93), $P =$	7	1.52 (0.42-5.51), $P =$
66b	h	7 (13.0)	0.038	(16.7)	0.52
	High/Hi	32	0.49 (0.21-1.15), $P =$	24	1.31 (0.45-3.83), $P =$
	gh	(59.3)	0.10	(57.1)	0.62
mTC	High/Lo	12	1.57 (0.20-12.22), $P =$	6	1.59 (0.46-5.57), $P =$

CD11	w	(23.5)	0.67	(13.6)	0.47
7&CD	Low/Hig	12	2.06 (0.26-16.17), <i>P</i> =	6	0.44 (0.13-1.54), <i>P</i> =
66b	h	(23.5)	0.49	(13.6)	0.20
	High/Hi	26	1.23 (0.16-9.23), <i>P</i> =	27	0.65 (0.24-1.74), <i>P</i> =
	gh	(51.0)	0.84	(61.4)	0.39
mIM	High/Lo	10	1.11 (0.24-5.24), <i>P</i> =	7	0.34 (0.09-1.24), <i>P</i> =
CD11	w	(19.2)	0.90	(16.3)	0.10
7&CD	Low/Hig	10	2.04 (0.44-9.53), <i>P</i> =	7	0.26 (0.07-0.98), <i>P</i> =
66b	h	(19.2)	0.36	(16.3)	0.05
	High/Hi	29	1.79 (0.42-7.60), <i>P</i> =	25	0.31 (0.10-0.93), <i>P</i> =
	gh	(55.8)	0.43	(58.1)	0.04
mOM	High/Lo	10	3.44 (0.43-27.66), <i>P</i> =	7	0.20 (0.05-0.74), <i>P</i> =
CD11	w	(18.9)	0.25	(16.3)	0.02
7&CD	Low/Hig	10	7.78 (0.95-63.38), <i>P</i> =	7	0.09 (0.02-0.37), <i>P</i> =
66b	h	(18.9)	0.055	(16.3)	0.001
	High/Hi	30	6.28 (0.84-46.80), <i>P</i> =	25	0.29 (0.10-0.88), <i>P</i> =
	gh	(56.6)	0.07	(58.1)	0.03
mPT	High/Lo	10	0.76 (0.16-3.66), <i>P</i> =	5	0.42 (0.11-1.59), <i>P</i> =
CD11	w	(18.9)	0.73	(11.6)	0.20
7&CD	Low/Hig	10	2.62 (0.56-12.31), <i>P</i> =	5	0.28 (0.07-1.07), <i>P</i> =
66b	h	(18.9)	0.22	(11.6)	0.06
	High/Hi	30	1.95 (0.46-8.28), <i>P</i> =	27	0.70 (0.26-1.85), <i>P</i> =
	gh	(56.6)	0.37	(62.8)	0.47

Notes: Bold values indicate statistical significance at the *P* < 0.05 level.

Abbreviations: DFS: disease-free survival; NM: adjacent non-tumor mucosa; ROIs: regions of interest; pCRC: primary colorectal cancer; LM: liver metastases; CRC: colorectal cancer; HR: hazard ratio; CI: confidence interval; pTC: tumor center of pCRC; pIM: inner margin of pCRC; pOM: outer margin of pCRC; pPT: peritumor area of pCRC; mTC: tumor center of metastasis; mIM: inner margin of LM; mOM: outer margin of LM; mPT: peritumor area of

LM. N: number of patients with high cell densities and proportions. HR (95% CI): Hazard ratio (95% confidence interval) shows the relative risk compared with 1.00 for the low density.

Supplementary Table 15 Associations of clinical and pathology variables in primary colorectal cancer and liver metastasis with DFS (univariable analysis) in patients with synchronous and metachronous liver metastasis

Variables	Group	Synchronous		Metachronous	
		N (%)	HR (95% CI), P - value	N (%)	HR (95% CI), P - value
DFS					
Gender	Male	34 (61.8)	1.00	29 (65.9)	1.00
	Female	21 (38.2)	0.76 (0.42-1.37), P = 0.37	15 (34.1)	1.44 (0.74-2.81), P = 0.29
Age	Above median	25 (45.5)	1.00	25 (56.8)	1.00
	Under median	30 (54.5)	1.66 (0.93-2.95), P = 0.09	19 (43.2)	1.96 (1.01-3.80), P = 0.046
Size of pCRC	Under median	27 (49.1)	1.00	22 (50.0)	1.00
	Above median	28 (50.9)	0.99 (0.56-1.75), P = 0.97	22 (50.0)	1.38 (0.71-2.68), P = 0.34
Grade of pCRC	Low	48 (88.9)	1.00	40 (90.9)	1.00
	High	6 (11.1)	0.65 (0.25-1.64), P = 0.36	4 (9.1)	0.39 (0.09-1.62), P = 0.19
Sidedness	Right	12 (21.8)	1.00	8 (18.2)	1.00

