A quantitative tumor-wide analysis of morphological heterogeneity of colorectal adenocarcinoma

MP Dragomir *et al*., *J Pathol Clin Res*, https://doi.org/10.1002/2056-4538.70034

Supplementary Figures S1–S3
Supplementary Table S1

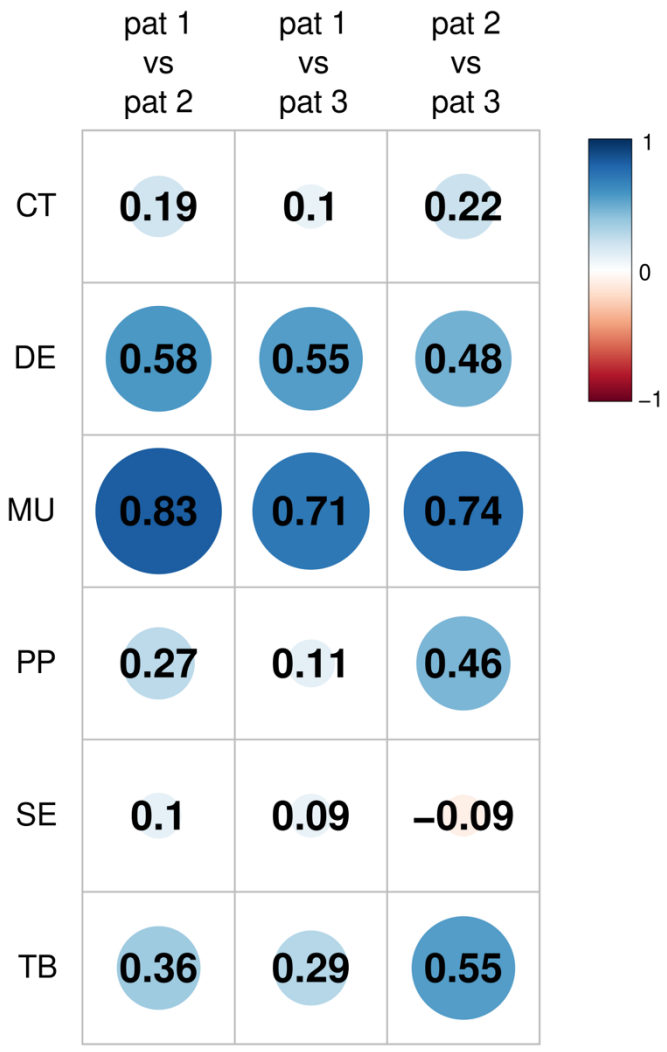

Figure S1. Pairwise analysis of operator agreement by kappa coefficient for individual morphologies, where values represent weak (0.4–0.59), moderate (0.6–0.79), strong (0.8–0.9), and almost perfect (>0.9) agreement.

