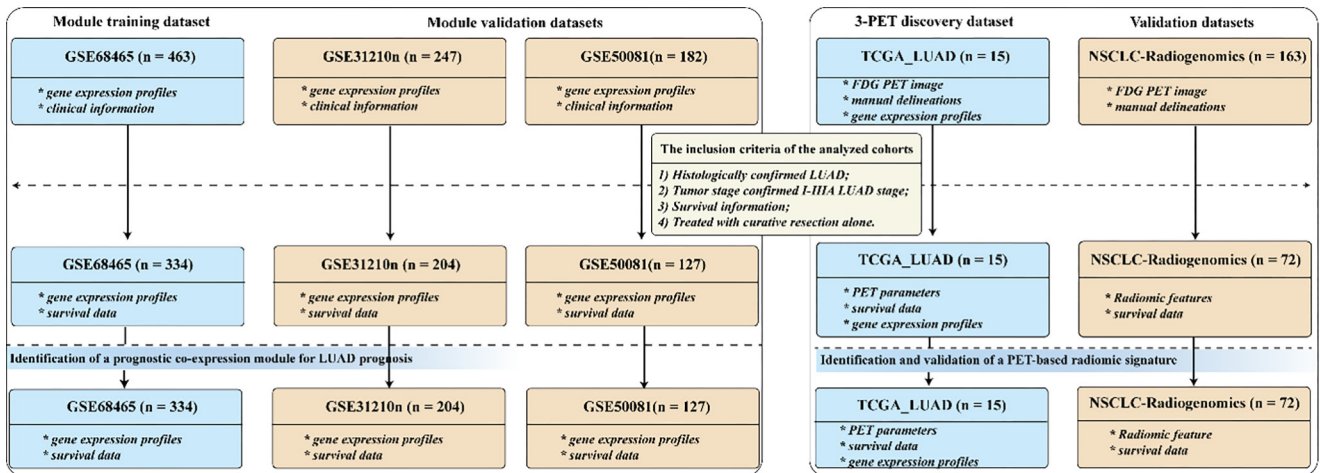


## Weighted gene coexpression network analysis

The “pickSoftThreshold” function was used to determine the proper soft-thresholding power ( $\beta$ ) that fit the criteria of the approximate scale-free topology of the network. An adjacency matrix was then built with a soft-thresholding power of 6 in this study. The correlation matrix was transformed into an adjacency matrix (matrix of connection strength) using the power function, and pairwise topologic overlap between genes was calculated. Hierarchical clustering was constructed to identify distinct modules using the “blockwiseModules” function with the parameters minModuleSize and mergeCutHeight set to 50 and 0.25, respectively, in the weighted gene coexpression network analysis. Genes that were not assigned to any module were labeled in gray color.

## Calculation formula for the radiomic signature

Risk score =  $0.12310108 \times (\text{third quartile}) - 0.09250096 \times (\text{SD}) - 0.11141270 \times (\text{median}) - 0.03370519$ .



**Figure S1** The inclusion criteria and flowchart of the analyzed datasets. FDG, fluorodeoxyglucose; LUAD, lung adenocarcinoma; NSCLC, non-small cell lung cancer; PET; positron emission tomography; TCGA, The Cancer Genome Atlas.