	Left	43	0.91 (0.46-1.81), <i>P</i> =	36 (81.8)	0.70 (0.31-1.62), <i>P</i> =
		(78.2)	0.78		0.41
N grade	0	13	1.00	13 (29.5)	1.00
		(23.6)			
	1-2	42	1.25 (0.65-2.42), <i>P</i> =	31 (70.5)	1.18 (0.59-2.34), <i>P</i> =
		(76.4)	0.50		0.65
Size of LM	Under	31	1.00	17 (38.6)	1.00
	median	(56.4)			
	Above	24	0.77 (0.43-1.37), <i>P</i> =	27 (61.4)	1.10 (0.56-2.14), <i>P</i> =
	median	(43.6)	0.38		0.78
Number	Under	25	1.00	25 (58.1)	1.00
LM	median	(46.3)			
	Above	29	1.24 (0.70-2.21), <i>P</i> =	18 (41.9)	1.55 (0.79-3.06), <i>P</i> =
	median	(53.7)	0.46		0.20
Grade of	Low	21	1.00	18 (42.9)	1.00
LM		(39.6)			
	High	32	0.87 (0.49-1.58), <i>P</i> =	24 (57.1)	1.32 (0.68-2.54), <i>P</i> =
		(60.4)	0.66		0.41
Margin of	R0	40	1.00	29 (69.0)	1.00
LM		(76.9)			
	R1	12	1.43 (0.73-2.83), <i>P</i> =	13 (31.0)	1.52 (0.74-3.10), <i>P</i> =
		(23.1)	0.300		0.25
CHT	Other	24 (43.6)	1.00	28 (63.6)	1.00
regimen	FOLFOX		1.44 (0.81-2.56), <i>P</i> =		0.77 (0.39-1.51), <i>P</i> =
		31 (56.4)	0.21	16 (36.4)	0.45
Use of	No	29 (59.2)	1.00	30 (75.0)	1.00
targeted	Yes		1.48 (0.80-2.71), <i>P</i> =		1.50 (0.69-3.25), <i>P</i> =
therapy		20 (40.8)	0.21	10 (25.0)	0.31

Notes: Bold values indicate statistical significance at the *P*< 0.05 level. Median age: synchronous =

62, metachronous = 64; median size for primary tumor: synchronous = 4.3 cm, metachronous = 3.5 cm; median size of liver metastasis: synchronous = 2.0 cm, metachronous = 2.7 cm. Abbreviations: pCRC: primary colorectal cancer; LM: liver metastases; CRC: colorectal cancer; HR: hazard ratio; CI: confidence interval; DFS: disease-free survival; CHT: chemotherapy.

Supplementary Table 16 Hazard ratios for DFS between high vs low densities of CD66b+ polymorphonuclear neutrophils and CD117+ mast cells in the nontumor mucosa and per individual regions of interests of primary colorectal cancer and liver metastasis in the overall cohort of 99 colorectal cancer patients

	N (%)	HR (95% CI), <i>P</i> - value
CD66b+ polymorphonuclear neutrophils		
NM	75 (76.5)	1.68 (0.98-2.73), <i>P</i> = 0.07
pTC	71 (74.7)	0.73 (0.46-1.22), <i>P</i> = 0.22
pIM	71 (74.7)	0.97 (0.60-1.62), <i>P</i> = 0.09
pOM	70 (74.4)	1.62 (0.98-2.83), <i>P</i> = 0.06
pPT	70 (74.4)	1.05 (0.65-1.79), <i>P</i> = 0.84
mTC	74 (77.9)	0.71 (0.45-1.18), <i>P</i> = 0.18
mIM	74 (77.9)	1.14 (0.70-1.94), <i>P</i> = 0.59
mOM	74 (77.9)	1.44 (0.88-2.47), <i>P</i> = 0.15
mPT	74 (77.9)	1.66 (1.00-2.90), <i>P</i> = 0.048
CD117+ mast cells		
NM	74 (76.2)	1.20 (0.73-2.04), <i>P</i> = 0.49
pTC	72 (75.0)	1.25 (0.77-2.12), <i>P</i> = 0.39
pIM	74 (75.5)	1.05 (0.66-1.73), <i>P</i> = 0.85

pOM	72 (75.0)	0.87 (0.55-1.44), <i>P</i> = 0.58
pPT	72 (75.0)	0.97 (0.61-1.62), <i>P</i> = 0.91
mTC	75 (78.9)	0.89 (0.55-1.48), <i>P</i> = 0.63
mIM	74 (77.0)	0.87 (0.54-1.47), <i>P</i> = 0.59
mOM	74 (77.0)	1.35 (0.82-2.36), <i>P</i> = 0.25
mPT	74 (77.0)	0.99 (0.61-1.66), <i>P</i> = 0.97

