

## Supplementary materials

### **Radiomic and clinical data integration using machine learning predict the efficacy of anti-PD-1 antibodies-based combinational treatment in advanced breast cancer: a multi-centered study**

#### **Appendix S1: The inclusion and exclusion criteria**

The inclusion criteria were as follows: (1) Female patients with metastatic breast cancer confirmed by pathology and receiving combined immunotherapy; (2) There should be CE-CT examination of neck, chest or abdomen within 4 weeks before combined immunotherapy, and there must be segmented soft tissue lesions in CE-CT(including liver, chest wall, lymph nodes, breast, and soft tissue lesions adjacent to bone metastasis); (3) Patients should have complete clinical and pathological data.

The exclusion criteria were as follows: (1) Two radiologists unanimously confirmed that the tumor boundary was unclear and difficult to determine or there was no clear three-dimensional region of interest (ROI) of the tumor; (2) Poor CT image quality; (3) The follow-up time is less than 6 weeks (excluding patients with disease progression or death); (4) Baseline without CE-CT image.

#### **Appendix S2: Summary of R packages used**

Logistic regression and Cox regression were performed using the `glm` and `coxph` functions in the R language. The clinical model was constructed using the `rms` package and ROC curves were plotted using the `pROC` package. Calibrate function was used to plot the calibration curve, while violin plots and waterfall plots were generated using the `ggplot2` package. Decision curve analysis (DCA) and clinical impact curve (CIC) were plotted using the `rmDA` package. Survival analysis for progression-free survival (PFS) was conducted using the `survival`, `survminer`, and `survivalROC` packages.

**Table S1** CT scan parameters for each study center

Center	Sun Yat-sen Memorial Hospital, Sun Yat-sen University	Affiliated Cancer Hospital of Sun Yat-sen University	The First Hospital of Sun Yat-sen University
CT Manufacturer and Model	GE Medical Systems (Discovery CT750HD/Revolution EVO); SIEMENS (SOMATOM Force)	United Imaging Healthcare (uCT780/ uCT960+); GE Medical Systems (Discovery CT750HD/Revolution CT); SIEMENS (SOMATOM Force)	Philips (IQon-Spectral CT); TOSHIBA (Aquilion PRIME)
Tube Voltage	90-140 KeV (median 120 keV)		
Reconstruction thickness	Layer thickness: 1mm, 1.25mm, 1.5mm, 2.0mm/layer spacing: 1mm, 1.25mm, 1.5mm, 2.0mm		
Matrix	512×512 pixels		

**Table S2** 1130 radiomics features extracted from baseline CE-CT images using 3D slicer ( V.4.11.20210226; <https://www.slicer.org/> )

Feature Category	Number of features	Feature Name
Original_Shape	14	1.Elongation
		2.Flatness
		3.Least Axis Length
		4.Major Axis Length
		5.Maximum 2D Diameter (Column)
		6.Maximum 2D Diameter (Row)
		7.Maximum 2D Diameter (Slice)
		8.Maximum 3D Diameter
		9.Mesh Volume
		10.Minor Axis Length
		11.Sphericity
		12.Surface Area
		13.Surface Volume Ratio
		14.Voxel Volume
Original_First Order Histogram Features	18	1.The 10th percentile of X
		2.The 90th percentile of X
		3.Energy
		4.Entropy
		5.Interquartile Range
		6.Kurtosis
		7.Maximum
		8.Mean Absolute Deviation

