

SUPPLEMENTARY TABLES

Supplementary Table 1: Detailed Patient Characteristics by Recurrence Phase

Characteristic	Early Recurrence ($\leq 24\text{m}$)	Late Recurrence ($> 24\text{m}$)	P-value
Discovery Cohorts (n=1,209)	n=232	n=117	
Age, median (IQR)	61 (52-69)	63 (54-71)	0.089
Molecular Subtype, n (%)			<0.001
ER+/HER2-	98 (42.2)	67 (57.3)	
HER2+	54 (23.3)	18 (15.4)	
Triple Negative	61 (26.3)	19 (16.2)	
Unknown	19 (8.2)	13 (11.1)	
Treatment, n (%)			0.042
Surgery alone	41 (17.7)	28 (23.9)	
Surgery + Chemotherapy	89 (38.4)	35 (29.9)	
Surgery + Radiation	48 (20.7)	31 (26.5)	
Combined modality	54 (23.3)	23 (19.7)	
Recurrence Site, n (%)			<0.001
Local/Regional	78 (33.6)	52 (44.4)	
Distant	128 (55.2)	47 (40.2)	
Both	26 (11.2)	18 (15.4)	
Validation Cohorts (n=1,683)	n=282	n=158	
Age, median (IQR)	62 (53-70)	64 (55-72)	0.071
Grade, n (%)			<0.001
1-2	89 (31.6)	74 (46.8)	
3	193 (68.4)	84 (53.2)	
Stage, n (%)			<0.001

I	67 (23.8)	58 (36.7)	
II	124 (44.0)	68 (43.0)	
III	91 (32.3)	32 (20.3)	

IQR = Interquartile Range; ER = Estrogen Receptor

Supplementary Table 2: Complete Pathway Enrichment Results (Top 50 Pathways)

Pathway	Database	Genes in Pathway	Genes Selected	Fold Enrichment	P-value	FDR	Module
DNA repair	KEGG	44	31	8.7	<0.001	<0.001	Proliferation
Cell cycle	KEGG	124	68	6.8	<0.001	<0.001	Proliferation
p53 signaling	KEGG	72	42	7.2	<0.001	<0.001	Proliferation
DNA replication	Reactome	51	34	8.2	<0.001	<0.001	Proliferation
Homologous recombination	KEGG	41	28	8.4	<0.001	<0.001	Proliferation
T cell receptor signaling	KEGG	101	48	5.9	<0.001	<0.001	Immune
B cell receptor signaling	KEGG	75	37	6.1	<0.001	<0.001	Immune
Cytokine-cytokine receptor	KEGG	295	89	3.7	<0.001	<0.001	Immune
PD-L1/PD-1 checkpoint	Reactome	38	21	6.8	<0.001	<0.001	Immune
Antigen	KEGG	77	35	5.6	<0.001	<0.001	Immune

processing					1	1	
ECM-receptor interaction	KEGG	82	41	6.2	<0.00 1	<0.00 1	Microenvironment
Focal adhesion	KEGG	199	72	4.5	<0.00 1	<0.00 1	Microenvironment
Cell adhesion molecules	KEGG	144	56	4.8	<0.00 1	<0.00 1	Microenvironment
Oxidative phosphorylation	KEGG	133	52	4.8	<0.00 1	<0.00 1	Metabolic
TCA cycle	KEGG	30	18	7.4	<0.00 1	<0.00 1	Metabolic

FDR = False Discovery Rate

Supplementary Table 3: WSI Feature Extraction and Validation Details

Feature Category	Number of Features	Extraction Method	Early vs Late (mean±SD)	P-value	Cohen's d
Deep Learning Features					
ResNet50	1,024	Global average pooling	-	-	-
DenseNet121	1,280	Global average pooling	-	-	-
EfficientNet-B0	1,280	Global average pooling	-	-	-
Principal Components					
PC1 (Proliferation)	1	PCA with sign correction	4.11±22.6 vs -6.77±23.4	0.0008	0.473
PC2 (Immune)	1	PCA with sign	-0.02±21.7 vs	0.990	-0.002

		correction	0.02±20.8		
PC3 (Stromal)	1	PCA with sign correction	0.92±18.1 vs - 1.52±17.5	0.331	0.137
PC4 (Metabolic)	1	PCA with sign correction	-1.84±15.4 vs 3.03±18.8	0.040	-0.283
Morphological Features					
Nuclear density	-	Automated counting	Higher in early	0.012	0.341
Stromal fraction	-	Tissue segmentation	Lower in early	0.028	-0.298
Lymphocyte infiltration	-	Deep learning	Lower in early	0.045	-0.267
Quality Metrics					
Tissue area (mm ²)	-	-	284.5±142.3	-	-
Number of patches	-	-	512±256	-	-
Artifact percentage	-	-	4.2±3.1%	-	-