**Table S1** Summary of key PET/CT parameters in the analyzed dataset

Parameter	Value
FDG dose (MBq)	138.90–572.25
FDG uptake time (min)	23.08–128.90

FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

**Table S2** Overview of the image-derived features that were used

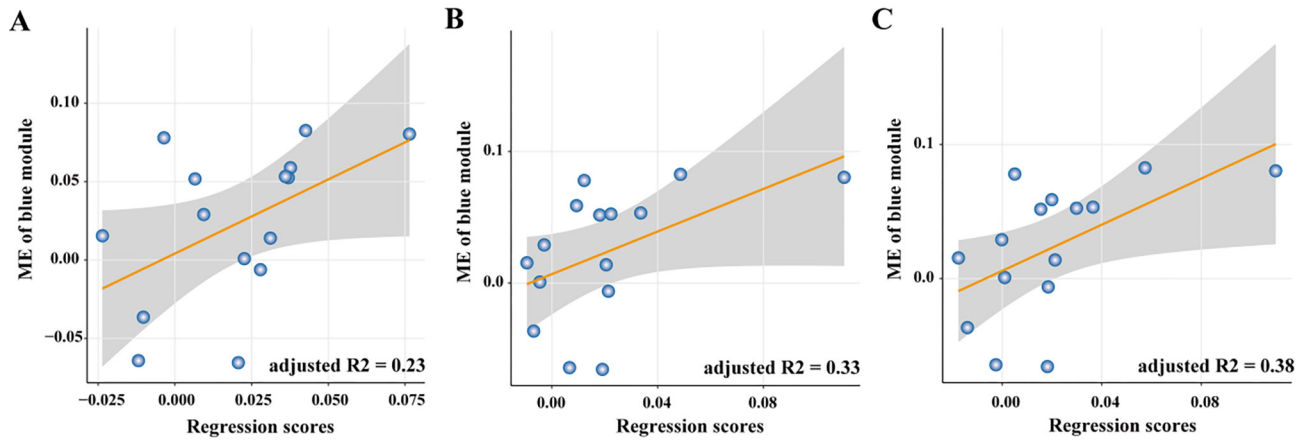
Feature name	Description	Feature type
SUV <sub>mean</sub>	SUV mean of ROI*	C
SUV <sub>min</sub>	SUV minimum of ROI	N
SUV <sub>max</sub>	SUV maximum of ROI	C
SUV <sub>peak</sub>	Maximum average gray value that is calculated from a 1 cm <sup>3</sup> sphere placed within the ROI	C
MTV	Metabolic tumor volume	C
TLG	Total lesion glycolysis	C
SD	Standard deviation of ROI	N
First quartile	25th percentile value in ROI	N
Median	50th percentile value in ROI	N
Third quartile	75th percentile value in ROI	N
Upper adjacent	First value in ROI not greater than 1.5 times the interquartile range	N
RMS	Root mean square value in ROI	N
Glycolysis Q1	Lesion glycolysis calculated from the 1st quarter of the grayscale range within the ROI	N
Glycolysis Q2	Lesion glycolysis calculated from the 2nd quarter of the grayscale range within the ROI	N
Glycolysis Q3	Lesion glycolysis calculated from the 3rd quarter of the grayscale range within the ROI	N
Glycolysis Q4	Lesion glycolysis calculated from the 4th quarter of the grayscale range within the ROI	N
Q1 distribution	Percent of gray values that fall within the 1st quarter of the grayscale range within the ROI	N
Q2 distribution	Percent of gray values that fall within the 2nd quarter of the grayscale range within the ROI	N
Q3 distribution	Percent of gray values that fall within the 3rd quarter of the grayscale range within the ROI	N
Q4 distribution	Percent of gray values that fall within the 4th quarter of the grayscale range within the ROI	N
SAM	Standardized added metabolic activity	N
SAM background	Local background estimator near ROI	N

ROI, region of interest; C, conventional; N, new.