Notes: Bold values indicate statistical significance at the *P* < 0.05 level. Abbreviations: NM: adjacent non-tumor mucosa; pCRC: primary colorectal cancer. LM: liver metastasis. PMNs: Polymorphonuclear neutrophils; MCs: mast cells; pTC: tumor center of pCRC; pIM: inner margin of pCRC; pOM: outer margin of pCRC; pPT: peritumor area of pCRC; mTC: tumor center of LM; mIM: inner margin of LM; mOM: outer margin of LM; mPT: peritumor area of LM. N: number of patients in “high” group. HR (95% CI): Hazard ratio (95% confidence interval) shows the relative risk compared with 1.00 for the “low” group.

Supplementary Table 17 Association between densities of CD66b+ polymorphonuclear neutrophils and CD117+ mast cells and “low” vs “high” TBS/T-stage status in overall cohort of 99 colorectal cancer patients

	CD66b+		CD117+	
	TBS/T-stage		TBS/T-stage	
	Low	High	Low	High
NM	11 (2-98) ¹	12 (1-424)	211 (42-626)	210 (69-477)
pTC	99 (3-1256)	59 (6-3561)	44 (1-234)	32 (3-637)

pIM	93	55	29	27
	(0-2016)	(1-3606)	(0-242)	(0-334)
pOM	58	57	74	74
	(1-1243)	(3-1768)	(3-382)	(2-491)
pPT	38	40	87	83
	(2-321)	(3-1917)	(15-284)	(8-383)
mTC	94	89	9	8
	(2-698)	(2-2704)	(0-148)	(0-111)
mIM	175	138	10	7
	(5-1384)	(11-4549)	(0-148)	(0-235)
mOM	216	193	20	21
	(3-1300)	(18-2600)	(3-126)	(2-149)
mPT	127	154	22	18
	(14-2105)	(16-2900)	(3-148)	(2-116)

¹: Median (min-max); Abbreviations: NM: adjacent non-tumor mucosa; pCRC: primary colorectal cancer. LM: liver metastasis. PMNs: Polymorphonuclear neutrophils; MCs: mast cells; pTC: tumor center of pCRC; pIM: inner margin of pCRC; pOM: outer margin of pCRC; pPT: peritumor area of pCRC; mTC: tumor center of LM; mIM: inner margin of LM; mOM: outer margin of LM; mPT: peritumor area of LM. N: number of patients in “high” group. HR (95% CI): Hazard ratio (95% confidence interval) shows the relative risk compared with 1.00 for the “low” group.

Supplementary Table 18 Association between densities of CD66b+ polymorphonuclear neutrophils and clinical and pathological variables in colorectal cancer patients with

synchronous and metachronous metastases

			Synchronous				Metachronous				
			TC	IM	OM	PT	TC	IM	OM	PT	
Gender	Male	pCR	54	95	58	42	70	62	64	43	
		C	(4-125	(4-201	(5-783)	(7-323)	(6-825)	(1-102	(1-1243	(2-217)	
		LM	6) ^s	6)	170	108	103	0)	)	181	
			59	123	(3-1240	(14-210	(4-529)	177	226	(16-680	
			(2-558	(5-933	)	5)		(10-74	(22-846	)	
	Female	pCR	57	37	33	21	109	91	138	43	
		C	(7-363	(1-450	(3-443)	(3-323)	(9-3561	(17-36	(17-176	(7-1917	
		LM	)	)	190	^c	)	05)	8)	)	
			98	101	(9-1485	124	160	435	556	253	
			(2-320	(11-66	)	(17-139	(23-270	(6-454	(43-260	(50-290	
Age	<=62	pCR	55	38	40	42	107	151	96	45	
		(syn)	C	(7-125	(1-201	(3-783)	(3-323)	(6-3561	(1-360	(3-1768	(2-1917
		<=63.5	LM	6)	6)	144	122	)	6)	)	)
		(met)		44	83	(3-1485	(14-155	131	214	264	167
			(2-558	(5-713	)	1)	(23-270	(10-45	(22-260	(16-290	
	>62	pCR	58	98	67	34	85	65	58	38	
		(syn)	C	(4-680	(4-148	(5-465)	(7-323)	(10-610	(6-880	(1-1243	(2-170)
		>63.5	LM	)	1)	190	117	)	)	)	203
		(met)		88	199	(18-124	(19-210	130	174	379	(28-842
			(8-320	(11-93	0)	5)	(4-698)	(6-138	(43-130	)	
Location	Right side	pCR	45	58	44	41	72	62	61	59	
		C	(6-363	(4-148	(11-386	(7-230)	(13-356	(29-36	(23-176	(11-191	