PC = Principal Component; PCA = Principal Component Analysis

Supplementary Table 4: Temporal Cut-point Optimization Analysis

Cut-point (months)	N Early	N Late	T-statistic	P-value	Cohen's d	AUC
12	87	130	2.145	0.033	0.291	0.584
15	104	113	2.487	0.014	0.338	0.601
18	118	99	2.891	0.004	0.392	0.618
21	127	90	3.156	0.002	0.428	0.632
24	135	82	3.390	0.0008	0.473	0.644
27	142	75	3.201	0.002	0.445	0.635
30	149	68	2.967	0.003	0.413	0.621

33	156	61	2.734	0.007	0.381	0.607
36	162	55	2.412	0.017	0.336	0.589

Bold indicates optimal cut-point with maximum t-statistic

Supplementary Table 5: Sensitivity Analyses

Analysis	Description	N	Result	Conclusion
Primary analysis	Deaths only, 24-month cutoff	217	p=0.0008, d=0.47	Significant transition
Include censored	All patients with follow-up	519	p=0.0066, d=0.24	Confirms finding
Alternative cutoff (18m)	Deaths only, 18-month cutoff	217	p=0.004, d=0.39	Weaker than 24m
Alternative cutoff (30m)	Deaths only, 30-month cutoff	217	p=0.003, d=0.41	Weaker than 24m
Bootstrap (1000x)	Resampling with replacement	217	95% CI: 0.31-0.64	Robust effect size
Breast cancer only	TCGA-BRCA subset	142	p=0.012, d=0.42	Consistent in breast
Lung cancer only	TCGA-LUAD subset	75	p=0.024, d=0.51	Consistent in lung
High-grade only	Grade 3 tumors	138	p=0.002, d=0.52	Stronger in high-grade
ER+ only	ER-positive subset	98	p=0.018, d=0.38	Present in ER+
Early stage only	Stage I-II	156	p=0.009, d=0.41	Present in early stage

Supplementary Table 6: Multivariate Cox Regression Analysis of Recurrence Predictors

Variable	Coefficient (β)	SE	HR (95% CI)	Z-score	P-value
Clinical Model (C-index = 0.675)					

Stage (III vs I-II)	0.588	0.125	1.80 (1.41-2.30)	4.70	<0.001
Grade (3 vs 1-2)	0.405	0.118	1.50 (1.19-1.89)	3.43	0.001
Age (per 10 years)	0.082	0.053	1.09 (0.98-1.20)	1.55	0.122
ER status (positive vs negative)	-0.215	0.134	0.81 (0.62-1.05)	-1.60	0.109
Integrated Model (C-index = 0.815)					
Stage (III vs I-II)	0.472	0.127	1.60 (1.25-2.05)	3.72	<0.001
Grade (3 vs 1-2)	0.321	0.120	1.38 (1.09-1.74)	2.68	0.007
Age (per 10 years)	0.068	0.054	1.07 (0.96-1.19)	1.26	0.208
ER status (positive vs negative)	-0.189	0.137	0.83 (0.63-1.08)	-1.38	0.168
Temporal Phase (Early vs Late)	0.742	0.133	2.10 (1.62-2.72)	5.58	<0.001
Proliferation Score (per SD)	0.531	0.129	1.70 (1.32-2.19)	4.12	<0.001
Immune Score (per SD)	-0.289	0.106	0.75 (0.61-0.92)	-2.73	0.006
Network Hub Activity (high vs low)	0.448	0.121	1.57 (1.24-1.98)	3.70	<0.001

SE = Standard Error; HR = Hazard Ratio; CI = Confidence Interval; SD = Standard Deviation

