Supplementary

Section 1: MRI sequence parameters for the CCF cohort of the test set

The MR images were acquired in a routine clinical workflow on 1.5 Tesla scanners using Siemens (Trio, SYNGO MR A30 4VA30A software, Munich, Germany), with a 12 channel head matrix coil. Post contrast T1w sequences (Gd-T1w) were acquired using a weight adjusted doses of 0.1mmol/kg gadolinium based contrast agent (GBCA; Gadobutrol, Gadavist®, Bayer Healthcare Pharmaceuticals, New Jersey, USA) that was administered intravenously.

T2w-FLAIR sequences were acquired prior to contrast administration. This ensured that the hyper-intense regions from the enhancing region of the tumor habitat did not manifest on T2w-FLAIR MR images. T2w images were acquired immediately after gadolinium (Gd) intravenous administration. This optimized the total scanning time and allowed for contrast circulation during T2w image acquisition. Lastly, routine scans with contrast Gd-T1w sequences are obtained immediately following T2w sequence.

Sequence parameters for pre- and post- contrast T1w, T2w and T2w-FLAIR are as follows:

- T1w and GdT1w images (3D axial) – Flip Angle = 90°, repetition time (TR) = 550 - 1000 ms and echo time (TE) = 3-12ms
- T2w images (2D axial) – Flip Angle = 90°, slice thickness = 5mm, repetition time (TR) = 3000-5550 ms and echo time (TE) = 85 – 105 ms
- T2w-FLAIR images (2D axial) – Slice thickness = 5mm, repetition time (TR) = 8000 – 10000 ms and echo time (TE) = 90 - 150 ms

Section 2 : List of features extracted

Features	Description
Size	Including Width, Height, Depth of bounding box (3 features)
Area	from 2D slices of each nodule, calculate number of pixels in a given ROI
Perimeter	from 2D slices of each nodule
Eccentricity	foci of the ellipse and to major axis length (eg, a circle has 0 eccentricity; an ellipse has a value between 0 and 1)
Extent	ratio of pixels in the region to pixels in the total bounding box
Compactness	ratio of the perimeter squared to the product of 4π and area
Radial distance	distances from center of each slice to contour points
Roughness	perimeter of slices divided by convex perimeter
Elongation	from major and minor axis
Convexity	from convex hull
Equivalent Diameter	Diameter of circle with same area of slices
Sphericity	3D compactness

Table S1: *List of shape features extracted*

Feature category	Descriptor	Intuitive description	Relevance to GBM pathophysiology
Laws features	E5, L5, S5, R5 (combination in X,Y and Z directions)	E- Edges, L- Level, S- Spots, R- Ripples	Accounting for characteristic qualitative appearance of wave, ripple, edge and spots within an ROI

Gabor features		This filter bank has characteristics of spatial locality and orientation selectivity	Captures the prominent direction in which the intensity changes occur
Haralick features	Inverse difference moment (IDM)	IDM is a reflection of the presence or absence of uniformity, and hence is a measure of local regions of homogeneity High IDM: Higher presence of locally uniform windows in GLCM. Low IDM: Higher presence of locally heterogeneous windows in GLCM	Captures the underlying lesion heterogeneity
	Correlation	Quantifies the linear patterns in an image based on the distance parameter.	Increased presence of linear patterns yield higher correlation values, lack of image linearity yield lower correlation values
	Sum Entropy	Measure of GLCM relationship to distribution of intensity with respect to entropy (measure of disorder)	Higher entropy is indicative of more chaotic arrangement in areas of high viable cell population
	Sum Variance	Measure of GLCM relationship to distribution of intensity with respect to variance. High sum variance: greater standard deviation of sum average. Low sum variance: low standard deviation of sum average	Possibly accounting for greater variation of scattered atypia and local accumulation of mitotic processes as observed on histopathology.

Table S2: *Pathophysiological significance of radiomic features which possibly reflect biological traits of GBM and can be captured on MRI*

Feature Category	**Implementation details**
Laws Energy	1) window size of kernels - 5 2) the 'same' option in MATLAB **conv command** was used to trim the outer part of the convolution and return only the central part, which was the same size as the input. 3) 1D Kernels used: L (Level) = [1 4 6 4 1] E (Edge) = [-1 -2 0 2 1] S (Spot) = [-1 0 2 0 -1] W (Wave) = [-1 2 0 -2 1] R (Ripple) = [1 -4 6 -4 1] 4) Three 1-D kernels were combined via matrix multiple to generate a 5 x 5 x 5 kernel (now 3-D); all permutations of three 1-D kernels were implemented
Gabor	The real component of the Gabor filter response in 3D at a particular (x,y,z) location was defined as: $$g_{\lambda,\theta\varphi,\sigma,\gamma}(x,y,z) = \exp\left(-\frac{x^{*2}+y'^{2}+z^{*2}}{2\sigma^{2}}\right)\cos\left(2\pi\frac{x^{*}}{\lambda}+\varphi\right)$$ where $$x' = xcos\theta_{xy} - ysin\theta_{xy}$$ $$y' = xsin\theta_{xy} + ycos\theta_{xy}$$ $$z^{*} = -x'sin\theta_{xz} + ycos\theta_{xz}$$ $$x^{*} = x'cos\theta_{xz} - zsin\theta_{xz}$$