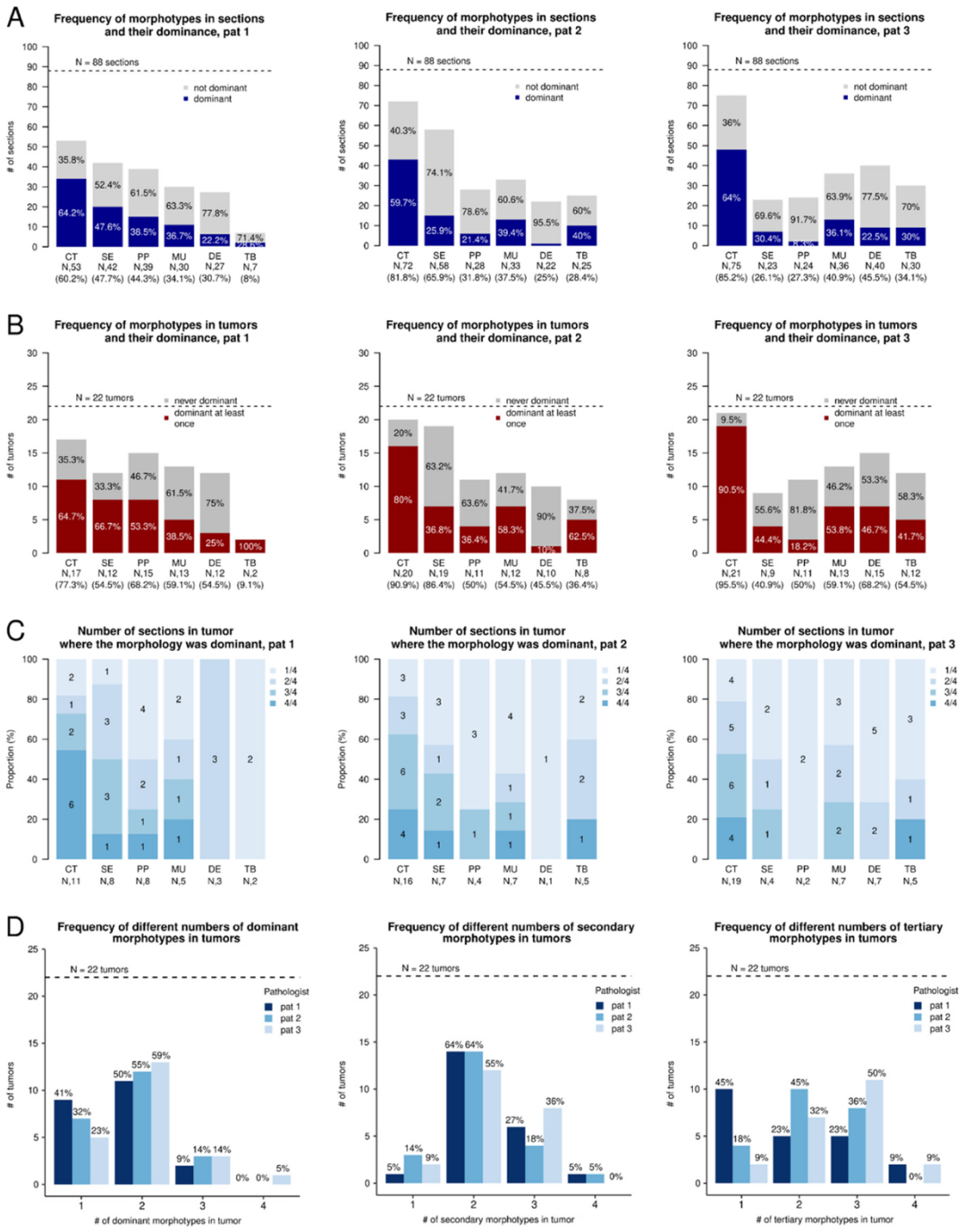

Figure S2. Frequency and area of dominant morphotypes across the examined sections and tumors after visual morphotype assessment. (**A**) Frequency of morphotypes in sections with respect to their dominance. (**B**) Frequency of morphotypes in tumors with respect to their dominance. (**C**) Frequency of sections in tumors where the morphology was dominant. 1/4 means the morphotype was dominant in one of the four examined slides of the tumor, etc. (**D**) Frequency of different numbers of dominant (left), secondary (middle), and tertiary (right) morphotypes across the four examined sections, as evaluated by three expert pathologists.

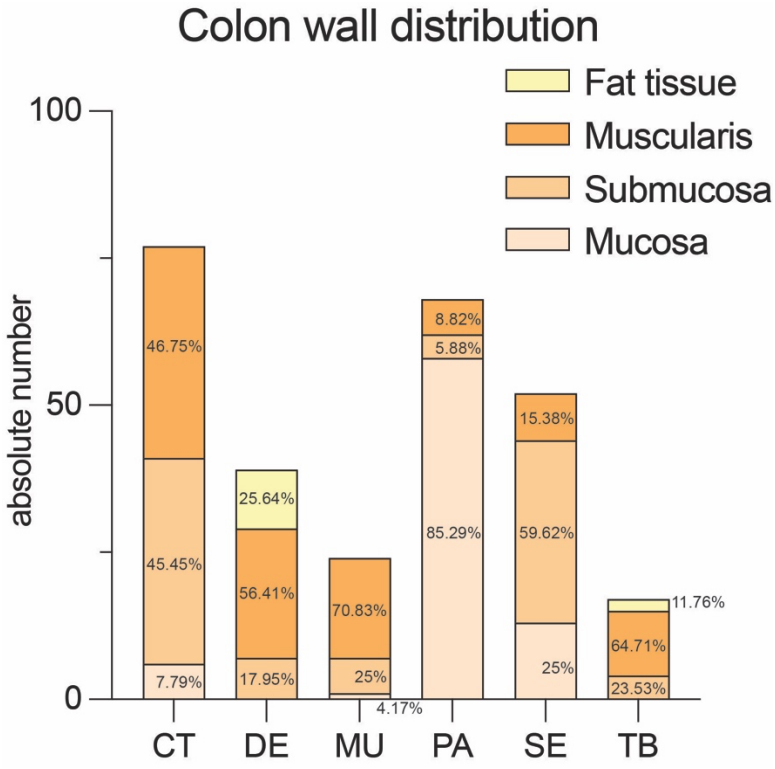

Figure S3. Frequency of morphotypes in sections with respect to their distribution across the colonic wall (mucosa, submucosa, muscularis propria, and fat tissue). For statistical analysis we compared the frequency of morphotypes in sections with respect to their distribution across the colonic wall in a binary analysis of superficial (mucosa and submucosa) versus deep (muscularis propria and fat tissue).