Grade	colon	LM	)	1)	)	199	1)	06)	8)	7)		
			65	228	190	(38-489	104	162	206	169		
			(5-320	(30-58	(34-880	)	(4-2704	(14-45	(47-260	(50-290		
			)	4)	)		)	49)	0)	0)		
	Left side colon	pCR	61	67	40	34	93	84	87	39		
			C	(4-125	(1-201	(3-783)	(3-323)	(6-825)	(1-150	(1-1243	(2-252)	
			LM	6)	6)	156	114	131	0)	)	185	
			64	95	(3-1485	(14-210	(17-698	199	307	(16-842		
			(2-558	(5-933	)	5)	)	(6-171	(22-130	)		
			)	)				5)	0)			
			1	pCR	70	58	34	42	92	51	46	25
			C	(12-12	(6-201	(16-783	(12-323	(10-640	(17-10	(17-350	(7-76)	
		LM	56)	6)	)	)	)	20)	)		116	
			66	152	160	128	116	174	212	(17-842		
			(2-270	(15-45	(37-638	(46-428	(24-698	(10-13	(26-128	)		
			)	7)	)	)	)	84)	0)			
	2	pCR	58	95	55	34	107	185	96	46		
			C	(4-363	(1-148	(3-465)	(3-323)	(9-3561	(6-360	(1-1768	(2-1917	
			LM	)	1)	190	110	)	6)	)	)	
			64	123	(3-1485	(14-210	131	186	278	170		
			(2-558	(5-933	)	5)	(4-2704	(6-454	(22-260	(16-290		
			)	)			)	9)	0)	0)		
			3	pCR	32	35	43	37	39	28	44	32
					C	(8-173	(13-37	(15-304	(21-89)	(6-160)	(1-445	(3-118)
	LM	)			7)	)	72	269	)	537	480	
	27	44			105	(19-373	(67-471	447	(402-88	(185-73		
			(8-143	(11-23	(9-429)	)	)	(109-1	3)	4)		
			)	2)				715)				
			N	0	pCR	54	56	40	34	93	69	63

stage		C	(4-680	(4-811	(5-443)	(7-323)	(9-640)	(25-10	(22-350	(7-149)
		LM	)	)	165	198	160	20)	)	222
			39	101	(75-880	(47-489	(25-698	283	353	(50-842
			(8-320	(13-58	)	)	)	(10-17	(33-128	)
			)	4)				15)	0)	
1		pCR	51	48	36	31	44	51	59	41
		C	(7-265	(1-148	(3-404)	(3-189)	(6-610)	(1-880	(3-1243	(2-217)
		LM	)	1)	150	99	115	)	)	160
			96	171	(9-1485	(19-210	(4-434)	177	307	(17-359
			(2-558	(9-933	)	5)		(14-87	(26-130	)
			)	)				8)	0)	
2		pCR	87	98	56	47	140	205	107	41
		C	(9-125	(12-20	(14-783	(10-323	(28-356	(6-360	(1-1768	(2-1917
		LM	6)	16)	)	)	1) ^c	6) ^c	)	)
			55	91	195	128	129	174	202	187
			(5-270	(5-658	(3-1176	(14-155	(23-270	(6-454	(22-260	(16-290
			)	)	)	1)	4)	9)	0)	0)
pCR	<4.4cm	pCR	60	39	37	29	99	66	63	43
C	(syn)	C	(4-125	(1-201	(3-783)	(3-323)	(6-610)	(1-150	(1-950)	(2-252)
size	<=3.5c	LM	6)	6)	163	98	142	0)	254	226
	m (met)		55	89	(3-1485	(14-210	(17-698	238	(22-128	(16-842
			(2-558	(5-933	)	5)	)	(15-17	0)	)
			)	)				15)		
	>=4.4c	pCR	55	88	98	41	77	168	97	42
	m (syn)	C	(6-363	(6-148	(5-465)	(7-230)	(16-356	(18-36	(17-176	(12-191
	>3.5cm	LM	)	1)	185	153	1)	06)	8)	7)
	(met)		88	112	(9-1176	(38-155	103	177	248	151
			(5-320	(13-65	)	1)	(4-2704	(6-454	(26-260	(17-290
			)	8)			)	9)	0)	0)