**Table S3** Univariate and multivariate Cox regression analysis in the analyzed gene expression datasets

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
GSE31210				
Overall survival analysis				
Expression of blue module	1,685 (24–114,404)	0.0006	233 (1.76–31,077)	0.0288
Stage (III vs. II vs. I)	4.07 (1.90–8.70)	0.0003	3.00 (1.37–6.55)	0.0058
Age (> 60 vs. ≤ 60)	1.24 (0.58–2.65)	0.5770	–	–
Sex (male vs. female)	2.24 (1.02–4.88)	0.0438	1.28 (0.44, 3.72)	0.6462
Smoking status (smoker vs. nonsmoker)	2.52 (1.13–5.62)	0.0238	1.48 (0.49, 4.50)	0.4866
GSE31210				
Recurrence-free survival analysis				
Expression of blue module	1,758 (93–32,917)	50.79E-07	845 (34.53–20,725)	30.62e-05
Stage (III vs. II vs. I)	3.55 (2.03–6.21)	80.48E-06	2.73 (1.55–4.82)	0.0005
Age (> 60 vs. ≤ 60)	1.53 (0.88–2.65)	0.1320		
Sex (male vs. female)	1.46 (0.85–2.50)	0.1730		
Smoking status (smoker vs. nonsmoker)	1.48 (0.86–2.55)	0.1530		
GSE50081				
Overall survival analysis				
Expression of blue module	60.96 (3.06–1213)	0.0071	56.42 (2.61–1,221)	0.0102
Stage (III vs. II vs. I)	2.19 (1.19–4.04)	0.0114	2.09 (1.14–3.85)	0.0174
Age (> 60 vs. ≤ 60)	2.03 (0.73–5.68)	0.1780		
Sex (male vs. female)	1.53 (0.83–2.81)	0.1690		
Smoking status (smoker vs. nonsmoker)	2.49 (0.89–7.03)	0.0832		
GSE50081				
Recurrence-free survival analysis				
Expression of blue module	12.76 (0.44–368)	0.1380	9.68 (0.29–318.54)	0.2028
Stage (III vs. II vs. I)	2.57 (1.32–5.01)	0.0054	2.48 (1.27–4.83)	0.0077
Age (> 60 vs. ≤ 60)	1.01 (0.42–2.43)	0.9810		
Sex (male vs. female)	1.27 (0.66–2.46)	0.4730		
Smoking status (smoker vs. nonsmoker)	0.97 (0.44–2.13)	0.9300		

HR, hazard ratio.

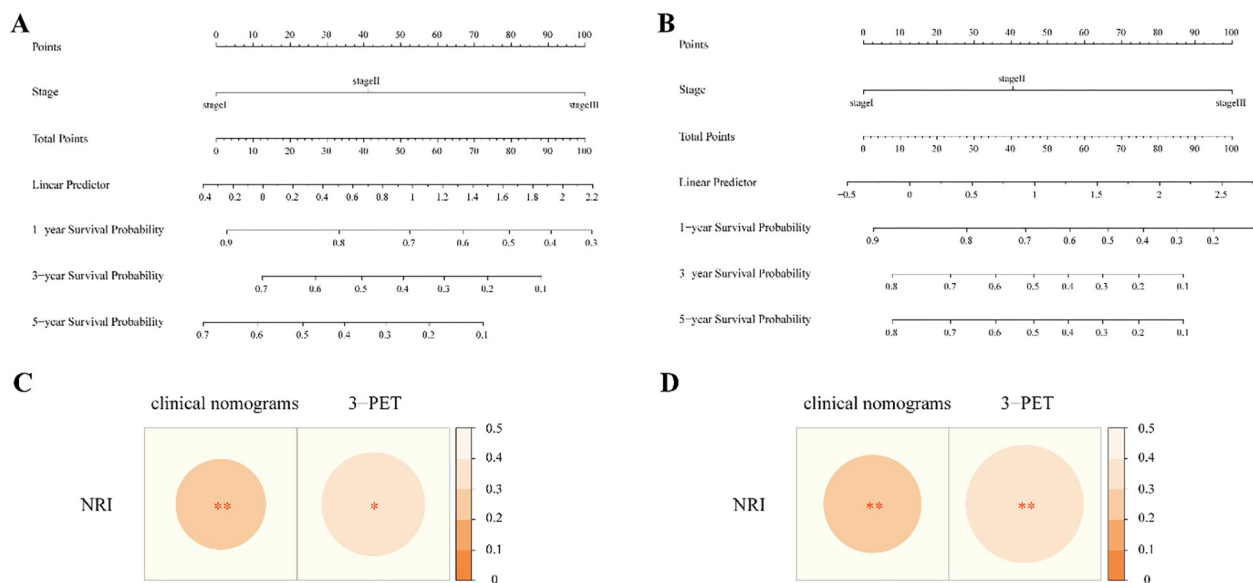


**Figure S2** Scatter plots of correlations between the expression of blue module and PET parameters in the 3-PET. (A) Standard deviation. (B) Median. (C) Third quartile. ME, module eigengene; PET, positron emission tomography.

