

Supplementary Table 1| Predictive value of ColoClass model in each differentiation subtype.

	UNDIFFERENTIATED	POORLY	MODERATELY	WELL	Total
Stroma	77.5 (249)	84.61 (2287)	83.38 (5290)	81.96 (1917)	83.21 (9743)
Healthy	93.30 (179)	83.97 (624)	68.68 (2002)	89.45 (616)	76.67 (3421)
Immune	99.31 (145)	94.86 (1225)	93.38 (3140)	96.2 (894)	94.21 (5404)
Tumor	83.6 (165)	80.99 (1820)	86.96 (4563)	80.1 (1543)	84.43 (8091)
Total	86.99 (738)	85.54 (5956)	84.6 (14995)	84.87 (4970)	84.97 (26659)

Supplementary Table 2| Clinical characteristics of the PETACC08 cohort patients included in the analysis.

	N=1018° (%)
Gender	
Female	426 (41.8)
Male	592 (58.2)
Treatment	
Folfox	514 (50.5)
Folfox + Cetuximab	504 (49.5)
Age - Mean (sd)	59.5 (9.35)
Histopathology grading	
Moderately	610 (59.9)
Well	184 (18.1)
Poorly	131 (12.9)
Undifferentiated	81 (7.9)
Unknown	12 (1.2)
T	
T1	26 (2.5)
T2	65 (6.4)
T3	725 (71.3)
T4	202 (19.8)
N	
N1	659 (64.7)
N2	359 (35.3)
Tumor side	
Left side	588 (57.8)
Right side	430 (42.2)
KRAS	
Mutated	469 (46.0)
Wild-type	549 (54.0)
BRAF	
Mutated	117 (11.5)
Wild-type	872 (85.6)
Unknown	29 (2.9)
MSS status	
MSI	96 (9.4)
MSS	903 (88.7)
Unknown	19 (1.9)

Supplementary Table 3 | Description of IM Relative Stromal Area in function of clinical parameters.

	T status				N status		Sideness		MMR status		Mutationnal RAS/RAF status		
	T1	T2	T3	T4	N1	N2	Left	Right	pMMR	dMMR	WT	KRAS	BRAF
Number	26	65	725	202	659	359	588	430	903	96	401	503	114
Mean	0.60	0.61	0.69	0.72	0.69	0.70	0.69	0.69	0.69	0.69	0.69	0.70	0.67
SD	0.13	0.17	0.13	0.14	0.14	0.14	0.14	0.14	0.14	0.16	0.15	0.14	0.15
Median	0.61	0.62	0.72	0.76	0.71	0.73	0.72	0.71	0.72	0.72	0.72	0.72	0.69
Min	0.27	0.08	0.19	0.11	0.11	0.08	0.11	0.08	0.11	0.08	0.19	0.11	0.08
Max	0.81	0.92	0.94	0.94	0.94	0.94	0.94	0.94	0.94	0.93	0.94	0.94	0.88
Lower CI 95%	0.54	0.57	0.68	0.70	0.68	0.69	0.68	0.68	0.68	0.65	0.67	0.68	0.64
Upper CI 95% Max	0.65	0.65	0.70	0.74	0.70	0.72	0.71	0.70	0.70	0.72	0.70	0.71	0.70

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Supplementary Table 4| List of variables retained in the lasso model.

Variable	Hazard-Ratio	95%-IC	p-value
OD Sum Haralick Contrast	1.247	0.984-1.572	0.07
Hematoxylin Haralick Angular second moment	0.713	0.517-0.985	0.04
Hematoxylin Haralick Inverse difference moment	1.283	0.750-2.193	0.36
DAB Haralick Angular second moment	1.081	0.840-1.391	0.54
Residual Haralick Sum variance	0.987	0.834-1.168	0.88
Red Haralick Sum entropy	1.225	0.674-2.225	0.51
Red Haralick Information measure of correlation	1.015	0.820-1.257	0.89
Saturation Haralick Sum of squares	0.977	0.802-1.191	0.82
Global p-value of model :	0.002		

Supplementary Table. 5 | Description of DGMate in function of clinical parameters.