Number of LM	=1	pCR	90	109	57	34	84	84	61	41
		C	(7-125	(1-201	(3-783)	(3-323)	(6-640)	(1-150	(3-1243	(2-252)
		LM	6)	6)	190	117	129	0)	)	156
			80	171	(3-1485	(14-210	(23-698	201	354	(16-736
			(8-457	(5-933	)	5)	)	(6-171	(22-130	)
			)	)				5)	0)	
	>1	pCR	55	55	35	39	95	60	93	43
		C	(4-244	(4-450	(5-443)	(7-323)	(28-356	(6-360	(1-1768	(2-1917
		LM	)	)	165	146	1)	6)	)	)
			51	100	(18-852	(17-659	100	157	222	208
			(2-558	(11-71	)	)	(4-2704	(10-45	(33-260	(28-290
			)	3)			)	49)	0)	0)
Size of LM	<2cm (syn)	pCR	64	98	50	41	81	65	57	43
		C	(4-125	(1-201	(3-783)	(3-323)	(6-610)	(1-723	(1-593)	(2-217)
		LM	6)	6)	99	94	133	)	222	183
			43	88	(9-1485	(17-117	(4-698)	162	(33-846	(28-680
			(2-457	(9-762	)	6)		(6-138	)	)
			)	)				4)		
	>=2cm (syn)	pCR	56	53	37	33	96	140	107	41
		C	(6-680	(6-811	(5-404)	(7-230)	(10-356	(17-36	(17-176	(7-1917
		LM	)	)	190	141	1)	06)	8)	)
			95	138	(3-1176	(14-155	128	199	354	213
			(10-55	(5-933	)	1)	(25-270	(10-45	(22-260	(16-290
			8)	)			4)	49)	0)	0)
Grade of LM	1	pCR	47	53	31	31	92	66	58	27
		C	(6-173	(4-450	(7-390)	(7-230)	(10-825	(17-10	(17-459	(11-176
		LM	)	)	186	136	)	20)	)	)
			57	91	(3-718)	(14-659	111	174	211	92
			(2-220	(5-658		)	(64-698	(6-138	(26-717	(17-359

		)	)		)	4)	)	)	
2	pCR	69	111	57	39	95	128	96	45
	C	(4-125	(1-201	(3-783)	(3-323)	(6-3561	(1-360	(1-1768	(2-1917
	LM	6)	6)	160	105	)	6)	)	)
		73	136	(29-148	(17-210	131	270	354	195
		(2-558	(9-933	5)	5)	(4-2704	(10-45	(22-260	(16-290
		)	)			)	49)	0)	0)

Notes: Median age: synchronous = 62, metachronous = 64; median size for primary tumor: synchronous = 4.3 cm, metachronous = 3.5 cm; median size of liver metastasis: synchronous = 2.0 cm, metachronous = 2.7 cm. [§] median (min-max); ^c*P* < 0.05.

Abbreviations: PMNs: Polymorphonuclear neutrophils; NM: adjacent non-tumor mucosa; pCRC: primary colorectal cancer; LM: liver metastases. TC: Tumor center; IM: Inner margin; OM: Outer margin; PT: Peritumor area.

Significant associations: In the synchronous group, greater cell densities of PMNs were found in PT of pCRC in males, and in IM and OM of metachronous LM in females.

Greater PMNs densities were found in IM of synchronous LM in the older patients.

In the metachronous group, greater PMN densities were observed in TC and IM of pCRC in the patients with N2 stage.

Supplementary Table 19 Association between densities of CD117+ mast cells and clinical and pathological variables in colorectal cancer patients with synchronous and metachronous metastases

			Synchronous				Metachronous			
			TC	IM	OM	PT	TC	IM	OM	PT
Gender	Male	pCR	47	44	94	88	34	22	72	88
		C	(1-637	(2-334	(9-491)	(15-383	(8-230	(0-196	(11-383	(16-284)
		LM	) [§]	)	33	)	)	)	)	21
			14(1-1	10	(4-149)	25	7	10	19	(2-77)
			68)	(0-129		(4-148)	(1-92)	(0-235	(4-71)	