		9.Mean Intensity
		10.Median Intensity
		11.Minimum Intensity
		12.Range
		13.Robust Mean Absolute Deviation
		14.Root Mean Squared
		15.Skewness
		16.Total Energy
		17.Uniformity
		18.Variance
Original_GLCM	24	1.Autocorrelation
		2.Cluster Prominence
		3.Cluster Shade
		4.Cluster Tendency
		5.Contrast
		6.Correlation
		7.Difference Average
		8.Difference Entropy
		9.Difference Variance
		10.ID(inverse difference)
		11.IDM(inverse difference moment)
		12.IDMN(inverse difference moment normalized)
		13.IDN(Inverse difference normalized)
		14.IMC1(Informational measure of correlation 1)
		15.IMC2(Informational measure of correlation 2)
		16.Inverse Variance
		17.Joint Average
		18.Joint Energy
		19.Joint Entropy
		20.MCC
		21.Maximum Probability
		22.Sum Average
		23.Sum Entropy
		24.Sum Squares
Original_GLDM	14	1.Dependence Entropy
		2.Dependence Non-Uniformity
		3.Dependence Non-Uniformity Normalized
		4.Dependence Variance
		5.Gray Level Non-Uniformity
		6.Gray Level Variance
		7.High Gray Level Emphasis
		8.Large Dependence Emphasis
		9.Large Dependence High Gray Level Emphasis

		10.Large Dependence Low Gray Level Emphasis
		11.Low Gray Level Emphasis
		12.Small Dependence Emphasis
		13.Small Dependence High Gray Level Emphasis
		14.Small Dependence Low Gray Level Emphasis
Original_GLRLM	16	1.Gray Level Non-Uniformity
		2.Gray Level Non-Uniformity Normalized
		3.Gray Level Variance
		4.High Gray Level Run Emphasis
		5.Long Run Emphasis
		6.Long Run High Gray Level Emphasis
		7.Long Run Low Gray Level Emphasis
		8.Low Gray Level Run Emphasis
		9.Run Entropy
		10.Run Length Non-Uniformity
		11.Run Length Non-Uniformity Normalized
		12.Run Percentage
		13.Run Variance
		14.Short Run Emphasis
		15.Short Run High Gray Level Emphasis
		16.Short Run Low Gray Level Emphasis
Original_GLSZM	16	1.Gray Level Non-Uniformity
		2.Gray Level Non-Uniformity Normalized
		3.Gray Level Variance
		4.High Gray Level Zone Emphasis
		5.Large Area Emphasis
		6.Large Area High Gray Level Emphasis
		7.Large Area Low Gray Level Emphasis
		8.Low Gray Level Zone Emphasis
		9.Size Zone Non-Uniformity
		10.Size Zone Non-Uniformity Normalized
		11.Small Area Emphasis
		12.Small Area High Gray Level Emphasis
		13.Small Area Low Gray Level Emphasis
		14.Zone Entropy
		15.Zone Percentage
		16.Zone Variance
Original_NGTDm	5	1.Busyness
		2.Coarseness
		3.Complexity
		4.Contrast
		5.Strength
Wavelet transform	744	wavelet-LLH

		wavelet-LHL
		wavelet-LHH
		wavelet-HLL
		wavelet-HLH
		wavelet-HHH
		wavelet-LLL
LoG transform	279	LoG-sigma-1mm-3D
		LoG-sigma-2mm-3D
		LoG-sigma-3mm-3D

**Table S3** Performance of the PD-L1 models in training and validation sets

Variables	PD-L1 model(CPS score)		PD-L1 model ( CPS cut off 10 )	
	Training set	Testing set	Training set	Testing set
AUC ( 95% CI )	0.555(0.442-0.669)	0.839(0.512-1.000)	0.530(0.433-0.628)	0.661(0.346-0.976)
SEN	0.622	0.750	0.378	0.750
SPE	0.545	1.000	0.682	0.571
ACC	0.573	0.909	0.573	0.636
PPV	0.434	1.000	0.400	0.500
NPV	0.720	0.875	0.662	0.800

Note: AUC: area under the receiver operating curve; CI: confidence interval; SEN: sensitivity; SPE: specificity; ACC: accuracy; PPV: positive predictive value; NPV: negative predictive value.

**Table S4** Pre-scores of predict models in training set and testing set

Training set	Non-responders ( N=110 )	Responders ( N=61 )	P value
Clinical Model	-0.707 ( -1.371, -0.346 )	-0.346 ( -0.707, 0.236 )	< 0.001
Radiomics Model	-1.232 ( -1.679, -0.782 )	0.487 ( 0.270, 0.731 )	< 0.001
Combined Model	-1.429 ( -1.843, -1.141 )	0.976 ( 0.510, 1.513 )	< 0.001

Note: Values refer to median (interquartile range).

