

Supplementary

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Supplementary Table 1: Individual patient data for the waterfall plot of radiotherapy response

ID	Response	Baseline Size(cm)	Post-RT Size(cm)	Change(%)
1	CR	0.6	0	100.0%
2	PR	2.7	1.8	33.3%
3	CR	1	0	100.0%
4	PD	5.5	8	-45.5%
5	PR	13	8.9	31.5%
6	SD	4.5	4.6	-2.2%
7	PR	3.3	2.2	33.3%
8	SD	1.8	1.9	-5.6%
9	PR	6	4.1	31.7%
10	PR	23.6	16.4	30.5%
11	PR	8.2	5.2	36.6%
12	PR	2.9	1.4	51.7%
13	SD	2.9	2.9	0.0%
14	SD	3	2.9	3.3%
15	PD	3.3	4.9	-48.5%
16	PD	2.2	3	-36.4%
17	SD	0.7	0.7	0.0%
18	PR	1	0.6	40.0%
19	SD	3.1	2.9	6.5%
20	SD	10.8	13.6	-25.9%
21	PR	3	2.1	30.0%
22	PR	2.5	1.5	40.0%
23	SD	4.1	3.9	4.9%
24	SD	3.4	3.5	-2.9%
25	PR	13.4	9.2	31.3%
26	SD	3.8	3.7	2.6%
27	PR	6.4	3.7	42.2%
28	SD	3.4	3.4	0.0%
29	PR	3.1	1.6	48.4%
30	SD	5.3	5	5.7%
31	SD	3.7	3.1	16.2%
32	PD	0.7	1.2	-71.4%
33	PR	6.1	3.8	37.7%
34	SD	3	2.4	20.0%
35	PR	7.5	3.9	48.0%
36	PR	4.7	1.9	59.6%
37	SD	9.1	7.7	15.4%
38	SD	3.1	2.7	12.9%

39	SD	5.4	4.5	16.7%
40	PR	10.3	6.7	35.0%
41	PR	4	2.4	40.0%
42	CR	0.5	0	100.0%
43	PR	6.9	2.8	59.4%
44	PR	1.5	0.5	66.7%
45	PR	3	1.8	40.0%
46	SD	8.7	8	8.0%
47	PR	2.3	1.2	47.8%
48	PR	7.4	4.9	33.8%
49	SD	3	2.6	13.3%
50	PD	3.1	4.3	-38.7%
51	PR	15.5	10.4	32.9%
52	SD	4.6	5.7	-23.9%
53	PR	8.3	5.7	31.3%
54	PD	11.6	15.7	-35.3%
55	PR	3.7	2.1	43.2%
56	SD	7.2	8.3	-15.3%
57	PR	4.5	2.9	35.6%
58	PR	5.6	4.1	26.8%
59	PR	3	2	33.3%
60	SD	7.8	8.8	-12.8%
61	PR	3.6	2.4	33.3%

Supplementary Table 2: Detailed parameters of the Sphingolipids-Only and Clinical-Only prediction models

Model	Variable	Beta	Odds Ratio (OR)	95% CI	p-value
Integrated Model	S1P	0.271	1.312	1.157-1.595	0.0006
Integrated Model	CER(d18:1/20:0)	-0.016	0.984	0.969-0.995	0.0168
Integrated Model	ALP (high vs low)	1.64	5.156	0.986-35.197	0.0658
Integrated Model	TBIL (high vs low)	1.558	4.751	0.699-44.346	0.1291
Integrated Model	(Intercept)	-12.583	0	0-0.002	0.0009
Sphingolipids-Only Model	S1P	0.24	1.271	1.142-1.48	0.0002
Sphingolipids-Only Model	CER(d18:1/20:0)	-0.014	0.986	0.972-0.995	0.0162
Sphingolipids-Only Model	(Intercept)	-10.212	0	0-0.0006	0.0006
Clinical-Only Model	ChildPugh_Score (A vs B)	1.187	3.276	0.984-11.611	0.0563
Clinical-Only Model	AFP (high vs low)	1.142	3.132	0.97-10.582	0.0582
Clinical-Only Model	(Intercept)	-0.964	0.381	0.173-0.78	0.0113

