Title

Limits of radiomic-based entropy as a surrogate of tumor heterogeneity: ROI-area, acquisition protocol and tissue site exert substantial influence

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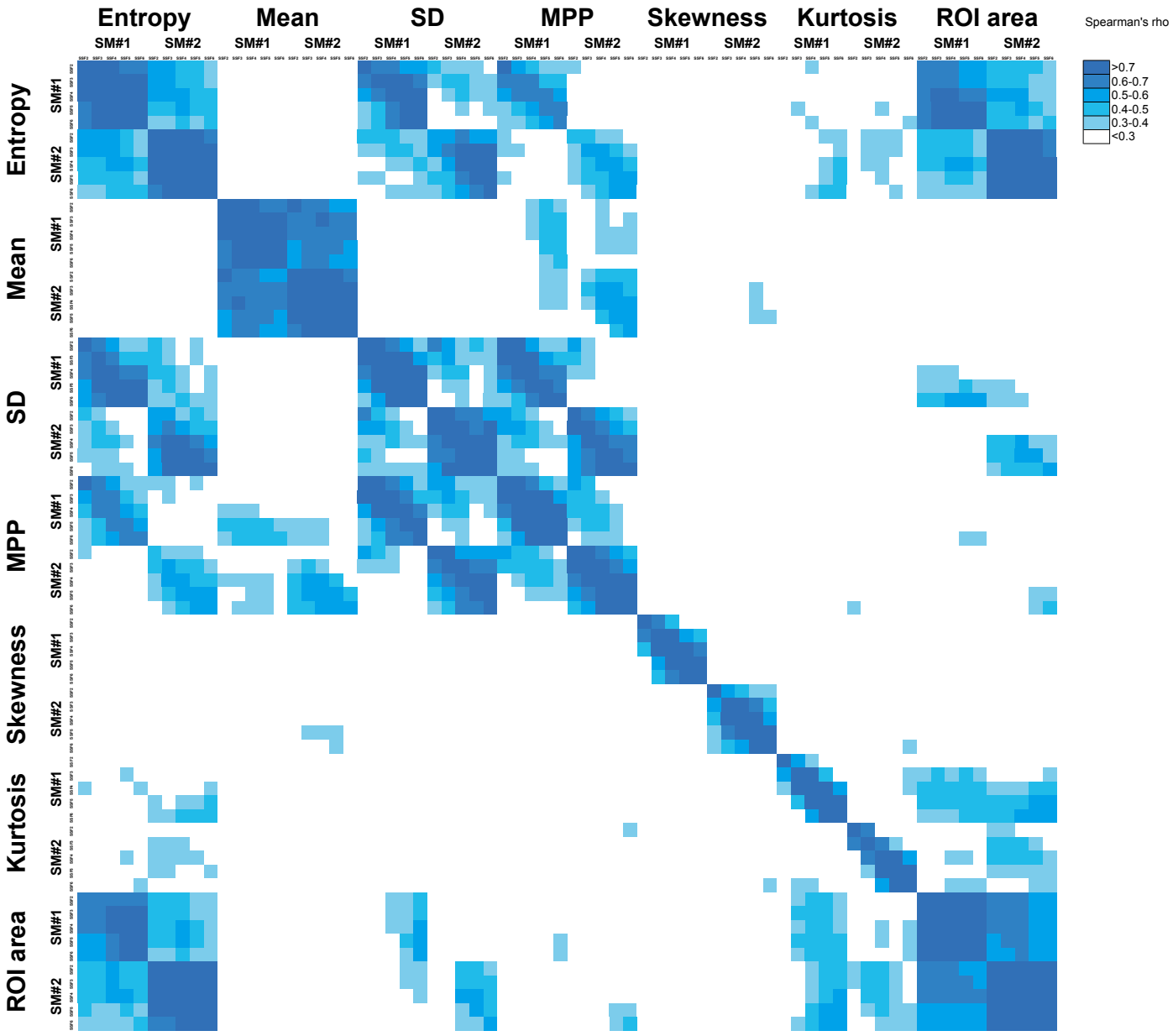
Supplemental Figure 1. Similarity of the imaging phenotype of 112 pairs of biopsy-proven synchronous metastases: inter and intra-tumor correlation

Figure 2 legend: Paired biopsy-proven synchronous metastases have a similar imaging phenotype as proved by the inter-tumor (#1 vs. #2) and intra-tumor (#1 vs. #1, #2 vs. #2) Spearman's rho correlation coefficient at various spatial scale filters (SSF2-6). Interestingly, we discovered a significant intra and inter-tumor correlation between entropy and the area of the ROI.