Testing set	Non-responders ( N=45 )	Responders ( N=24 )	P value
Clinical Model	-1.005 ( -1.045,-0.869 )	-0.446 ( -1.015,0.019 )	0.067
Radiomics Model	-1.100 ( -1.565,-0.764 )	0.495 ( 0.312,0.759 )	< 0.001

Combined Model      -1.405 ( -1.816,-1.091 )      1.121 ( 0.673,1.708 )      < 0.001

Note: Values refer to median (interquartile range).

**Table S5** C-indexes, corresponding 95% CIs, cut-off points and the relative HRs with 95% CIs of Radiomics model, and Combined model in predicting PFS for training and validation cohorts.

Cohort	Model	PFS Prediction					P value*
		cut-off point	C-index±SE	C-index 95% CI	HR	HR 95% CI	
Training cohort	Radiomics model	0.209	0.646±0.019	[0.609, 0.683]	2.705	[1.888, 3.876]	< 0.001
	Combined model	-0.086	0.646±0.019	[0.609, 0.683]	2.464	[1.720, 3.529]	< 0.001
Validation cohort	Radiomicsmodel	-0.424	0.627±0.036	[0.556, 0.698]	2.625	[1.506, 4.574]	0.001
	Combined model	-0.857	0.619±0.037	[0.546, 0.692]	2.564	[1.469, 4.475]	0.001

Note: SE: Standard Error; CI: confidence interval; HR: Hazard Ratio; \*using Log-rank test to determine the P-value.

**Table S6** The details information of PFS prediction for Radiomics model, and Combined model in predicting PFS for training and validation cohorts.

Value	Radiomics model Training set		Radiomics model Testing set		Combined model Training set		Combined model Testing set	
	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
	n	52	119	30	39	56	115	30
events	30	89	15	35	34	85	16	34
Median PFS ( m )	10.12	3.75	7.26	3.02	8.77	3.71	9.79	3.02
0.95%L CL	8.25	3.09	5.78	2.10	7.56	2.89	3.37	2.10
0.95% U CL	13.83	4.37	NA	4.93	10.64	4.37	NA	5.13

Note: NA:Not available.

**Table S7** The details information for the subgroup of “Comprehensive positive score” in training cohort and validation cohort

Performance	Radiomics model Training cohort		Radiomics model Validation cohort	
	CPS < 10	CPS ≥ 10	CPS < 10	CPS ≥ 10
AUC (95% CI)	0.996(0.989-1.000)	1.000	1.000	0.778(0.291-1.000)

SEN	0.957	1.000	1.000	0.667
SPE	0.978	1.000	1.000	1.000
ACC	0.971	1.000	1.000	0.833
PPV	0.957	1.000	1.000	1.000
NPV	0.978	1.000	1.000	0.750

Note: AUC: area under the receiver operating curve; CI: confidence interval; SEN: sensitivity; SPE: specificity; ACC: accuracy; PPV: positive predictive value; NPV: negative predictive value; CPS: Combined positive score.

Performance	Combined model Training cohort		Combined model Validation cohort	
	CPS < 10	CPS ≥ 10	CPS < 10	CPS ≥ 10
AUC (95% CI)	0.997(0.991-1.000)	1.000	1.000	1.000
SEN	1.000	1.000	1.000	1.000
SPE	0.956	1.000	1.000	1.000
ACC	0.971	1.000	1.000	1.000
PPV	0.920	1.000	1.000	1.000
NPV	1.000	1.000	1.000	1.000

Note: AUC: area under the receiver operating curve; CI: confidence interval; SEN: sensitivity; SPE: specificity; ACC: accuracy; PPV: positive predictive value; NPV: negative predictive value; CPS: Combined positive score.