Discovery:

	T status				N status		Sideness		MMR status		Mutationnal RAS/RAF status		
	T1	T2	T3	T4	N1	N2	Left	Right	pMM R	dMM R	WT	KRAS	BRAF
Number	20	43	505	145	455	258	419	294	636	68	283	352	78
Mean	0,240	0,108	0,001	0,068	0,027	0,048	0,030	0,043	0,008	0,074	0,301	0,298	0,361
SD	0,441	0,311	0,288	0,340	0,306	0,312	0,311	0,305	0,310	0,311	0,301	0,300	0,360
Median	0,204	0,125	0,019	0,064	0,034	0,040	0,039	0,058	0,020	0,098	-0,042	0,005	0,124
Min	1,524	0,670	1,491	1,222	1,524	1,222	1,524	1,222	1,524	0,617	-1,491	-0,921	-1,524
Max	0,621	0,665	0,734	0,910	0,910	0,784	0,910	0,827	0,910	0,827	0,827	0,910	0,684
Lower CI 95%	0,446	0,204	0,026	0,012	0,056	0,010	0,060	0,008	0,032	0,001	-0,081	-0,018	0,029
Upper CI 95%	-	-	-	-	-	-	-	-	-	-	-	-	-
Max	0,033	0,012	0,024	0,124	0,001	0,087	0,000	0,077	0,017	0,149	-0,011	0,044	0,191

Validation:

	T status				N status		Sideness		MMR status		Mutationnal RAS/RAF status		
	T1	T2	T3	T4	N1	N2	Left	Right	pMM R	dMM R	WT	KRAS	BRAF
Number	6	22	220	57	204	101	169	136	267	28	118	151	36
Mean	0,240	0,228	0,001	0,044	0,067	0,095	0,064	0,050	0,012	0,042	-0,032	-0,024	0,092
SD	0,145	0,255	0,316	0,339	0,296	0,342	0,314	0,318	0,325	0,308	0,323	0,309	0,352
Median	0,226	0,224	0,009	0,025	0,079	0,095	0,063	0,021	0,018	0,055	-0,050	-0,038	0,056
Min	0,432	1,034	0,980	0,885	0,980	1,034	1,034	0,885	1,034	0,885	-0,980	-1,034	-0,885
Max	0,013	0,146	0,983	0,918	0,721	0,983	0,793	0,983	0,983	0,557	0,918	0,793	0,983
Lower CI 95%	0,392	0,341	0,043	0,046	0,108	0,027	0,112	0,004	0,051	0,162	-0,091	-0,073	-0,027
Upper CI 95%	-	-	-	-	-	-	-	-	-	-	-	-	-
Max	0,087	0,115	0,041	0,134	0,026	0,162	0,017	0,104	0,027	0,077	0,027	0,026	0,211

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Supplementary Table. 6| Description of immune infiltrates in function of clinical parameters.