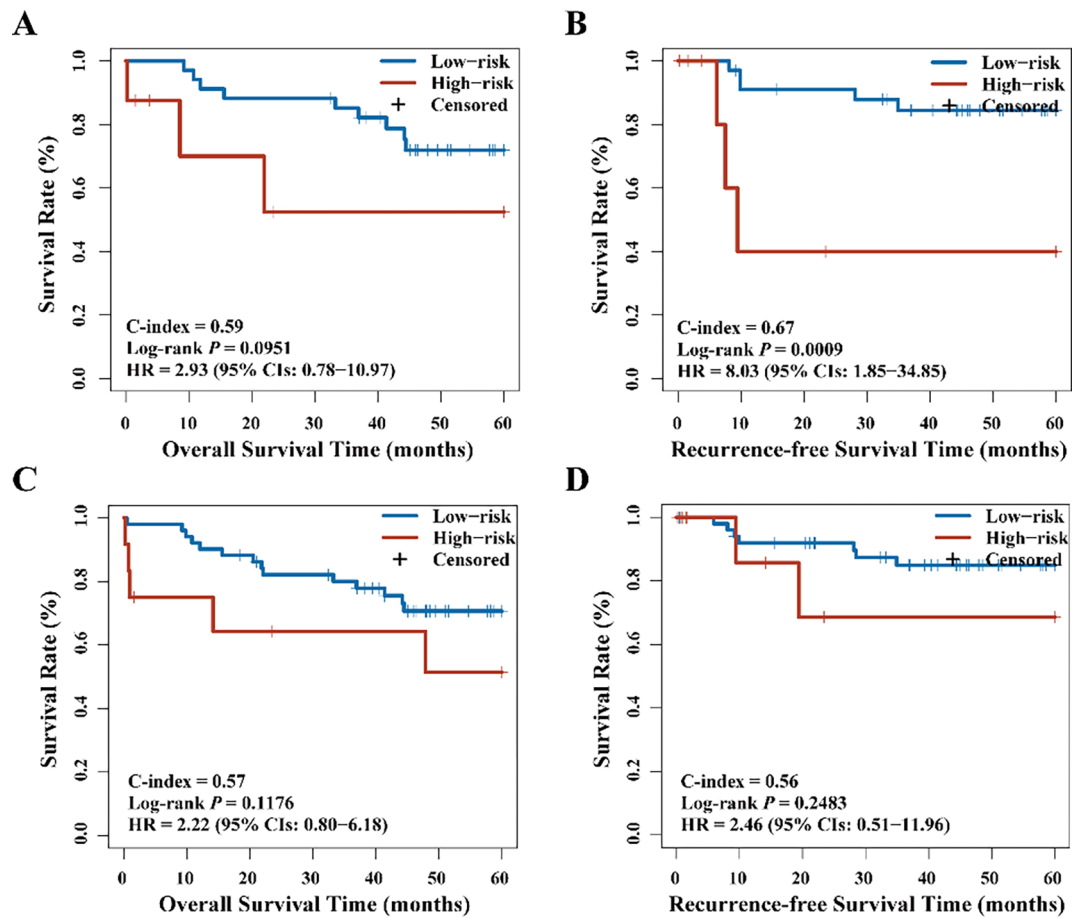
**Table S4** Univariate Cox regression analysis in the NR validation datasets

Variables	Overall survival		Recurrence-free survival	
	HR (95% CI)	P value	HR (95% CI)	P value
3-PET (high risk vs. low risk)	3.64 (1.66–7.98)	0.0012	4.96 (1.69–14.57)	0.0036
TNM stage (III vs. II vs. I)	3.25 (1.81–5.86)	80.6e-05	4.19 (2.03–8.64)	0.0001
Age (>60 vs. ≤60 years)	1.56 (0.37–6.60)	0.5460	1.80 (0.23–13.75)	0.5720
Sex (male vs. female)	2.04 (0.70–5.92)	0.1900	0.94 (0.29–2.99)	0.9140
Grade (high vs. medium vs. low)	1.38 (0.77–2.47)	0.2840	1.80 (0.82–3.95)	0.1420
Smoking status (smoker vs. nonsmoker)	1.32 (0.45–3.84)	0.6090	0.91 (0.25–3.27)	0.8870
Lymphovascular invasion (present vs. absent)	1.86 (1.01–3.43)	0.0470	1.86 (0.72–4.78)	0.1990
Pleural invasion (yes vs. no)	2.10 (0.90–4.88)	0.0852	1.91 (0.60–6.08)	0.2760
SUV <sub>max</sub> (>2.5 vs. ≤2.5)	1.96 (0.78–4.88)	0.1500	3.92 (0.88–17.57)	0.0740

NR, non-small cell lung cancer (NSCLC)–radiogenomics; HR, hazard ratio.