**Table S8** The details information for the subgroup of “molecular subgroup” in training cohort and validation cohort

Performance	Radiomics model Training cohort		Radiomics model Validation cohort	
	Non-TNBC	TNBC	Non-TNBC	TNBC
AUC (95%CI)	0.994(0.978-1.000)	0.997(0.992-1.000)	0.988(0.955-1.000)	0.910(0.789-1.000)
SEN	1.000	0.980	1.000	0.889
SPE	0.962	0.988	0.929	1.000
ACC	0.974	0.985	0.950	0.959
PPV	0.923	0.980	0.857	1.000
NPV	1.000	0.988	1.000	0.939

Note: AUC: area under the receiver operating curve; CI: confidence interval; SEN: sensitivity; SPE: specificity; ACC: accuracy; PPV: positive predictive value; NPV: negative predictive value; TNBC: triple negative breast cancer

Performance	Combined model Training cohort		Combined model Validation cohort	
	Non-TNBC	TNBC	Non-TNBC	TNBC
AUC (95%CI)	0.981(0.941-1.000)	0.999(0.999-1.000)	1.000	0.950(0.851-1.000)
SEN	0.917	1.000	1.000	0.944
SPE	1.000	0.976	1.000	1.000
ACC	0.974	0.985	1.000	0.980
PPV	1.000	0.961	1.000	1.000
NPV	0.963	1.000	1.000	0.969

Note: AUC: area under the receiver operating curve; CI: confidence interval; SEN: sensitivity; SPE: specificity;

ACC: accuracy; PPV: positive predictive value; NPV: negative predictive value; TNBC: triple negative breast cancer

**Table S9** The details information for the subgroup of “lines of previous therapy in the context of metastatic disease ” in training cohort and validation cohort

Performance	Radiomics model Training cohort		Radiomics model Validation cohort	
	1	≥2	1	≥2
AUC (95% CI)	0.993(0.981-1.000)	0.995(0.987-1.000)	1.000	0.843(0.655-1.000)
SEN	0.964	0.939	1.000	0.750
SPE	0.968	0.987	1.000	1.000
ACC	0.966	0.973	1.000	0.935
PPV	0.964	0.969	1.000	1.000
NPV	0.968	0.975	1.000	0.919

Note: AUC: area under the receiver operating curve; CI: confidence interval; SEN: sensitivity; SPE: specificity; ACC: accuracy; PPV: positive predictive value; NPV: negative predictive value.

Performance	Combined model Training cohort		Combined model Validation cohort	
	1	≥2	1	≥2
AUC (95% CI)	0.997(0.989-1.000)	0.998(0.996-1.000)	1.000	0.922(0.768-1.000)
SEN	0.964	1.000	1.000	0.917
SPE	1.000	0.975	1.000	1.000
ACC	0.983	0.982	1.000	0.978
PPV	1.000	0.943	1.000	1.000
NPV	0.969	1.000	1.000	0.971

Note: AUC: area under the receiver operating curve; CI: confidence interval; SEN: sensitivity; SPE: specificity; ACC: accuracy; PPV: positive predictive value; NPV: negative predictive value.

**Table S10** The details information for the subgroup of “number of metastatic sites” in training cohort and validation cohort

Performance	Radiomics model Training cohort		Radiomics model Validation cohort	
	1-2	≥3	1-2	≥3
AUC (95% CI)	0.999(0.998-1.000)	0.984(0.965-1.000)	0.857(0.691-1.000)	1.000
SEN	1.000	1.000	0.786	1.000
SPE	0.978	0.891	1.000	1.000
ACC	0.989	0.917	0.914	1.000
PPV	0.976	0.741	1.000	1.000
NPV	1.000	1.000	0.875	1.000

Note: AUC: area under the receiver operating curve; CI: confidence interval; SEN: sensitivity; SPE: specificity; ACC: accuracy; PPV: positive predictive value; NPV: negative predictive value.