Table S1 Additional study population statistics.

Stratified by gender				
	F	**M**	***p***	***p*-adj**
n	**72**	**89**		
CT (median [IQR])	44.79 [18.03, 62.44]	46.79 [26.75, 60.70]	0.484	0.692
DE (median [IQR])	5.53 [0.00, 12.69]	2.60 [0.00, 9.30]	0.069	0.144
MU (median [IQR])	0.00 [0.00, 7.24]	1.32 [0.00, 7.33]	0.668	0.828
PP (median [IQR])	12.63 [5.63, 26.66]	16.87 [9.38, 32.85]	0.075	0.145
SE (median [IQR])	4.94 [1.80, 13.82]	5.50 [1.75, 10.63]	0.799	0.918
TB (median [IQR])	**2.90 [0.00, 10.88]**	**0.00 [0.00, 2.74]**	**0.003**	**0.009**

Stratified by AJCC stage						
	I	**II**	**III**	**IV**	***p***	***p*-adj**
n	**24**	**67**	**43**	**27**		
CT (median [IQR])	46.90 [35.32, 65.42]	44.84 [20.63, 61.90]	50.68 [13.69, 59.29]	43.00 [30.36, 60.02]	0.929	0.949
DE (median [IQR])	**0.00 [0.00, 3.09]**	**3.53 [0.00, 8.66]**	**5.10 [0.00, 14.63]**	**10.28 [4.08, 24.30]**	**<0.001**	**<0.001**
MU (median [IQR])	0.00 [0.00, 3.73]	1.33 [0.00, 12.63]	1.57 [0.00, 10.46]	0.00 [0.00, 4.65]	0.466	0.692
PP (median [IQR])	20.30 [10.06, 42.55]	17.19 [9.22, 29.87]	13.10 [6.60, 26.21]	8.87 [5.14, 21.14]	0.046	0.110
SE (median [IQR])	5.98 [1.63, 16.95]	5.55 [2.31, 12.71]	5.06 [1.85, 9.46]	4.19 [0.00, 12.32]	0.838	0.924
TB (median [IQR])	0.65 [0.00, 5.04]	0.00 [0.00, 6.62]	0.00 [0.00, 7.19]	1.29 [0.00, 5.33]	0.996	0.996

Stratified by grade					
	1	**2**	**3**	***p***	***p*-adj**
n	**19**	**95**	**47**		
CT (median [IQR])	**56.93 [19.71, 61.70]**	**52.01 [38.28, 66.80]**	**23.33 [8.82, 43.43]**	**<0.001**	**<0.001**
DE (median [IQR])	3.64 [0.00, 9.80]	3.66 [0.00, 10.60]	4.30 [0.00, 12.83]	0.519	0.692
MU (median [IQR])	**0.00 [0.00, 6.73]**	**0.00 [0.00, 4.42]**	**3.81 [0.00, 38.09]**	**0.026**	**0.073**
PP (median [IQR])	**17.66 [11.10, 41.91]**	**16.13 [10.10, 32.60]**	**6.14 [1.56, 22.13]**	**<0.001**	**0.002**
SE (median [IQR])	8.40 [4.95, 13.34]	5.28 [1.80, 11.67]	3.91 [0.00, 12.25]	0.060	0.132
TB (median [IQR])	**0.00 [0.00, 0.00]**	**0.00 [0.00, 4.49]**	**3.20 [0.00, 27.86]**	**0.001**	**0.006**

Stratified by site							
	Right	**Transverse**	**Left**	**Rectosigmoid**	**Rectum**	***p***	***p*-adj**
n	**55**	**18**	**44**	**27**	**17**		
CT (median [IQR])	**24.62 [12.69, 42.92]**	**48.56 [26.82, 65.46]**	**49.16 [39.79, 62.50]**	**59.51 [44.31, 73.78]**	**59.32 [47.16, 64.91]**	**<0.001**	**<0.001**
DE (median [IQR])	4.73 [1.43, 14.31]	6.69 [0.53, 9.11]	1.49 [0.00, 8.26]	1.69 [0.00, 8.54]	3.66 [0.00, 14.01]	0.178	0.329
MU (median [IQR])	**4.94 [1.69, 20.55]**	**0.00 [0.00, 1.79]**	**0.00 [0.00, 2.43]**	**0.00 [0.00, 2.11]**	**0.00 [0.00, 1.32]**	**<0.001**	**<0.001**
PP (median [IQR])	12.51 [4.80, 32.88]	12.58 [4.07, 30.99]	19.74 [9.93, 34.19]	12.39 [7.86, 19.52]	15.17 [13.10, 23.44]	0.379	0.674
SE (median [IQR])	5.74 [1.65, 13.97]	4.16 [1.39, 11.80]	6.02 [1.98, 13.02]	5.28 [2.84, 12.00]	2.72 [0.00, 10.63]	0.858	0.924
TB (median [IQR])	**1.30 [0.00, 13.59]**	**4.22 [0.00, 9.95]**	**0.00 [0.00, 4.49]**	**0.00 [0.00, 3.20]**	**1.29 [0.00, 3.51]**	**0.038**	**0.096**