Immune cell at IM

		T status				N status		Sideness		MMR status		Mutationonal RAS/RAF status		
		T1	T2	T3	T4	N1	N2	Left	Right	pMMR	dMMR	WT	KRAS	BRAF
	Number	26	65	725	202	659	359	588	430	903	96	401	503	114
CD3	Mean	1618	1408	1046	986	1097	1026	1035	1122	1058	1149	1105	1030	1137
	SD	740	722	645	679	681	652	676	662	667	698	653	664	755
	Median	1540	1307	921	830	980	866	881	1022	926	1067	1010	901	868
	Min	660	194	0	31	39	0	39	0	0	117	31	0	39
	Max	3209	3529	4454	4761	4761	3465	4761	3657	926	1067	4454	4761	3718
	Lower CI 95%	1319	1229	999	892	1045	958	980	1059	1014	1008	1041	972	997
	Upper CI 95% Max	1916	1587	1093	1081	1149	1093	1090	1185	1101	1290	1169	1088	1277
CD8	Mean	326	295	218	242	229	232	588	430	225	281	236	220	254
	SD	281	285	247	266	249	266	215	250	253	281	272	241	251
	Median	198	222	143	150	150	148	245	266	144	208	152	142	164
	Min	2	5	1	2	1	1	1	1	1	2	1	1	8
	Max	908	1271	2166	1567	2158	2166	2158	2166	2166	1380	2166	1806	1380
	Lower CI 95%	213	224	200	205	210	204	195	225	209	224	209	199	208
	Upper CI 95% Max	440	365	236	279	248	259	235	276	242	338	262	241	301

Immune cell at TC

		T status				N status		Sideness		MMR status		Mutationonal RAS/RAF status		
		T1	T2	T3	T4	N1	N2	Left	Right	pMMR	dMMR	WT	KRAS	BRAF
	Number	26	65	725	202	659	359	588	430	903	96	401	503	114
CD3	Mean	814	708	544	513	574	520	530	589	532	751	568	525	642
	SD	377	424	402	444	406	431	400	434	393	562	408	392	520
	Median	777	676	459	366	481	410	438	504	446	588	492	429	490
	Min	199	74	0	2	7	0	7	0	0	17	2	0	7
	Max	1889	2067	2781	2523	2675	2781	2781	2675	2781	2523	2523	2675	2781
	Lower CI 95%	662	603	515	452	543	476	498	548	507	637	528	491	546
	Upper CI 95% Max	966	813	573	575	605	565	563	630	558	865	608	560	739
CD8	Mean	149	139	119	129	122	126	110	141	116	192	116	118	173
	SD	175	198	168	184	162	192	160	189	163	248	172	156	235
	Median	90	84	59	63	64	59	58	72	60	102	56	66	90
	Min	0	3	1	1	0	2	0	1	0	1	0	1	5
	Max	740	1222	1773	1369	1473	1773	1773	1473	1773	1369	1773	1473	1185
	Lower CI 95%	78	90	107	103	109	106	97	123	105	142	99	104	129
	Upper CI 95% Max	220	188	131	154	134	146	123	158	126	242	133	131	216

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Supplementary Table 7 | Univariate analysis variable prognostic role in relapse free survival.

PETTAC8 patients (n=1018)								
Univariate cox models								
	Discovery cohort (N=713)				Validation cohort (N=305)			
	N° (%)	Hazard ratio	IC 95%	p-value	N° (%)	Hazard ratio	IC 95%	p-value
Gender								
Female	284 (39.8)	1			142 (46.6)	1		
Male	429 (60.2)	0.954	0.724-1.257	0.74	163 (53.4)	1.207	0.784-1.86	0.39
Treatment								
Folfox	355 (49.8)	1			159 (52.1)	1		
Folfox + Cetux	358 (50.2)	1.048	0.800-1.373	0.73	146 (47.9)	1.313	0.855-2.017	0.21
Age - Mean (sd)	59.5 (9.35)	1.009	0.879-1.158	0.9	60.2 (9.03)	0.919	0.746-1.132	0.43
Histopathology grading								
Moderately	435 (61.0)	1			175 (57.4)	1		
Well	134 (18.8)	0.83	0.565-1.218	0.34	50 (16.4)	1.004	0.595-1.694	0.99
Poorly	130 (18.2)	1.435	1.031-1.998	0.03	1 (0.3)	1.207	0.675-2.158	0.53
Undifferentiated	5 (0.7)	0.694	0.097-4.967	0.72	76 (24.9)	?	?	?
Unknown	9 (1.3)	-	-	-	3 (1.0)	-	-	-
T								
T1	20 (2.8)	0.43	0.18-1.05	0.06	6 (2.0)	0.94	0.24-3.69	0.93
T2	43 (6.0)	0.42	0.22-0.80	0.009	22 (7.2)	0.81	0.58-2.62	0.58
T3	505 (70.8)	1			220 (72.1)	1		
T4	145 (20.3)	2.29	1.58-3.32	0.0001	57 (18.7)	2.99	1.83-4.91	0.0001
N								
N1	455 (63.8)	1			204 (66.9)	1		
N2	258 (36.2)	2.464	1.879-3.231	6.87E-11	101 (33.1)	2.302	1.500-3.533	1.00E-04
Tumor side								
Left side	419 (58.8)	1			169 (55.4)	1		
Right side	294 (41.2)	0.994	0.755-1.308	0.97	136 (44.6)	0.791	0.511-1.226	0.29
KRAS					166 (54.4)			
Wild-type	383 (53.7)	1				1		
Mutated	330 (46.3)	1.602	1.221-2.105	0.0007	139 (45.6)	1.094	0.713-1.68	0.68