Supplementary Table 3: Calibration data for the integrated clinical-sphingolipid model (Model 1)

Probability_Group	Predicted_Probability_Range	Actual_Probability
[-0.001,0.1]	[-0.001,0.1]	0.045454545
(0.1,0.2]	(0.1,0.2]	0
(0.2,0.3]	(0.2,0.3]	1
(0.3,0.4]	(0.3,0.4]	0.25
(0.4,0.5]	(0.4,0.5]	0
(0.5,0.6]	(0.5,0.6]	0.6
(0.6,0.7]	(0.6,0.7]	0.5
(0.7,0.8]	(0.7,0.8]	0.75
(0.8,0.9]	(0.8,0.9]	1
(0.9,1]	(0.9,1]	1

Supplementary Table 4: Decision curve analysis data for the integrated clinical-sphingolipid model (Model 1)

Threshold	Multivariate_NetBenefit	S1P_Only_NetBenefit	AFP_Only_NetBenefit
0	0.459	0.459	0.459
0.01	0.4554	0.4537	0.4536
0.02	0.4517	0.4483	0.448
0.03	0.4315	0.4438	0.4423
0.04	0.4296	0.4385	0.4365
0.05	0.4271	0.4357	0.4305
0.06	0.4269	0.4308	0.4245
0.07	0.4241	0.4282	0.4183
0.08	0.4227	0.4248	0.412
0.09	0.4232	0.4233	0.4055
0.1	0.4208	0.4189	0.3989
0.11	0.4203	0.398	0.3922
0.12	0.418	0.3934	0.3852
0.13	0.4157	0.3887	0.3782
0.14	0.4133	0.3866	0.3709
0.15	0.4108	0.3819	0.3635
0.16	0.4083	0.3833	0.356
0.17	0.4057	0.3855	0.3482
0.18	0.403	0.3814	0.3403
0.19	0.4042	0.3773	0.3321
0.2	0.4016	0.3607	0.3238
0.21	0.399	0.3609	0.3152
0.22	0.3964	0.3569	0.3064
0.23	0.3773	0.3364	0.2974
0.24	0.3745	0.3374	0.2882
0.25	0.3716	0.3333	0.2787
0.26	0.3686	0.3292	0.2689
0.27	0.3656	0.3249	0.2589
0.28	0.3625	0.327	0.2486
0.29	0.3593	0.3295	0.2381
0.3	0.356	0.3091	0.2272
0.31	0.3526	0.3124	0.216
0.32	0.3327	0.3086	0.2044
0.33	0.3291	0.3127	0.1926
0.34	0.3254	0.2926	0.1868
0.35	0.3216	0.2888	0.1841
0.36	0.3268	0.2848	0.1814
0.37	0.3232	0.2904	0.1785

0.38	0.3295	0.2866	0.1756
0.39	0.3365	0.2663	0.1725
0.4	0.3333	0.2623	0.1694
0.41	0.3415	0.2417	0.1662
0.42	0.3386	0.2493	0.1628
0.43	0.3356	0.2453	0.1593
0.44	0.3454	0.2412	0.1557
0.45	0.3428	0.237	0.152
0.46	0.354	0.2325	0.1481
0.47	0.3517	0.2425	0.1441
0.48	0.3493	0.2383	0.14
0.49	0.3468	0.2498	0.1356
0.5	0.3443	0.2459	0.1311
0.51	0.3416	0.2419	0.1265
0.52	0.3388	0.2377	0.1216
0.53	0.3195	0.2333	0.1165
0.54	0.3165	0.2316	0.1112
0.55	0.3169	0.2113	0.1056
0.56	0.3145	0.1908	0.0999
0.57	0.3336	0.1864	0.0938
0.58	0.3318	0.1819	0.0874
0.59	0.3299	0.1771	0.0808
0.6	0.3115	0.1967	0.0738
0.61	0.3094	0.1761	0.0664
0.62	0.3339	0.1717	0.0587
0.63	0.3327	0.167	0.0505
0.64	0.3315	0.1621	0.0419
0.65	0.3302	0.171	0.0328
0.66	0.3124	0.1668	0.0231
0.67	0.311	0.1624	0.0129
0.68	0.3094	0.1578	0.002
0.69	0.3078	0.1528	0
0.7	0.306	0.1475	0
0.71	0.2877	0.1419	0
0.72	0.2857	0.1358	0
0.73	0.2835	0.2016	0
0.74	0.2812	0.1992	0
0.75	0.3279	0.1967	0
0.76	0.3279	0.194	0
0.77	0.3279	0.191	0
0.78	0.2951	0.1878	0
0.79	0.2951	0.1678	0
0.8	0.2951	0.1639	0

