Supplementary Materials

Tumor Margin Contains Prognostic Information: Radiomic Margin Characteristics Analysis in Lung Adenocarcinoma Patients

Geewon Lee, Hyunjin Park, Ho Yun Lee, Joong Hyun Ahn, Insuk Sohn, Seung-Hak Lee and Jhingook Kim

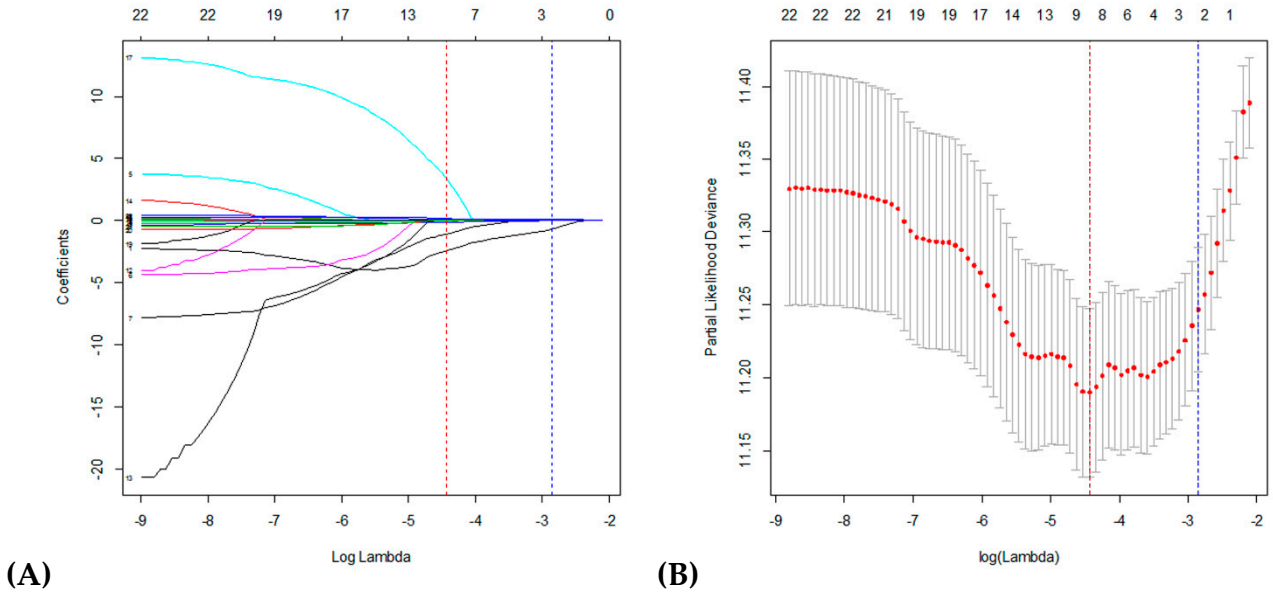
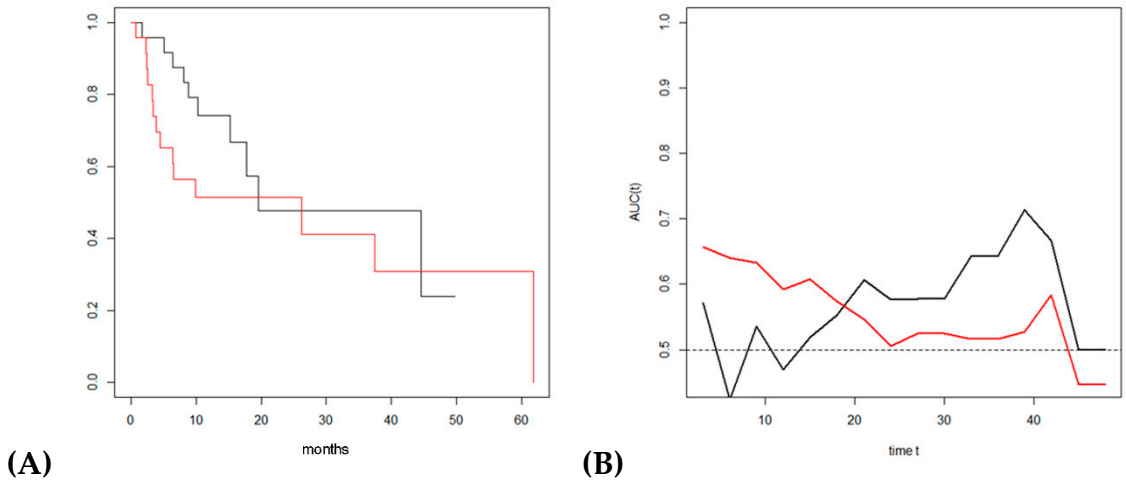
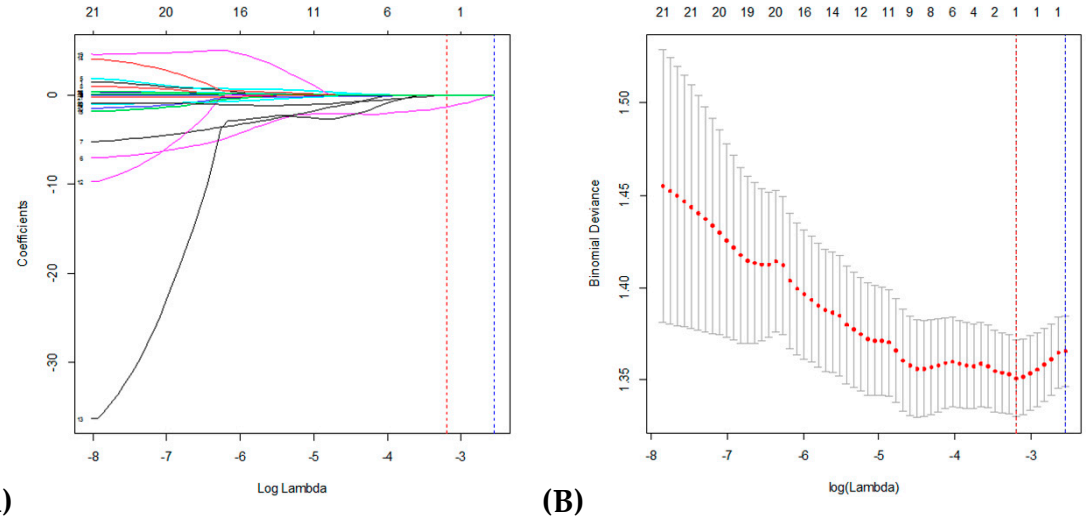