**Figure S3** The clinical nomogram and performance improvement evaluation of the radiomic nomogram. (A) The clinical nomogram for overall survival. (B) The clinical nomogram for recurrence-free survival. (C) Performance improvement of the radiomic nomogram compared with the clinical nomogram model and 3-PET estimated for overall survival by net reclassification improvement (NRI) methods. (D) Performance improvement of the radiomic nomogram compared with clinical nomogram model and 3-PET estimated for recurrence-free survival by net reclassification improvement (NRI) methods. The corresponding significance is shown by asterisks (\* $P < 0.05$  and \*\* $P < 0.01$ ).



**Figure S4** Kaplan-Meier curves for patients with early-stage disease in the non-small cell lung cancer (NSCLC)–radiogenomics (NR) dataset. (A) Kaplan-Meier curves for overall survival of 45 patients with stage T1 disease. (B) Kaplan-Meier curves for recurrence-free survival of 45 patients with stage T1 disease. (C) Kaplan-Meier curves for overall survival of 63 patients with stage N0 disease. (D) Kaplan-Meier curves for recurrence-free survival of 63 patients with stage N0 disease.

**Table S5** Gene enrichment analysis of significantly correlated genes with radiomic features in 3-PET based on the KEGG database

Feature	Pathway	FDR	Gene symbol
Standard deviation	Cell cycle	2.66E-05	TTK, SKP1, PRKDC, CDC6, PLK1, CDC20, MCM6, CCND1, CDC25C, MAD2L1, YWHAQ, CCNE1, CCNA2, CDC16, MAD2L2, TFDP1, HDAC1, CCNB2, CDK1, CCNB3, MCM4, ORC1, CCNB1, ANAPC11, BUB1B
Standard deviation	Huntington's disease	0.0009	PSMB5, POLR2I, TUBA1C, POLR2F, PSMA7, CYCS, ATP5PF, WIPI2, UQCRH, PSMC3, PIK3C3, CASP3, NDUFA6, UQCRHL, BBC3, GPX8, MAP3K5, PSMC4, PSMB2, KLC3, PSMB7, HDAC1, ATG2A, NDUFB6, DNAH1, TUBA1B, HAP1, UQCRFS1, CLTA, NDUFA4, VDAC2, PSMC1, SDHB, UQCRQ, TUBB2B, PLCB2, POLR2D, COX6B1
Standard deviation	Parkinson's disease	0.0037	PSMB5, TUBA1C, PSMA7, CYCS, ATP5PF, UQCRH, PSMC3, CASP3, NDUFA6, UQCRHL, PARK7, MAP3K5, PSMC4, PSMB2, KLC3, GNAI3, PSMB7, EIF2S1, MAOB, NDUFB6, SNCA, TUBA1B, UBE2L3, UQCRFS1, NDUFA4, VDAC2, PSMC1, SDHB, UQCRQ, TUBB2B, COX6B1
Standard deviation	Progesterone-mediated oocyte maturation	0.004	RPS6KA2, PLK1, SPDYE2, CDC25C, MAD2L1, CCNA2, CDC16, MAD2L2, GNAI3, AURKA, CCNB2, CDK1, MOS, CCNB3, CCNB1, ANAPC11, ADCY9
Standard deviation	Oocyte meiosis	0.0105	RPS6KA2, SKP1, PLK1, CDC20, SPDYE2, PPP2CA, CDC25C, MAD2L1, YWHAQ, CCNE1, CDC16, MAD2L2, AURKA, CCNB2, CDK1, MOS, CCNB1, ANAPC11, ADCY9