	$$\sigma = \frac{\lambda(2^B+1)}{\pi(2^B-1)}\sqrt{\frac{\ln(2)}{2}}$$ The necessary parameters are defined below along with their implemented values: • θ_{xy}: orientation in x-y plane; $\theta_{xy} \in \{0, \pi/6, \pi/3, \pi/2, 2\pi/3, 5\pi/6\}$ radians • θ_{xz}: orientation in x-z plane; $\theta_{xz} \in \{0, \pi/4, \pi/2, 3\pi/4\}$ radians • B: bandwidth, or half-response spatial frequency; fixed at $B = 1$ (therefore $\sigma \approx 0.56\lambda$) • λ: wavelength of cosine factor; determined such that 7*0.56*σ would equate to the window size of a m x m x m kernel; λ ∈ {0.88, 1.4142, 2.0750, 2.828, 5.6569, 11.3137} • σ: specified based on B, λ. Isotropic filter, so σ same in all directions • φ: phase offset; fixed at $\varphi = 0$ in all directions
Haralick	1) image quantization approach - Uniform (i.e. equal distances between original gray levels and quantized bins) 2) number of bins - 128 (i.e. 128 gray levels) 3) offset - 1 (i.e., search D = 1 pixels away from pixel of interest) 4) number of directions - 4 directions (bi-directional), 3 orientations (x-y, x-z, y-z) - horizontal: 0 or 180 degrees - right diagonal: 45 or 135 degrees - vertical: 90 or 270 degrees - left diagonal:135 or 315 degrees 5) extraction method - symmetrically 6) aggregation approach for final feature estimation - For each pixel of interest, gray-level co-occurrence matrix (GLCM) calculations were summed among all pixels within a fixed m x m x m window centered around the pixel, to create a single symmetric co-occurrence matrix - Features were extracted from this symmetric co-occurrence matrix for each pixel of interest, yielding 13 GLCM feature representations for each pixel of interest (visualized as heatmaps)

Table S3: *Implementation details of the features extracted*

Section 3 : Gd-T1w Radiomic Risk Score

The radiomic signature was constructed using the following formula:

Gd-T1w Radiomic Risk Score = median-R5S5E5 of Necrotic core (0.242897454) + kurtosis-energy (ws=5) of Necrotic core (0.241360718) + Skewness-E5E5S5 of Enhancing region (0.156897908) + Median-R5R5R5 of Enhancing region (0.140568729) + Skewness-S5R5R5 of Edematous region (0.134099892) + Skewness-XY Orient=1.0472, XZ Orient=2.3562, Bandwidth=1, Wavelength=11.3137 of Enhancing region (0.132285255) + Skewness-R5S5L5 of Necrotic core (0.127261674) + Kurtosis-R5S5R5 of Enhancing region (0.123944592) + Median-S5S5R5 of Edematous region (0.081681921) + Kurtosis-XY Orient=1.5708, XZ Orient=0, Bandwidth=1, Wavelength=1.4142 of Enhancing region (0.064584818) + Skewness-R5L5L5 (0.059900374) of Necrotic core + Kurtosis-XY Orient=1.5708, XZ

Orient=1.5708, Bandwidth=1, Wavelength=5.6569 (0.0522149) of Necrotic core + Sphericity of Edematous region (0.045438219) + Median R5R5L5 of Enhancing region (0.030598447) + Kurtosis-XY Orient=1.5708, XZ Orient=1.5708, Bandwidth=1, Wavelength=5.6569 of Edematous Region (0.020506011) + Skewness-R5L5S5 of Edematous region (0.01850727) + Std-XY Orient=1.0472, XZ Orient=1.5708, Bandwidth=1, Wavelength=11.3137 of Necrotic core (0.001913863) + Skewness-E5R5S5 of Enhancing region (-0.028723416) + Median-E5R5E5 of Necrotic core (-0.038645031) + Convexity of Edematous region (-0.044854456) + Median-R5L5E5 of Enhancing region (-0.049591168) + Elongation of Edematous region (-0.09991949) + Median-R5L5E5 of Enhancing region (-0.136694365) + Median-L5E5L5 of Edematous region (-0.148396663) + Kurtosis-XY Orient=1.5708, XZ Orient=2.3562, Bandwidth=1, Wavelength=5.6569 of Necrotic core (-0.169581107)

Section 4 : Clinical characteristics of Gd-T1w radiomic risk score groups

Clinical characteristics of Gd-T1w radiomic risk score groups							
Clinical Variable		**Training Cohort**		**p-value**	**Test Cohort**		**p-value**
		Low Risk	**High Risk**		**Low Risk**	**High Risk**	
Mean Progression Free Survival (in days)		409.8	152.8	<0.0001 *	463.8	242.3	0.0073 *
Age (in years)		55.8	60.2	0.0837	60.3	56.9	0.1858
Gender	Female	25	22	0.5652	14	17	0.6681
	Male	44	39		19	21	
MGMT Status	Methylated	22	17	0.4849	16	16	0.3748
	Unmethylated	17	15		16	21	
IDH Status	Wild type	54	48	0.6062	23	33	0.9360
	Mutated	3	3		5	3	