Performance	Combined model Training cohort	Combined model Validation cohort
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	1-2	≥3	1-2	≥3
AUC (95% CI)	1.000	0.988(0.971-1.000)	0.932(0.799-1.000)	1.000
SEN	1.000	0.950	0.929	1.000
SPE	1.000	0.953	1.000	1.000
ACC	1.000	0.952	0.971	1.000
PPV	1.000	0.864	1.000	1.000
NPV	1.000	0.984	0.955	1.000

Note: AUC: area under the receiver operating curve; CI: confidence interval; SEN: sensitivity; SPE: specificity; ACC: accuracy; PPV: positive predictive value; NPV: negative predictive value.

**Table S11** The details information for the subgroup of “Visceral metastasis” in training cohort and validation cohort

Performance	Radiomics model Training cohort		Radiomics model Validation cohort	
	No	Yes	No	Yes
AUC (95% CI)	0.997(0.989-1.000)	0.994(0.984-1.000)	0.900(0.736-1.000)	0.939(0.818-1.000)
SEN	0.971	0.923	0.800	0.929
SPE	1.000	1.000	1.000	1.000
ACC	0.987	0.979	0.926	0.976
PPV	1.000	1.000	1.000	1.000
NPV	0.977	0.971	0.895	0.966

Note: AUC: area under the receiver operating curve; CI: confidence interval; SEN: sensitivity; SPE: specificity; ACC: accuracy; PPV: positive predictive value; NPV: negative predictive value.

Performance	Combined model Training cohort		Combined model Validation cohort	
	No	Yes	No	Yes
AUC (95% CI)	0.997(0.991-1.000)	0.997(0.992-1.000)	0.900(0.704-1.000)	1.000
SEN	0.971	1.000	0.900	1.000
SPE	1.000	0.956	1.000	1.000
ACC	0.987	0.968	0.963	1.000
PPV	1.000	0.897	1.000	1.000
NPV	0.977	1.000	0.944	1.000

Note: AUC: area under the receiver operating curve; CI: confidence interval; SEN: sensitivity; SPE: specificity; ACC: accuracy; PPV: positive predictive value; NPV: negative predictive value.

**Table S12** The details information for the subgroup of “Combined immunotherapy regimen” in training cohort and validation cohort

Performance	Radiomics model Training cohort		Radiomics model Validation cohort	
	Immunotherapy + Chemotherapy	Immunotherapy + Antiangiogenic therapy	Immunotherapy +Chemotherapy	Immunotherapy + Antiangiogenic therapy
		±Chemotherapy		±Chemotherapy
AUC	0.996	0.993	0.980	0.717

(95% CI)	( 0.989-1.000 )	( 0.983-1.000 )	( 0.939-1.000 )	( 0.361-1.000 )
SEN	0.964	0.939	0.944	0.667
SPE	0.982	0.981	1.000	1.000
ACC	0.976	0.966	0.977	0.923
PPV	0.964	0.969	1.000	1.000
NPV	0.982	0.964	0.962	0.909

Note: AUC: area under the receiver operating curve; CI: confidence interval; SEN: sensitivity; SPE: specificity; ACC: accuracy; PPV: positive predictive value; NPV: negative predictive value.

Performance	Combined model Training cohort		Combined model Validation cohort	
	Immunotherapy + chemotherapy	Immunotherapy + antiangiogenic therapy± chemotherapy	Immunotherapy + chemotherapy	Immunotherapy + antiangiogenic therapy± chemotherapy
AUC	0.995	0.998	1.000	0.850
(95% CI)	( 0.984-1.000 )	( 0.995-1.000 )		( 0.555-1.000 )
SEN	0.964	1.000	1.000	0.833
SPE	1.000	0.963	1.000	1.000
ACC	0.988	0.977	1.000	0.962
PPV	1.000	0.943	1.000	1.000
NPV	0.982	1.000	1.000	0.952

Note: AUC: area under the receiver operating curve; CI: confidence interval; SEN: sensitivity; SPE: specificity; ACC: accuracy; PPV: positive predictive value; NPV: negative predictive value.