0.81	0.2951	0.1432	0
0.82	0.2951	0.2131	0
0.83	0.2787	0.1967	0
0.84	0.2623	0.1967	0
0.85	0.2623	0.1967	0
0.86	0.2623	0.1803	0
0.87	0.2623	0.1475	0
0.88	0.2295	0.1475	0
0.89	0.2295	0.1311	0
0.9	0.2295	0.1148	0
0.91	0.2295	0.1148	0
0.92	0.2295	0.082	0
0.93	0.2295	0.082	0
0.94	0.2295	0.0656	0
0.95	0.1967	0.0656	0
0.96	0.1639	0.0492	0
0.97	0.1475	0.0492	0
0.98	0.1311	0.0492	0
0.99	0.0984	0.0164	0
1	NA	NA	NA

Supplementary Table 5: Comprehensive performance metrics of the integrated clinical-sphingolipid model (Model 1) across classification thresholds

Threshold	Accuracy	Sensitivity	Specificity	Precision	Recall	F1_Score
0.1	0.787	0.964	0.636	0.692	0.964	0.806
0.2	0.82	0.964	0.697	0.73	0.964	0.831
0.3	0.803	0.929	0.697	0.722	0.929	0.813
0.4	0.836	0.893	0.788	0.781	0.893	0.833
0.5	0.885	0.893	0.879	0.862	0.893	0.877
0.6	0.869	0.786	0.939	0.917	0.786	0.846
0.7	0.869	0.75	0.97	0.955	0.75	0.84
0.8	0.836	0.643	1	1	0.643	0.783
0.9	0.77	0.5	1	1	0.5	0.667

Supplementary Table 6: Baseline plasma CER/S1P ratio profiles of hepatocellular carcinoma patients stratified by radiotherapy response

Plasma Sphingolipids	Total (n = 61)	Responders (n = 33)	Non-responders (n = 28)	P value	FDR-adjusted P value
CER(d18:1/16:0)/S1P	4.25(3.34;6.52)	5.10(3.98;7.75)	3.53(2.77;4.32)	1.5E-4***	6.00E-04***
CER(d18:1/18:0)/S1P	1.51(0.99;2.32)	1.98(1.25;2.96)	1.19(0.73;1.67)	2.7E-4***	6.00E-04***
CER(d18:1/20:0)/S1P	3.34(2.26;4.84)	4.47(3.07;5.93)	2.73(1.70;3.42)	3.5E-5***	4.20E-04***
CER(d18:1/22:0)/S1P	50.43(32.13;71.54)	67.96(45.43;84.45)	35.79(29.85;51.67)	1.7E-4***	6.00E-04***
CER(d18:1/24:0)/S1P	188.64(119.78;271.30)	232.48(156.14;331.02)	137.97(108.91;193.72)	1.4E-3**	1.53E-03**
CER(d18:1/26:0)/S1P	1.49(1.21;2.09)	1.99(1.33;2.72)	1.30(1.02;1.78)	1.2E-3**	1.44E-03**
CER(d18:1/18:1)/S1P	0.08(0.05;0.12)	0.11(0.06;0.14)	0.06(0.04;0.09)	2.4E-3**	2.40E-03**
CER(d18:1/20:1)/S1P	0.29(0.22;0.36)	0.33(0.28;0.45)	0.25(0.19;0.32)	9.3E-5***	5.58E-04***
CER(d18:1/22:1)/S1P	0.41(0.34;0.56)	0.49(0.39;0.69)	0.34(0.29;0.43)	1.8E-4***	6.00E-04***
CER(d18:1/24:1)/S1P	28.09(18.56;44.76)	36.65(23.26;57.70)	22.03(13.35;28.36)	3.3E-4***	6.00E-04***
CER(d18:1/26:1)/S1P	0.85(0.61;1.23)	1.09(0.82;1.70)	0.68(0.54;0.92)	6.0E-4***	8.00E-04***
Total CERs(d18:1)/S1P	274.64(188.94;410.55)	391.24(256.67;496.17)	206.79(178.94;271.50)	1.9E-4***	6.00E-04***