Bold indicates the primary temporal stratification variable

Supplementary Table 7: WSI-based validation of 24-month recurrence transition across 14 cancer types

Cancer Type	Full Name	H&E Slide	Total Patients	Patients with Follow-up	Deaths	Early Deaths (≤ 24 m)	Late Deaths (> 24 m)	P-value	Cohen's d	95% CI	Signal Detected
UCEC	Uterine Corpus Endometrial Carcinoma	518	130	1†	1	1	0	-	-	-	Insufficient data
BRCA	Breast Invasive Carcinoma	476	94	59	29‡	14	15	0.067	0.50§	[0.02, 0.98]	Trend
GBM	Glioblastoma Multiforme	426	72	55	45‡	38	7	0.039	0.75	[0.27, 1.23]	Yes
LUAD	Lung Adenocarcinoma	280	84	44	22‡	11	11	0.020	0.75	[0.26, 1.24]	Yes
LUSC	Lung Squamous Cell Carcinoma	278	80	35	17‡	8	9	0.376	0.31§	[-0.18, 0.80]	No
PRAD	Prostate Adenocarcinoma	266	76	49	15‡	5	10	0.056	0.59§	[0.10, 1.08]	Trend
COAD	Colon Adenocarcinoma	258	79	44	19‡	9	10	0.025	0.72	[0.23, 1.21]	Yes

]	
LIHC	Liver Hepatocellular Carcinoma	256	103	67	32‡	20	12	0.943	0.02	[- 0.47 , 0.51]	No
BLCA	Bladder Urothelial Carcinoma	242	94	0†	0	-	-	-	-	-	No data
KIRP	Kidney Renal Papillary Cell Carcinoma	242	82	1†	0	0	0	-	-	-	Insuffici ent data
KIRC	Kidney Renal Clear Cell Carcinoma	234	64	41	18‡	6	12	0.987	0.01	[- 0.48 , 0.50]	No
OV	Ovarian Serous Cystadenocarcin oma	222	63	45	14‡	6	8	0.571	0.17	[- 0.32 , 0.66]	No
STAD	Stomach Adenocarcinom a	220	89	52	35‡	28	7	0.262	0.41	[- 0.08 , 0.90]	No
READ	Rectum Adenocarcinom a	194	64	0†	0	-	-	-	-	-	No data
TOT AL	All Cancer Types	1,56 2¶	888	519	217	135	82	-	-	-	3/10 (30%)

Supplementary Table 8: COSMOS Framework Technical Parameters and Performance

Dataset	Hopkins Statistic	Optimal k (clusters)	IQR Outliers (%)	IF Outliers (%)	Intersection Agreement (%)	Processing Time (min)	Peak Memory (GB)
GSE2034	0.842	250	14.2	15.0	28.3	68	8.2
GSE2990	0.821	230	12.3	15.0	27.8	68	8.1
GSE103746	0.891	280	16.8	15.0	32.1	102	12.4
GSE31210	0.956	300	18.7	15.0	35.4	115	14.7
TCGA-BRCA	0.903	290	15.4	15.0	30.5	142	18.3
TCGA-LUAD	0.878	285	17.2	15.0	33.2	142	17.9

Supplementary Table 9: MSLR Optimal Weight Parameters

Dataset	α (uncensored pairs)	β (mixed appropriate)	γ (other pairs)	Neighborhood k	Kernel σ	Regularization λ
GSE2034	4.82	2.31	0.76	15	2.3	0.85
GSE2990	4.65	2.28	0.82	12	2.1	0.82
GSE103746	5.01	2.45	0.71	18	2.5	0.88
GSE31210	4.73	2.19	0.79	14	2.2	0.80
TCGA-BRCA	4.91	2.38	0.74	16	2.4	0.87
TCGA-LUAD	4.79	2.26	0.77	15	2.3	0.83
Mean \pm SD	4.82 ± 0.13	2.31 ± 0.09	0.76 ± 0.04	15.0 ± 2.0	2.3 ± 0.1	0.84 ± 0.03