				)			)			
	Female	pCR	20	19(2-5	54	62	30	36	66	90
		C	(3-224	7) ^c	(10-151	(17-171	(2-221	(0-201	(2-202)	(8-181)
		LM	) ^c	8(1-14	) ^c	)	)	)	11	13
			10	8)	22	19	2	3	(2-35) ^c	(3-45)
			(1-73)		(4-89)	(3-77)	(0-41)	(0-15)		
Age	<=62	pCR	43	30	74	83	33	36	72	75
	(syn)	C	(1-637	(2-334	(10-491	(17-383	(11-10	(6-62)	(2-164)	(8-175)
	<=63.5	LM	)	)	)	)	1)	6	18	19
	(met)		14	9	31	22	7	(1-235	(2-69)	(2-77)
			(1-112	(0-148	(4-149)	(3-148)	(0-92)	)		
			)	)						
	>62	pCR	36	31	83	87	36	18	72	98
	(syn)	C	(6-234	(3-227	(9-243)	(15-279	(2-230	(0-201	(3-383)	(16-284)
	>63.5	LM	)	)	27	)	)	)	13	13
	(met)		12	10	(5-126)	20	7	5	(4-71)	(3-53)
		(1-168	(1-80)		(6-116)	(0-55)	(0-52)			
		)								
Locat ion	Right	pCR	50	54	139	142	29	41	99	114
	side	C	(6-637	(9-334	(27-491	(37-383	(11-22	(1-201	(59-383	(27-284)
	colon	LM	)	)	)	)	1)	)	)	25
			16	13	41	20	11	14	18	(3-77)
			(2-58)	(2-114	(10-98)	(5-116)	(1-33)	(2-52)	(3-70)	
				)						
	Left	pCR	35	26	75	82	34	22	63	83
	side	C	(1-234	(2-242	(9-243)	(15-173	(2-230	(0-196	(2-164)	(8-200)
	colon	LM	)	)	28	) ^c	)	)	^c	14
			11	10	(4-149)	21	6	5	16	(2-49)

			(1-168)	(0-148)		(3-148)	(0-92)	(0-235)	(2-71)	
Grade	1	pCR	22	27	64	81	28	23	75	85
		C	(6-234	(3-227	(9-243)	(15-173	(2-221	(0-201	(3-383)	(16-284)
		LM	)	)	27	)	)	)	19	15
			10	10	(7-126)	20	5	4	(4-70)	(5-77)
			(1-168)	(3-99)		(5-76)	(0-32)	(1-52)		
	2	pCR	35	27	75	84	34	25	72	90
		C	(1-637	(2-334	(10-491	(17-383	(9-230	(0-196	(11-164	(16-200)
		LM	)	)	)	)	)	)	)	13
			15	14	32	21	7	5	16	(2-49)
			(1-111)	(0-129)	(4-149)	(3-148)	(0-92)	(0-235)	(2-71)	
3	pCR	52	71	106	89	49	27	59	49	
	C	(14-13	(23-24	(57-200	(57-124	(8-75)	(10-46	(2-72)	(8-94)	
	LM	9)	2)	)	)	15	)	18	18	
		6	5	21	26	(5-33)	8	(9-60)	(3-35)	
		(1-73)	(1-148)	(4-89)	(4-43)		(4-43)			
N stage	0	pCR	23	25	75	86	32	25	78	93
		C	(6-177	(3-174	(9-221)	(15-240	(2-230	(1-196	(2-148)	(8-175)
		LM	)	)	28	)	)	)	15	14
			6	13	(10-115	25	3	5	(2-53)	(3-77)
			(2-47)	(2-44)	)	(5-116)	(0-17)	(1-28)		
	1	pCR	35	31	75	83	42	25	72	84
		C	(3-637	(2-334	(10-491	(17-383	(6-138	(0-80)	(10-383	(27-284)
		LM	)	)	)	)	)	5	)	21
			14	8	21	19	7	(1-52)	17	(3-53)