P < 0.01, *P < 0.001(Mann-Whitney U test)

Supplementary Table 7: Analysis of covariance (ANCOVA) results for CER/S1P ratio variables controlling for S1P concentration

Variable	Responders_Mean	NonResponders_Mean	F_value	P_value	FDR_adjusted_P	FDR<0.1
CER(d18:1/16:0)/S1P	3.761	6.821	1.428	0.2369	0.2584	NS
CER(d18:1/18:0)/S1P	1.3639	2.9286	0.807	0.3726	0.3726	NS
CER(d18:1/20:0)/S1P	2.7231	5.7015	1.605	0.2103	0.2584	NS
CER(d18:1/22:0)/S1P	39.5798	68.5381	5.792	0.0193	0.0547	†
CER(d18:1/24:0)/S1P	156.078	244.8308	10.228	0.0022	0.0144	†
CER(d18:1/26:0)/S1P	1.3571	2.0004	9.13	0.0037	0.0150	†
CER(d18:1/18:1)/S1P	0.0665	0.1137	4.51	0.0380	0.0759	†
CER(d18:1/20:1)/S1P	0.2508	0.4015	1.542	0.2193	0.2584	NS
CER(d18:1/22:1)/S1P	0.3601	0.6373	2.114	0.1513	0.2270	NS
CER(d18:1/24:1)/S1P	22.9299	45.2079	2.158	0.1472	0.2270	NS
CER(d18:1/26:1)/S1P	0.7381	1.2459	5.472	0.0228	0.0547	†
Total						
CERs(d18:1)/S1P	229.2082	378.4267	10.077	0.0024	0.0144	†

†, FDR-adjusted P value < 0.1; NS, not significant.

Supplementary Table 8: Final variable selection by LASSO regression for the ceramide/S1P ratio-based model

Variable	Coefficient	Selected
(Intercept)	0.5314	Yes
AFP	0	No
TBIL	0	No
Child Pugh Score	0	No
ALP	0	No
CER(d18:1/22:0) /S1P	0	No
CER(d18:1/24:0) /S1P	0	No
CER(d18:1/26:0) /S1P	0	No
CER(d18:1/18:1) /S1P	0	No
CER(d18:1/26:1) /S1P	-0.2052	Yes
Total CERs(d18:1) /S1P	-0.0016	Yes

Supplementary Table 9: Calibration data for the ceramide/S1P ratio-based model (Model 2)

Probability_Group	Predicted_Probability_Range	Actual_Probability
[0.0045,0.101]	[0.0045,0.101]	0
(0.101,0.197]	(0.101,0.197]	0
(0.197,0.293]	(0.197,0.293]	0.167
(0.293,0.389]	(0.293,0.389]	0.667
(0.389,0.485]	(0.389,0.485]	1
(0.485,0.581]	(0.485,0.581]	0.625
(0.581,0.677]	(0.581,0.677]	0.778
(0.677,0.773]	(0.677,0.773]	0.667
(0.773,0.868]	(0.773,0.868]	0.5
(0.868,0.965]	(0.868,0.965]	0.857

Supplementary Table 10: Decision curve analysis data for the ceramide/S1P ratio-based model (Model 2)