Table S3: *Clinical characteristics of Gd-T1w MRI radiomic risk groups. P values were computed by using Student t test for continuous variable and Fisher exact test for categorical data. Abbreviations: MGMT - O-6-Methylguanine-DNA Methyltransferase, IDH - Isocitrate dehydrogenase.*

Section 5 : Gene Ontology (GO) Analysis

Web-based application, GOView (http://www.webgestalt.org/GOView/) was used to visualize and compare the 57 GO biological processes in a directed acyclic graph (DAG) to reveal relationships among these processes. GOView enabled comparison of multiple GO processes to identify the common and specific biological themes, by exploring the semantic relationships between the 'parent' and 'child' biological processes. [1] It was observed that most of the biological processes involved in GO pathways were implicated in cell adhesion, cell proliferation, differentiation and angiogenesis.

[1] Wang et al., "WebGestalt 2017."

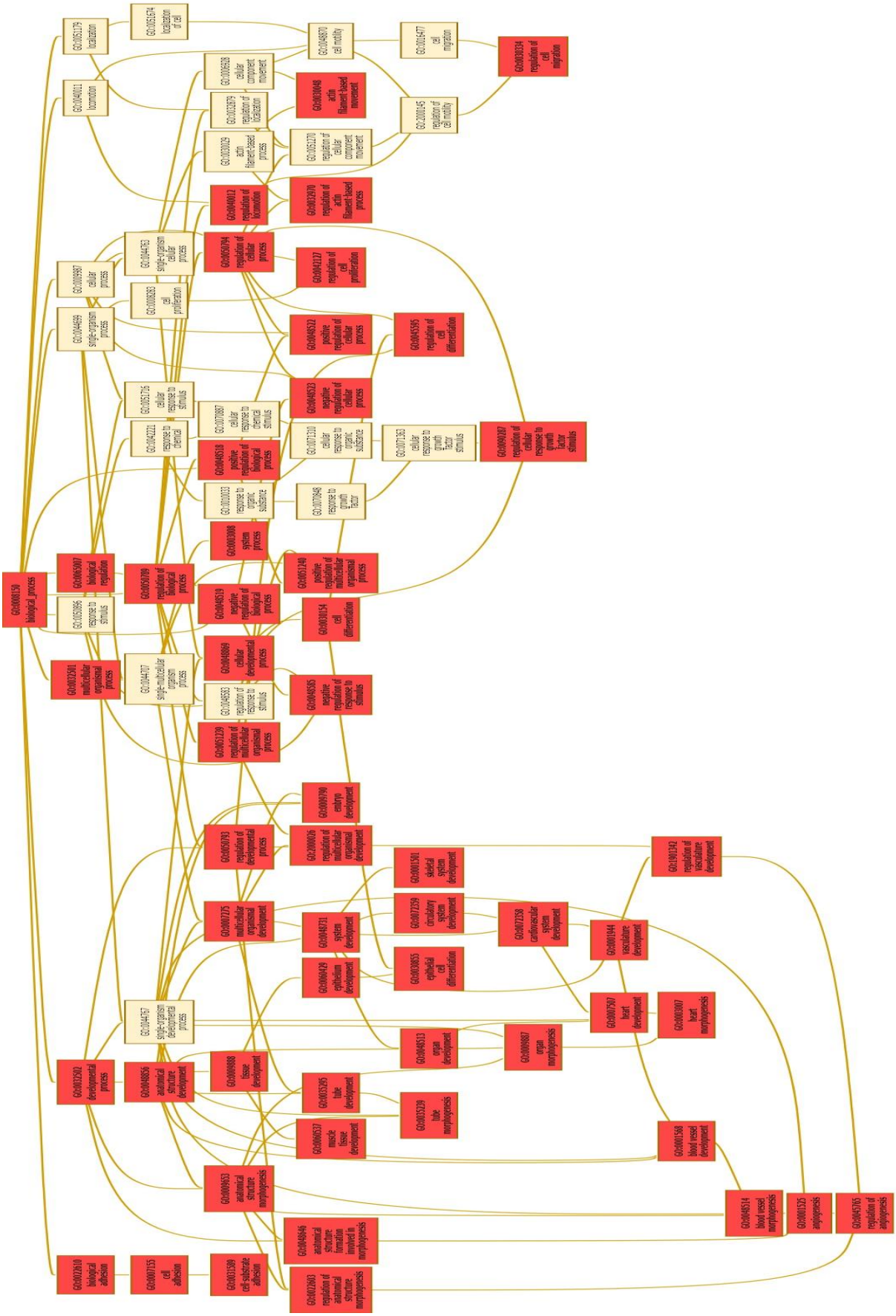

Figure S5: *Gene Ontology Directed Acyclic Graph (GO-DAG)*