			(1-112)	(1-148)	(5-124)	(6-148)	(1-50)	(6-71)	
	2	pCR	58	47	77	91	30	23	62 90
		C	(1-234	(2-242	(18-243	(18-279	(9-221	(4-201	(19-202 (16-181)
		LM	)	)	)	)	)	)	13
			16	7	34	26	8	10	13 (2-36)
			(1-168	(0-129	(4-149)	(3-96)	(1-92)	(0-235	(3-69)
			)	)				)	
pCR	<4.4cm	pCR	48	30	75	83	33	25	62 59
C	(syn)	C	(3-637	(2-334	(10-491	(17-383	(2-221	(0-201	(2-202) (8-181)
size	<=3.5c	LM	)	)	)	)	)	)	13 14
	m (met)		14	14	33	25	5	4	(2-60) (2-77)
			(1-112	(0-129	(5-149)	(5-148)	(0-55)	(0-43)	
			)	)					
	>=4.4c	pCR	36	30	77	87	32	16	72 96
	m (syn)	C	(1-234	(2-227	(18-243	(18-279	(8-230	(1-196	(20-164 (22-200)
	>3.5cm	LM	)	)	)	)	)	)	13
	(met)		13	9	21	19	8	10	17 (3-49)
			(1-168	(0-148	(4-126)	(3-116)	(1-92)	(0-235	(3-71)
			)	)				)	
Num	=1	pCR	35	36	79	85	33	34	68 80
ber		C	(3-637	(2-334	(10-491	(17-383	(2-221	(0-201	(3-383) (16-284)
of		LM	)	)	)	)	)	)	18 15
LM			17	20	32	22	6	10	(2-70) (3-77)
			(1-112	(2-148	(4-149)	(3-48)	(0-55)	(0-52)	
			)	)					
	>1	pCR	45	29	73	84	32	22	73 90
		C	(1-234	(2-227	(9-243)	(15-279	(6-230	(0-196	(2-148) (8-200)
		LM	)	)	21	)	)	)	15 13

			6 (1-168)	7 (0-80) c	(4-126)	20 (4-96)	7 (1-92)	4 (0-235)	(4-71)	(2-49)
Size of LM	<2cm (syn)	pCR	35 (1-234)	24 (2-242)	74 (9-243)	84 (15-187)	30 (2-230)	22 (0-201)	72 (2-383)	90 (8-284)
	<2.7cm (met)	LM	14 (1-168)	10 (0-148)	20 (7-149)	19 (5-85)	7 (0-55)	5 (0-52)	13 (3-70)	13 (2-53)
	>=2cm (syn)	pCR	41 (6-637)	37 (2-334)	76 (14-491)	83 (17-383)	34 (8-178)	26 (0-80)	73 (3-164)	85 (16-200)
	>=2.7cm (met)	LM	10 (1-112)	8 (1-114)	28 (4-98)	20 (3-116)	5 (0-92)	10 (1-235)	24 (2-71)	25 (3-77) c
Grade of LM	1	pCR	37 (6-637)	30 (3-334)	66 (22-491)	87 (21-383)	29 (2-230)	13 (0-201)	59 (3-202)	85 (16-200)
		LM	10 (1-112)	5 (0-148)	16 (4-98)	20 (3-116)	5 (0-92)	4 (0-235)	15 (4-71)	13 (5-77)
	2	pCR	36 (1-224)	28 (2-242)	83 (9-223)	83 (15-187)	34 (9-178)	31 (0-62)	72 (2-383)	88 (8-284)
		LM	17 (1-111)	14 (0-149)	33 (6-149)	19 (6-148)	7 (0-41)	7 (0-52)	17 (2-70)	19 (2-53)

Notes: Median age: synchronous = 62, metachronous = 64; median size for primary tumor: synchronous = 4.3 cm, metachronous = 3.5 cm; median size of liver metastasis: synchronous

= 2.0 cm, metachronous = 2.7 cm. § median (min-max); ° $P < 0.05$.

Abbreviations: NM: adjacent non-tumor mucosa; pCRC: primary colorectal cancer; LM: liver metastases. TC: Tumor center; IM: Inner margin; OM: Outer margin; PT: Peritumor area.

Significant associations: In synchronous group, greater density of MCs was observed in TC, IM, OM of pCRC and OM of metachronous LM in males.

Greater MCs densities were also found in PT of synchronous right-sided pCRC, and in OM of right-sided pCRC in the metachronous group.

Greater cell densities were also found in IM of synchronous LM in patients with only one LM. Greater cell density was observed in the PT of larger metachronous LM.

Supplementary Table 20 Association between immune cells and chemotherapy before and after liver resection in colorectal cancer patients with synchronous and metachronous metastases