Threshold	Model2_NetBenefit	Sphingolipid_Only_NetBenefit	AFP_Only_NetBenefit
0	0.459	0.459	0.459
0.01	0.4539	0.4536	0.4536
0.02	0.4493	0.4483	0.448
0.03	0.4443	0.4428	0.4423
0.04	0.4406	0.4378	0.4365
0.05	0.4366	0.434	0.4305
0.06	0.4329	0.4297	0.4245
0.07	0.4294	0.4257	0.4183
0.08	0.4262	0.4205	0.412
0.09	0.4217	0.4152	0.4055
0.1	0.4189	0.4098	0.3989
0.11	0.4165	0.3899	0.3922
0.12	0.4121	0.3845	0.3852
0.13	0.4076	0.3838	0.3782
0.14	0.4083	0.3839	0.3709
0.15	0.4041	0.379	0.3635
0.16	0.4028	0.3739	0.356
0.17	0.3986	0.3688	0.3482
0.18	0.3978	0.3635	0.3403
0.19	0.3975	0.358	0.3321
0.2	0.3934	0.3525	0.3238
0.21	0.3937	0.3511	0.3152
0.22	0.3943	0.3455	0.3064
0.23	0.3954	0.3398	0.2974
0.24	0.3753	0.3391	0.2882
0.25	0.3716	0.3333	0.2787
0.26	0.3677	0.311	0.2689
0.27	0.3759	0.305	0.2589
0.28	0.3725	0.2987	0.2486
0.29	0.369	0.2923	0.2381
0.3	0.3653	0.2857	0.2272

0.31	0.3452	0.2789	0.216
0.32	0.3414	0.2719	0.2044
0.33	0.3374	0.2647	0.1926
0.34	0.3169	0.2573	0.1868
0.35	0.3216	0.2585	0.1841
0.36	0.3176	0.2439	0.1814
0.37	0.3136	0.2201	0.1785
0.38	0.3094	0.2327	0.1756
0.39	0.305	0.2094	0.1725
0.4	0.3005	0.2131	0.1694
0.41	0.2959	0.2062	0.1662
0.42	0.2911	0.199	0.1628
0.43	0.2698	0.1915	0.1593
0.44	0.2646	0.2096	0.1557
0.45	0.2593	0.2027	0.152
0.46	0.2538	0.1791	0.1481
0.47	0.2317	0.1698	0.1441
0.48	0.2257	0.1627	0.14
0.49	0.2353	0.1389	0.1356
0.5	0.2459	0.1311	0.1311
0.51	0.2405	0.1402	0.1265
0.52	0.235	0.1339	0.1216
0.53	0.1964	0.1636	0.1165
0.54	0.1903	0.1768	0.1112
0.55	0.184	0.1712	0.1056
0.56	0.1446	0.1654	0.0999
0.57	0.1376	0.1266	0.0938
0.58	0.114	0.1038	0.0874
0.59	0.0972	0.0972	0.0808
0.6	0.0902	0.0738	0.0738
0.61	0.0664	0.05	0.0664
0.62	0.0854	0.0259	0.0587
0.63	0.0899	0.0292	0.0505
0.64	0.0838	0.0055	0.0419
0.65	0.0773	0.0117	0.0328
0.66	0.0704	0.0203	0.0231
0.67	0.0139	0.0149	0.0129
0.68	0.041	0.0451	0.002
0.69	0.0344	0.0418	0
0.7	0.0109	0.0219	0
0.71	0.0034	0.0181	0
0.72	-0.0047	0.0562	0
0.73	-0.0134	0.054	0

0.74	-0.0227	0.0353	0
0.75	-0.0492	0.0328	0
0.76	-0.0601	0.0137	0
0.77	-0.072	-0.0221	0
0.78	-0.0849	0.0328	0
0.79	-0.0375	0.0328	0
0.8	-0.0492	0.0164	0
0.81	0.0078	0.0164	0
0.82	-0.0018	0.0164	0
0.83	-0.0289	0	0
0.84	0.0451	0	0
0.85	0.0219	0	0
0.86	-0.0023	0	0
0.87	-0.0113	0	0
0.88	0.0984	0	0
0.89	0.082	0	0
0.9	0.0492	0	0
0.91	0.0492	0	0
0.92	0.0328	0	0
0.93	0.0328	0	0
0.94	0.0328	0	0
0.95	0.0164	0	0
0.96	0.0164	0	0
0.97	0	0	0
0.98	0	0	0
0.99	0	0	0
1	NA	NA	NA

Supplementary Table 11: Comprehensive performance metrics of the ceramide/S1P ratio-based model (Model 2) across classification thresholds