Figure S1. Selection of radiomics features for the prediction of overall survival using the LASSO logistic regression model. (**A**) LASSO coefficients produced by the regression analysis. Eight marginal radiomics features were selected. (**B**) Selection of the tuning parameter (lambda) in the LASSO model via LOOCV (leave one out cross-validation). Dotted red and blue vertical lines were drawn at the optimal values by minimum criteria and 1-s.e. criteria, respectively.



(A) **(B)**

Figure S2. (**A**) Survival curves of the validation group stratified by the median of predicted survival according to the model incorporating both clinical variables and radiomics features. (Red line, group with lower survival; Black line, group with better survival). (**B**) Time-dependent AUC demonstrates that the model incorporating clinical variables and radiomics features showed better performance for predicting early survival of less than 20 months (Red line, clinical variables and radiomics features; Black line, clinical variables only).



(A) **(B)**

Figure S3. Selection of radiomics features for the prediction of the MP subtype using the LASSO logistic regression model. (**A**) LASSO map shows coefficients plotted against the log(lambda) sequence. Only the sphericity value radiomics feature (pink line, 6th variable) was selected. (**B**) LASSO coefficient analysis of the radiomics features. Using LOOCV (leave one out cross-validation), the minimum value of log(lambda) was found to be −1.373. Dotted red and blue vertical lines were drawn at the optimal values by minimum criteria and 1-s.e. criteria, respectively.

Table S1. Definition of extracted radiomics features.

	Parameter	Formula	Description
Filter-based features (LoG) [19]	Mean	$\text{Mean} = \frac{1}{\mathrm{N}}\sum_{\mathrm{i}}^{\mathrm{N}} \mathrm{G(i)}$ Where G denote the filtered 3d image matrix with N voxel.	Measurement of mean of ROI image processed by LoG filter
	Max	$\text{Max} = Max(G(i))$ Where G denotes the filtered 3d image matrix with N voxel.	Measurement of max intensity value of ROI image processed by LoG filter
	Min	$\text{Min} = Min(G(i))$ Where G denotes the filtered 3d image matrix with N voxel.	Measurement of minimum intensity value of ROI image processed by LoG filter
	Median	$\text{Median} = \frac{\mathrm{G(i)}}{2}$ Where G denote the filtered 3d image matrix	Measurement of median intensity value of ROI image processed by LoG filter
	Standard deviation (Std)	$\text{Std} = \left(\frac{1}{\mathrm{N}-1}\sum_{\mathrm{i=1}}^{\mathrm{N}} (\mathrm{G(i)} - \bar{G})^2\right)^{1/2}$ Where G denote the filtered 3d image matrix with N voxel.	Measurement of standard deviation of ROI image processed by LoG filter
	Skewness	$\text{Skewness} = \frac{E(G-\mu)^3}{\sigma^3}$ Where μ is the mean of G, σ is the standard deviation of G, E is the expectation operator.	Measurement of skewness of ROI image processed by LoG filter
	Kurtosis	$\text{Kurtosis} = \frac{E(G-\mu)^4}{\sigma^4}$ Where μ is the mean of G σ is the standard deviation of G, E is the expectation operator.	Measurement of kurtosis of ROI image processed by LoG filter
	Uniformity	$\text{Uniformity} = \sum_{i=1}^{N_l} P(i)^2$ Where P denotes the first-order histogram with N_l discrete intensity levels.	Measurement of uniformity of ROI image processed by LoG filter
Shape- and size-based features [8,19]	Compactness	$\text{Compactness} = \frac{V}{\sqrt{\pi} A^{\frac{3}{2}}}$ Where V denotes the volume, and A denotes the surface area of the volume of interest (VOI)	Quantifies how close an object is to the smoothest shape, the circle
	Surface area	$\text{SA} = \sum_{i=1}^{N} \frac{1}{2}\lvert a_i b_i \times a_i c_i \rvert$ Where N is the total number of triangles (coved surface area), and a, b, c are edge vectors	The surface area of the ROI
	Convexity	$\text{Convexity} = \frac{V}{V'}$ Where V denotes tumor volume, and V' denotes convex hull volume	Measures ratio of the ROI volume contained within the tumor to the calculated convex hull volume
	Sphericity	$\text{Sphericity} = \frac{\pi^{\frac{1}{3}} \times (6\mathrm{V})^{\frac{2}{3}}}{\mathrm{A}}$ Where A denotes area, and V denotes tumor volume	Measures of the roundness of the ROI
	Spherical disproportion	$\text{Spherical disproportion} = \frac{A}{4\pi R^2}$ Where R is the radius of a sphere with the same volume as the tumor	The ratio of the surface area of the ROI to the surface area of a sphere with the same volume as the ROI
	Maximum 3D diameter	See description in the next column	Measures of the maximum 3D ROI diameter. It is measured as the largest pairwise Euclidean distance, between surface voxels of the ROI
	Surface to volume ratio (SVR)	$\text{SVR} = \frac{A}{V}$ Where A is area, and V is volume	Surface to volume ratio in ROI
	Volume	$\text{Volume} = \mathrm{R} * \text{number of voxels}$ Where R denote the 3d image resolution	Volume of tumor (ROI)
	Mass	$\text{Mass} = \mathrm{V} * \mathrm{D}$ Where V denote the tumor volume, D denotes the tumor density	Mass of tumor (ROI)
	Density	$\text{Density} = \frac{M}{V}$	Density of tumor (ROI)