Standard deviation	Ribosome	0.022	RPL38, RPL9, MRPS16, RPL27, RPS8, RPL26L1, RPS17, RPS21, RPL17-C18orf32, RPL35, MRPL11, MRPL15, MRPL30, RPL11, RPL21, MRPS14, RPL4, MRPS7, MRPL12
Standard deviation	Alzheimer's disease	0.0343	ATP2A1, PSMB5, TUBA1C, PSMA7, CYCS, ATP5PF, WIPI2, UQCRH, PSMC3, PIK3C3, CASP3, NDUFA6, CACNA1F, UQCRHL, RTN3, AXIN1, NRAS, MAP3K5, PSMC4, PSMB2, KLC3, PSMB7, EIF2S1, ATG2A, NDUFB6, SNCA, TUBA1B, UQCRFS1, NDUFA4, CACNA1S, VDAC2, PSMC1, SDHB, UQCRQ, TUBB2B, PLCB2, COX6B1
Standard deviation	DNA replication	0.0462	RNASEH2B, RFC5, POLE2, RFC3, RNASEH2A, MCM6, RFC2, MCM4
Standard deviation	P53 signaling pathway	0.0483	CYCS, CASP3, GTSE1, RRM2, BBC3, CCND1, CCNE1, TNFRSF10A, TNFRSF10B, CCNB2, CDK1, CCNB1
Median	Cell cycle	1.57E-07	YWHAB, ANAPC1, CUL1, PRKDC, CDC6, CDK2, PLK1, STAG1, SMC3, CDC20, MCM6, CDC25C, ESPL1, CDKN1B, GADD45G, CCNA2, TFDP1, CCNB2, E2F4, CDC25A, GADD45B, MCM2, MCM4, MCM3, CDK6, ORC1, CCNB1, BUB1B, CDC23
Median	RNA transport	0.0007	TGS1, UPF1, ALYREF, NUP188, EIF4EBP2, XPO5, TACC3, EIF3B, XPOT, POP1, PABPC3, NCBP2, THOC6, EIF2S1, EIF2B2, NUP214, POM121C, RPP38, EIF5B, EIF4G1, PRMT5, UPF3B, RANGAP1, NUP93, NUP50, NUP153, EIF4A2
Median	Oocyte meiosis	0.0295	YWHAB, ANAPC1, CUL1, CALM2, CDK2, PLK1, SMC3, CDC20, CDC25C, ESPL1, AURKA, CCNB2, PPP2R5D, MOS, PPP2R1B, PPP2R5E, PPP2CB, CCNB1, CDC23
Third quartile	Cell cycle	3.37E-10	YWHAB, CUL1, TTK, PRKDC, CDC6, CDC45, CDK2, PLK1, CDC20, MCM6, CDC25C, MAD2L1, ESPL1, CCNE1, GADD45G, CCNA2, CDC16, TFDP1, HDAC1, CCNB2, CDK1, BUB1, RBL1, CDC25A, GADD45B, MCM2, MCM4, MCM3, ORC1, CCNB1, BUB1B
Third quartile	DNA replication	0.0004	RFC5, FEN1, POLE2, RFC3, RNASEH2A, PRIM1, MCM6, MCM2, RFC2, MCM4, MCM3
Third quartile	Proteasome	0.0128	PSMB5, PSMA7, PSMC3, ADRM1, PSMC4, PSMB2, PSMD2, PSMB7, POMP, PSMC1
Third quartile	P53 signaling pathway	0.0128	ADGRB1, CDK2, GTSE1, SESN2, RRM2, BBC3, CCNE1, GADD45G, TNFRSF10B, CCNB2, CDK1, GADD45B, CCNB1
Third quartile	Oocyte meiosis	0.0128	YWHAB, CUL1, RPS6KA2, CDK2, PLK1, CDC20, CDC25C, MAD2L1, ESPL1, CCNE1, CDC16, AURKA, CCNB2, CDK1, BUB1, MOS, PPP2CB, CCNB1
Third quartile	Progesterone-mediated oocyte maturation	0.0453	RPS6KA2, CDK2, PLK1, CDC25C, MAD2L1, CCNA2, CDC16, AURKA, CCNB2, CDK1, BUB1, MOS, CDC25A, CCNB1

Note: FDR, false discovery rate; KEGG, Kyoto Encyclopedia of Genes and Genomes; PET, positron emission tomography.