Variables	Cell type and location	Synchronous group (37 patients before and 12 after)				Metachronous group (11 patients before and 32 after)			
		TC	IM	OM	PT	TC	IM	OM	PT
CHT before liver surgery	CD66b	47	42 (1-2016)	45 (3-783)	41 (3-323)	122	187 (6-3606)	117 (1-1768)	38 (2-1917)
	pCRC	(4-1256) ¹	89 (11-713)	146 (9-1485)	105	(10-3561)	168	207	148
CHT after liver surgery	CD66b LM	47 (2-558)	76 (11-190)	27 (5-285)	(17-1551)	89 (4-2704)	(14-4549)	(22-2600)	(16-2900)
	CD66b	63 (11-174)	246 (5-933)	349 (3-718)	22 (9-230)	77 (6-640)	68 (0.5-1500)	61 (3-1243)	45 (2-252)
	pCRC	95 (4-270)			148 (14-428)	136 (17-529)	186 (6-795)	294	183 (17-842)
	CD66b LM							(26-1280)	
CHT before liver surgery	CD117	35 (1-637)	30 (2-334)	74 (10-491)	83 (17-383)	33 (2-178)	22 (0-62)	66 (2-143)	90 (8-175)
	pCRC	13 (1-112)	8 (0-148)	29 (4-149)	19 (3-116)	7 (0-92)	8 (1-235)	16 (2-60)	8 (2-35)
CHT after liver surgery	CD117 LM	82 (6-234)	40 (9-227)	83 (27-243)	87 (25-279)	32 (8-230)	25 (0-201)	72 (3-382)	87 (16-284)
	CD117	14 (4-168)	14 (0-80)	29 (7-126)	27 (5-148)	6 (0-55)	5 (0-52)	16 (3-71)	15 (3-77)
	pCRC								

CD117 LM

¹Median (min-max) cell densities

Abbreviations: CRC: colorectal cancer; pCRC: primary colorectal cancer; LM: liver metastases; TC: tumor center; IM: inner margin; OM: outer margin; PT: peritumor zone; CHT: chemotherapy

Supplementary Table 21 Association between immune cells and FOLFOX-based chemotherapy versus other in colorectal cancer patients with synchronous and metachronous metastases

Chemoth erapy regimen	Cell and location	Synchronous (31 patients FOLFOX and 24 other)				Metachronous (16 patients FOLFOX and 28 other)			
		TC	IM	OM	PT	TC	IM	OM	PT
FOLFOX	CD66b	60 (4-1256)	65 (4-2016)	40 (5-783)	37 (7-323)	76 (9-610)	133 (18-1500)	78 (17-950)	41 (7-252)
	pCRC	57 (2-558)	89 (5-713)	144 (3-638)	98 (14-659)	118 (4-374)	156 (10-795)	374	229 (16-842)
Other	CD66b LM	52 (6-680)	58 (1-1481)	55 (3-389)	34 (3-230)	98 (6-3561)	74 (0-3606)	(22-1280)	44 (2-1917)
	CD66b	95 (4-320) ^d	232 (9-933) ^d	190 (9-1485)	152	131	199 (6-4549)	72 (1-1768)	160 (17-2900)
	pCRC				(29-2105)	(23-2704)		226	
	CD66b LM							(26-2600)	
FOLFOX	CD117	47 (11-637)	40 (2-334)	74 (14-491)	81 (17-383)	33 (8-81)	12 (0-80)	61 (11-115)	83 (22-200)

	pCRC	15 (1-168)	14 (0-129)	23 (4-149)	19 (3-116)	8 (1-55)	5 (0-44)	13 (4-71)	14 (2-49)
Other	CD117 LM	22 (1-200)	24 (2-242)	83 (9-205)	86 (15-279)	34 (2-230)	34 (0-201)	74 (2-382)	94 (8-284)
	CD117	10 (1-73)	8 (0-148)	33 (4-124)	25 (4-148)	6 (0-92)	6 (0-235)	17 (2-70)	14 (3-77)
	pCRC								
	CD117 LM								

Notes: ^d $P < 0.05$.

Abbreviations: CRC: colorectal cancer; pCRC: primary colorectal cancer; LM: liver metastases; TC: tumor center; IM: inner margin; OM: outer margin; PT: peritumor zone. Significant associations: Stage IV patients receiving FOLFOX chemotherapy had smaller densities of PMNs in TC and IM of LM.

Supplementary Table 22 Association between cell densities in nontumor mucosa of CD66b+ polymorphonuclear neutrophils and CD117 mast cells and distance of resection margin from tumor in colorectal cancer patients with synchronous and metachronous metastases

		Synchronous		Metachronous	
		Cell density	<i>P</i> - value	Cell density	<i>P</i> - value
CD66b	Under median	11 (3-208) ¹		11 (1-98)	

CD117	Above median	13 (2-424)	0.25	14 (2-63)	0.78
	Under median	192 (88-382)		207 (42-626)	
	Above median	246 (69-456)	0.42	218 (119-477)	0.70

Note: ¹median (min-max);

Median distance from tumor: synchronous = 35 mm, metachronous = 32 mm

Abbreviations: NM: adjacent non-tumor mucosa; PMNs: Polymorphonuclear neutrophils; MCs: mast cells; CRC: colorectal cancer.