Stratified by pT						
	T1	**T2**	**T3**	**T4**	***p***	***p*-adj**
n	**8**	**25**	**115**	**13**		
CT (median [IQR])	47.81 [45.98, 53.60]	47.36 [32.29, 66.98]	44.75 [18.84, 60.67]	52.01 [29.38, 66.62]	0.578	0.750
DE (median [IQR])	**0.00 [0.00, 0.00]**	**1.39 [0.00, 7.01]**	**4.11 [0.00, 11.18]**	**12.67 [4.46, 25.44]**	**0.001**	**0.005**
MU (median [IQR])	0.00 [0.00, 0.00]	1.57 [0.00, 4.83]	1.49 [0.00, 9.67]	0.00 [0.00, 10.13]	0.059	0.132
PP (median [IQR])	**28.81 [21.54, 42.55]**	**15.17 [9.53, 40.71]**	**14.47 [7.90, 28.55]**	**3.48 [1.66, 5.00]**	**<0.001**	**<0.001**
SE (median [IQR])	2.41 [1.21, 15.97]	8.13 [2.03, 15.23]	5.55 [1.87, 12.71]	1.90 [0.00, 3.65]	0.073	0.145
TB (median [IQR])	0.00 [0.00, 4.62]	0.00 [0.00, 4.91]	0.00 [0.00, 6.54]	3.12 [0.00, 6.69]	0.803	0.918

Stratified by pN					
	N0	**N1**	**N2**	***p***	***p*-adj**
n	**94**	**41**	**26**		
CT (median [IQR])	45.80 [21.50, 63.39]	47.38 [27.79, 59.26]	40.31 [10.68, 59.46]	0.474	0.692
DE (median [IQR])	**2.02 [0.00, 7.63]**	**5.10 [0.00, 19.09]**	**9.90 [5.15, 19.99]**	**<0.001**	**<0.001**
MU (median [IQR])	0.00 [0.00, 5.88]	1.30 [0.00, 10.29]	3.10 [0.00, 6.58]	0.673	0.828
PP (median [IQR])	**17.73 [10.06, 34.11]**	**12.67 [6.88, 24.62]**	**8.49 [3.86, 14.04]**	**0.012**	**0.036**
SE (median [IQR])	5.85 [1.98, 13.01]	5.59 [1.79, 10.31]	3.16 [0.00, 13.16]	0.458	0.692
TB (median [IQR])	0.00 [0.00, 5.97]	0.00 [0.00, 4.31]	0.64 [0.00, 10.28]	0.782	0.918

Stratified by pM				
	M0	**M1**	***p***	***p*-adj**
n	**134**	**27**		
CT (median [IQR])	46.71 [20.82, 61.93]	43.00 [30.36, 60.02]	0.885	0.923
DE (median [IQR])	**2.76 [0.00, 9.28]**	**10.28 [4.08, 24.30]**	**<0.001**	**0.002**
MU (median [IQR])	1.32 [0.00, 9.86]	0.00 [0.00, 4.65]	0.482	0.692
PP (median [IQR])	**15.45 [8.43, 31.86]**	**8.87 [5.14, 21.14]**	**0.032**	**0.086**
SE (median [IQR])	5.47 [1.90, 12.77]	4.19 [0.00, 12.32]	0.490	0.692
TB (median [IQR])	0.00 [0.00, 6.43]	1.29 [0.00, 5.33]	0.884	0.923

Stratified by MSI				
	MSI	**MSS**	***p***	***p*-adj**
n	**104**	**27**		
CT (median [IQR])	**17.92 [8.82, 31.74]**	**53.35 [35.76, 65.77]**	**<0.001**	**<0.001**
DE (median [IQR])	4.30 [0.00, 12.06]	2.61 [0.00, 10.12]	0.510	0.692
MU (median [IQR])	**12.95 [0.00, 42.30]**	**0.00 [0.00, 3.30]**	**<0.001**	**0.0015**
PP (median [IQR])	**8.49 [1.43, 14.44]**	**15.17 [9.14, 28.32]**	**0.002**	**0.007**
SE (median [IQR])	4.68 [0.00, 12.38]	5.04 [1.79, 12.65]	0.498	0.692
TB (median [IQR])	**12.21 [0.00, 41.67]**	**0.00 [0.00, 3.22]**	**<0.001**	**<0.001**