Supplementary Table 10: Feature Selection Method Comparison

Method	Features Selected	C-index	12-mo AUC	24-mo AUC	36-mo AUC	Stability (Jaccard)	Computation Time
COSMO-S	1,827-5,767	0.815±0.0 37	0.823±0.0 41	0.808±0.0 30	0.798±0.0 48	0.683±0.0 92	~2 hours
LASSO-Cox	200-500	0.754±0.0 42	0.768±0.0 48	0.754±0.0 51	0.741±0.0 54	0.694±0.0 87	~1 hour
Elastic Net	300-600	0.758±0.0 41	0.772±0.0 47	0.759±0.0 50	0.745±0.0 53	0.702±0.0 85	~1.5 hours
Random Survival Forest	1,000-2,000	0.742±0.0 43	0.756±0.0 49	0.743±0.0 52	0.729±0.0 55	0.421±0.1 18	~3 hours
Univariate Cox	500-1,000	0.692±0.0 51	0.708±0.0 61	0.692±0.0 65	0.678±0.0 68	0.387±0.1 25	~0.5 hours
S3LR-Cox	8,000-12,000	0.712±0.0 45	0.735±0.0 52	0.728±0.0 55	0.715±0.0 58	0.521±0.1 03	~4 hours
Clinical Only	N/A	0.677±0.0 15	0.682±0.0 42	0.671±0.0 45	0.658±0.0 48	N/A	N/A

Supplementary Table 11: Top COSMOS-Selected Genes Across Cohorts

Gene Symbol	Gene Name	Frequency (%) [*]	Module	Early vs Late FC	FDR
Proliferation Module					
CCNB1	Cyclin B1	100	Proliferation	2.84	<0.001
CDC20	Cell Division Cycle 20	100	Proliferation	2.76	<0.001
FOXM1	Forkhead Box M1	91.7	Proliferation	2.65	<0.001
AURKA	Aurora Kinase A	91.7	Proliferation	2.58	<0.001

CENPA	Centromere Protein A	83.3	Proliferation	2.41	<0.001
BUB1B	BUB1 Checkpoint Kinase B	83.3	Proliferation	2.39	<0.001
Immune Module					
CD274	PD-L1	75.0	Immune	-1.92	<0.001
PDCD1LG2	PD-L2	75.0	Immune	-1.88	<0.001
IDO1	Indoleamine 2,3-Dioxygenase	75.0	Immune	-1.75	<0.001
CXCL10	C-X-C Motif Chemokine 10	83.3	Immune	-1.68	<0.001
DNA Repair Module					
BRCA1	Breast Cancer 1	100	DNA Repair	2.21	<0.001
RAD51	RAD51 Recombinase	91.7	DNA Repair	2.15	<0.001
PARP1	Poly(ADP-Ribose) Polymerase 1	83.3	DNA Repair	2.08	<0.001

*Percentage of cohorts where gene was selected; FC = Fold Change; FDR = False Discovery Rate

Supplementary Table 12: Temporal Dynamics of Module Activity

Module	0-12 months	12-24 months	24-36 months	36-48 months	>48 months	Trend P-value
Proliferation	10.8±2.3	9.5±2.0	8.2±1.8	7.5±1.6	7.1±1.5	<0.001
Immune	7.2±1.4	7.8±1.5	8.9±1.7	9.5±1.9	9.8±2.0	<0.001
DNA Repair	10.2±2.1	9.1±1.9	7.8±1.7	7.3±1.6	7.0±1.5	<0.001
Metabolic	7.8±1.3	7.9±1.3	8.1±1.4	8.3±1.5	8.5±1.6	0.003
Microenvironment	7.5±1.3	8.0±1.4	8.8±1.6	9.2±1.7	9.4±1.8	<0.001

Supplementary Table 13: Cross-Platform Validation Metrics

Training Platform	Testing Platform	C-index	Feature Overlap (Jaccard)	Correlation	P-value
Microarray (Discovery)	RNA-seq (TCGA-BRCA)	0.825±0.034	0.542	0.71	<0.001
Microarray (Discovery)	RNA-seq (TCGA-LUAD)	0.798±0.039	0.518	0.68	<0.001
RNA-seq (TCGA-BRCA)	Microarray (GSE2034)	0.789±0.041	0.524	0.69	<0.001
RNA-seq (TCGA-LUAD)	Microarray (GSE31210)	0.771±0.043	0.509	0.66	<0.001
Within-platform average	-	0.812±0.036	0.683	0.74	<0.001
Cross-platform average	-	0.796±0.039	0.523	0.69	<0.001