		Where V denote the tumor volume, M denote the tumor mass	
	Roundness factor (2D)	Roundness factor $= \frac{4\pi \cdot Area}{Perimeter^2}$	Measure of circularity of a ROI
	Eccentricity (2D)	Eccentricity $= c/a$ Where c is the distance from the center to a focus and a is the distance from that focus to a vertex	Measure of how the tumor shape is close to the circle
	Solidity (2D)	Solidity $= \frac{Area}{Convex\ area}$	Measure of convexity of a ROI on the 2D image
Fractal-based features [18,20]	Lacunarity (Box-counting method)	See description in the next column	Measure of the texture or distribution of gaps within an image
	Dimension (Box-counting method)	Fractal dimension $= \lim_{r \to 0} \frac{\log(N_r)}{\log(1/r)}$ Where N_r is the number of voxels, and r is the each of different side lengths	Fractal dimension quantifies morphological complexity and provides information on the self-similarity properties
	Fractal signature dissimilarity (Blanket method)	See description in the next column	Measure of tumor heterogeneity infromation

Note–LoG, Laplacian of Gaussian; ROI, region of interest.

Table S2. Patient characteristics of the thoracic surgical database and external validation group.

	Thoracic Surgical Database N **= 334**	**External Validation** N **= 47**
Sex		
Male	184	28
Female	150	19
Age (Mean ± SD)	60.9 ± 9.96	68.1 ± 10
Overall Survival (Mean)	66.7 months	10.6 months
Death	85 (25.4%)	24 (51.1%)

Table S3. Model only using commonly existing clinical variables for the prediction of overall survival (C-index: 0.747) for external validation.

Selected Variables	**Reference**	p **Value**	**OR**	**95% CI**
Sex	Male	0.012	1.820	1.142–2.903
Age		<0.001	1.042	1.018–1.067
TNM stage 2	TNM stage 1	<0.001	3.422	2.040–5.740
TNM stage 3	TNM stage 1	<0.001	4.247	2.496–7.227

Note–OR, odd's ratio; CI, confidence interval.

Table S4. Model using commonly existing clinical variables and all radiomics features for the prediction of overall survival (C-index: 0.778) for external validation.

Selected Variables	Reference	*p* Value	OR	95% CI
Sex	Male	0.007	1.926	1.195–3.104
Age		<0.001	1.593	1.244–2.041
TNM stage 2	TNM stage 1	<0.001	2.823	1.589–5.016
TNM stage 3	TNM stage 1	<0.001	4.505	2.558–7.933
Convexity		<0.001	0.567	0.413–0.779
LoG Uniformity 0.5		0.042	0.693	0.486–0.987
LoG Kurtosis 1		<0.001	1.100	1.044–1.159
Roundness Factor		<0.001	4.257	2.094–8.653
Lacunarity		0.021	0.570	0.353–0.920

Note–OR, odd's ratio; CI, confidence interval.

Table S5. Percentages of MP subtype according to the predominant subtype of lung adenocarcinoma.

Predominant Subtype (%)	Lepidic	Acinar	Papillary	MP	Solid
MP absent	68.8	48.3	33.3	0	93.2
MP present	31.3	51.7	66.7	100	6.9

Note: MP, micropapillary; * Due to rounding, not all percentages total 100.