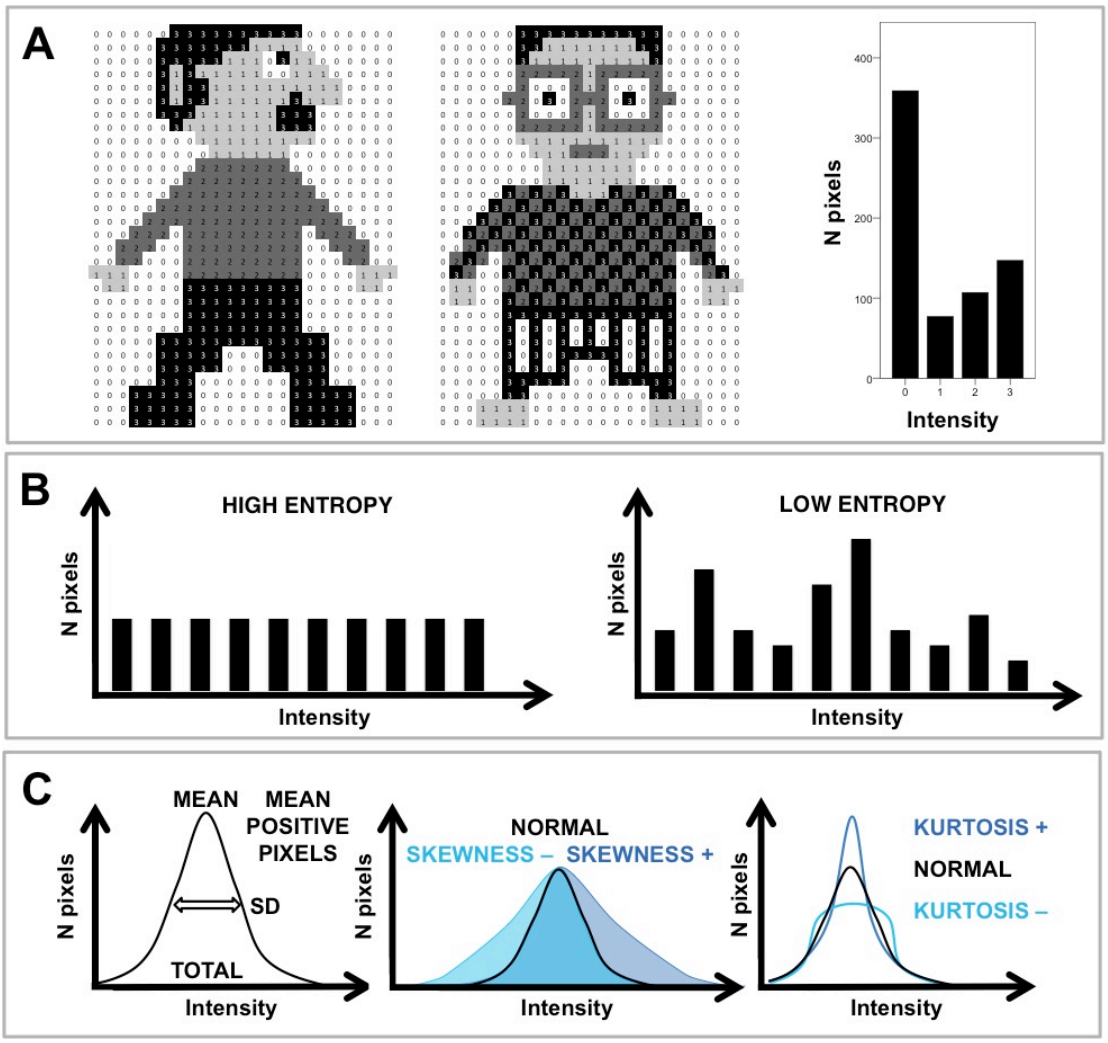
Supplemental Figure 2. Meaning of voxel intensity histogram analysis

Histogram analysis evaluates the number of voxels within the ROI (y-axis) for each tissue density measured in Hounsfield unit by Photon X attenuation (x-axis).

A. Shannon's entropy considers that all pixels are independent (from its neighbor) and identically distributed and thus does not perceive the heterogeneity of voxels spatial distribution. It explains that the picture at the left and the middle have the same histogram and thus the same entropy.

B. Entropy is considered as a surrogate of the heterogeneity of voxels intensity distribution.

C. Texrad extracts 6 features: Mean (average level of intensity), Mean Positive Pixel, Standard Deviation (SD, dispersion of intensity around the mean), Skewness (asymmetry of the histogram: is zero if the histogram is symmetrical around the mean, and is otherwise either positive or negative depending whether it is skewed above or below the mean), Kurtosis (peakedness, normalized to zero for a Gaussian-shaped histogram), Entropy (uniformity or randomness) and Total (number of pixels of the ROI).