BRAF								
Wild-type	614 (86.1)	1			258 (84.6)	1		
Mutated	80 (11.2)	1.017	0.659- 1.57	0.94	37 (12.1)	1.08	0.556- 2.096	0.82
Unknown	19 (2.7)	-	-	-	10 (3.3)	-	-	-
MSS status								
MSS	636 (89.2)	1			267 (87.5)	1		
MSI	68 (9.5)	0.714	0.442- 1.207	0.21	28 (9.2)	1.122	0.54- 2.356	0.76
Unknown	9 (1.3)	-	-	-	10 (3.3)	-	-	-
CD3 TC	552.66 (424.36)	0.794	0.679- 0.929	4.00E- 03	560.87 (394.95)	0.653	0.494- 0.863	0.003
Stroma Area IM	0.69 (0.14)	1.271	1.098- 1.472	1.00E- 03	0.69 (0.14)	1.292	1.018- 1.639	0.04
Digital score	0 (0.31)	2.718	1.718- 4.3	1.93E- 05	-0.01 (0.32)	2.598	1.314- 5.137	0.006

Supplementary Table 8| Univariate analysis of the prognostic role of Dgmate and Dgmunes in relapse free survival in Stage 3 subgroup.

	Dgmate			Dgmunes		
	Hazard ratio	IC95%	p-value	Hazard ratio	IC95%	p-value
T3N1						
N=474	2.36	(1.11-5.01)	0.026	2.69	(1.42-5.11)	0.024
T3N2						
N=251	2.01	(1.03-3.93)	0.04	2.12	(1.23-3.66)	0.006

Supplementary Table 9| Logistic regression testing prediction capacity of digital variable to predict clinical variables .

T stage estimation using logistic regression

Variable	Odds ratio	95% CI	P value
Stromal area	1.2543	1.1238 to 1.9875	4.44e-05
CD3 TC	0.9995	0,9990 to 0.9998	0.043
DGMate	4.3153	2.2649 to 7.9872	6.96e-05

N stage estimation using logistic regression

Variable	Odds ratio	95% CI	P value
Stromal area	0,9942	0,9868 to 1,0017	0.129
CD3 TC	1,0001	0,9997 to 1,0004	0.722
DGMate	0,3647	0,2320 to 0,5732	1.23e-05

Differentiation stage estimation using logistic regression

Variable	Odds ratio	95% CI	P value
Stromal area	0,9950	0,9861 to 1,0040	0.2740
CD3 TC	1,0003	0,9998 to 1,0007	0.2267
DGMate	0,6104	0,3547 to 1,0504	0.0746

BRAF/RAS status estimation using logistic regression

Variable	Odds ratio	95% CI	P value
Stromal area	0,9991	0,9916 to 1,0066	0.80922
CD3 TC	1,0000	0,9997 to 1,0003	0.91369
DGMate	0,5238	0,3418 to 0,8026	0.00298

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