Supplemental Table 1. The variable Entropy is a logarithmic function of the area of the ROI in malignant and healthy tissues

Supplemental Table 1 legend. Logarithmic regression shows that the value of the variable Entropy is a function of the area of the ROI in every type of tissues (synchronous metastases, psoas muscle and aorta) in all SSFs. A similar equation is found in all cases. The high p-value ($p<0.001$) and R^2 show the prediction strength of this logarithmic model.

					p-value	R^2	F
SM#1	**Entropy SSF2 =**	3.07	+ 0.28	x ln(area of the ROI SSF2)	P<0.001	0.53	169
	Entropy SSF3 =	2.83	+ 0.29	x ln(area of the ROI SSF3)	P<0.001	0.51	154
	Entropy SSF4 =	1.89	+ 0.42	x ln(area of the ROI SSF4)	P<0.001	0.64	265
	Entropy SSF5 =	1.90	+ 0.40	x ln(area of the ROI SSF5)	P<0.001	0.65	262
	Entropy SSF6 =	1.19	+ 0.51	x ln(area of the ROI SSF6)	P<0.001	0.75	403
SM#2	**Entropy SSF2 =**	2.18	+ 0.42	x ln(area of the ROI SSF2)	P<0.001	0.74	317
	Entropy SSF3 =	1.78	+ 0.46	x ln(area of the ROI SSF3)	P<0.001	0.77	368
	Entropy SSF4 =	1.22	+ 0.54	x ln(area of the ROI SSF4)	P<0.001	0.84	535
	Entropy SSF5 =	1.23	+ 0.52	x ln(area of the ROI SSF5)	P<0.001	0.81	394
	Entropy SSF6 =	1.09	+ 0.54	x ln(area of the ROI SSF6)	P<0.001	0.79	307
Muscle	**Entropy SSF2 =**	2.92	+ 0.31	x ln(area of the ROI SSF2)	P<0.001	0.30	62
	Entropy SSF3 =	2.62	+ 0.31	x ln(area of the ROI SSF3)	P<0.001	0.36	79
	Entropy SSF4 =	1.54	+ 0.46	x ln(area of the ROI SSF4)	P<0.001	0.66	270
	Entropy SSF5 =	0.64	+ 0.60	x ln(area of the ROI SSF5)	P<0.001	0.82	611
	Entropy SSF6 =	0.55	+ 0.60	x ln(area of the ROI SSF6)	P<0.001	0.84	626
Aorta	**Entropy SSF2 =**	3.33	+ 0.21	x ln(area of the ROI SSF2)	P<0.001	0.40	98
	Entropy SSF3 =	2.94	+ 0.23	x ln(area of the ROI SSF3)	P<0.001	0.46	124
	Entropy SSF4 =	2.38	+ 0.30	x ln(area of the ROI SSF4)	P<0.001	0.59	207
	Entropy SSF5 =	1.51	+ 0.42	x ln(area of the ROI SSF5)	P<0.001	0.67	296
	Entropy SSF6 =	1.96	+ 0.35	x ln(area of the ROI SSF6)	P<0.001	0.59	194

Supplemental Table 2. Example of quality criteria for the implementation of imaging biomarkers into the clinics

Supplemental Table 1 legend. Example of quality criteria that might be used in further studies. Imaging biomarkers were measured in 112 patients in two synchronous metastases, psoas muscle and aorta (n=448).

* p <0.05

	ENTROPY	MEAN	SD	MPP	SKEWNESS	KURTOSIS
Redundancy The biomarker is strongly correlated with another one (r>0.7)	SD		MPP, Ent.	SD		
Recognition of the similarity between synchronous metastases Spearman's rho coefficient between SM#1 vs. SM#2 (n=112 pairs)	.52*	.68*	.43*	.43*	.24	-.02
Volume-dependence Spearman's rho coefficient with the area of the ROI (n=448)	.75*	-.06*	.21*	.08*	.04*	.52*
Stability across spatial scale filters (SSF) Spearman's rho coefficient between all SSF (n=448)	.83*	.83*	.73*	.73*	.58*	.48*

Supplemental Table 3. Stability of imaging biomarkers across spatial scale filters within the same ROI of the same lesions

Supplemental Table 3 legend. The values of imaging features are compared according to different SSF in 448 ROI (112 patients: SM#1, SM#2, psoas muscle and aorta). We see that Skewness and Kurtosis are volatile parameters. Spearman's Rho correlation coefficient is significant ($p<0.05$) in all cases.

MEAN	SSF2	SSF3	SSF4	SSF5
SSF3	.89			
SSF4	.78	.94		
SSF5	.69	.88	.96	
SSF6	.62	.80	.87	.94

SKEWNESS	SSF2	SSF3	SSF4	SSF5
SSF3	.69			
SSF4	.44	.82		
SSF5	.27	.60	.85	
SSF6	.23	.45	.65	.85

SD	SSF2	SSF3	SSF4	SSF5
SSF3	.85			
SSF4	.68	.91		
SSF5	.55	.77	.93	
SSF6	.38	.55	.75	.88

KURTOSIS	SSF2	SSF3	SSF4	SSF5
SSF3	.52			
SSF4	.33	.73		
SSF5	.23	.49	.80	
SSF6	.24	.30	.50	.75

ENTROPY	SSF2	SSF3	SSF4	SSF5
SSF3	.92			
SSF4	.82	.93		
SSF5	.71	.83	.95	
SSF6	.61	.71	.87	.95

ROI AREA	SSF2	SSF3	SSF4	SSF5
SSF3	.99			
SSF4	.96	.97		
SSF5	.90	.94	.98	
SSF6	.83	.88	.95	.97

MPP	SSF2	SSF3	SSF4	SSF5
SSF3	.83			
SSF4	.68	.89		
SSF5	.51	.73	.92	
SSF6	.40	.60	.82	.95