Threshold	Accuracy	Sensitivity	Specificity	Precision	F1_Score
0.1	0.639	1	0.333	0.56	0.718
0.2	0.738	1	0.515	0.636	0.778
0.3	0.803	0.964	0.667	0.711	0.818
0.4	0.787	0.893	0.697	0.714	0.794
0.5	0.787	0.821	0.758	0.742	0.78
0.6	0.689	0.571	0.788	0.696	0.627
0.7	0.639	0.357	0.879	0.714	0.476
0.8	0.639	0.321	0.909	0.75	0.45
0.9	0.59	0.107	1	1	0.194

Supplementary Table 12: Sphingolipid fold change data for the longitudinal analysis heatmap

num ber	ID	outc ome	SPH(Lo g2FC)	S1P(Lo g2FC)	CER(d1 8:1/16: 0)	CER(d1 8:1/18: 0)	CER(d1 8:1/20: 0)	CER(d1 8:1/22: 0)	CER(d1 8:1/24: 0)	CER(d1 8:1/26: 0)	CER(d 18:1/1 8:1)	CER(d 18:1/2 0:1)	CER(d 18:1/2 2:1)	CER(d 18:1/2 4:1)	CER(d 18:1/2 6:1)	Total CE R(d18:1)
1	5	1	0.407	0.073	0.526	0.804	0.146	-0.417	-1.107	-0.386	-0.361	-0.541	-0.326	-0.317	-0.052	-0.724
2	6	0	0.164	0.041	-0.021	0.303	0.394	0.187	0.545	1.183	0.320	0.193	0.284	0.383	0.765	0.461
3	8	1	0.240	0.005	-0.281	-0.785	-0.405	-0.327	-0.042	-0.063	-1.826	-0.926	-0.805	-1.176	-0.695	-0.195
4	10	1	0.378	0.186	-0.533	-0.996	-0.761	-0.713	-0.661	-0.749	-0.734	-0.164	-0.321	-1.132	-0.668	-0.715
5	11	0	0.050	-0.184	0.228	-0.072	-0.047	0.245	0.189	-0.160	-0.277	0.048	0.077	-0.198	-0.430	0.152
6	12	0	-0.094	-0.625	0.455	-0.072	0.310	0.915	1.501	1.589	-0.002	-0.029	0.256	0.309	0.434	1.041
7	13	0	-0.737	0.089	0.392	0.484	0.824	1.112	1.051	0.658	0.954	0.275	0.535	0.204	0.086	0.913
8	18	1	0.810	0.235	-0.170	0.167	-0.612	-2.180	-2.530	-1.490	0.452	-0.028	-0.514	0.045	0.503	-2.060
9	23	1	-0.248	0.632	0.360	-0.093	-0.335	-1.119	-1.519	-1.184	-0.083	-0.177	-0.470	-0.627	-0.600	-1.312
10	27	0	0.037	-0.114	0.079	0.482	0.175	-0.212	-0.098	0.141	0.343	0.146	0.018	0.081	0.293	-0.092
11	30	0	-0.316	-0.235	0.178	0.035	0.003	0.487	0.796	0.571	-0.838	-0.328	-0.288	-0.291	0.234	0.595
12	31	0	-0.077	-0.171	-0.334	0.793	0.927	1.168	1.034	0.622	0.745	0.595	0.627	1.006	0.519	0.993
13	41	1	2.447	0.452	2.287	3.530	2.677	1.411	0.275	-0.015	2.672	0.806	1.192	1.603	1.173	0.977
14	48	1	0.129	-0.450	-0.462	-0.432	-0.385	-0.091	-0.290	-0.567	0.042	-0.140	-0.222	-1.413	-1.452	-0.493
15	51	0	-0.787	-0.788	-1.024	-1.656	-1.757	-1.743	-2.019	-0.341	-1.198	-0.597	-0.779	-1.763	-1.926	-1.868
16	53	0	-0.669	-0.184	0.225	0.140	0.359	0.596	0.681	0.146	-0.451	-0.309	0.003	0.319	0.329	0.606
17	58	0	0.725	0.469	-0.440	-0.895	-0.904	-0.359	0.504	1.045	-2.126	-0.272	-0.361	-0.871	0.304	0.160
18	66	0	-0.481	-0.861	0.343	0.663	0.114	-0.331	-0.378	-0.215	0.856	0.036	-0.119	-0.149	-0.211	-0.307

19	73	0	-0.098	0.057	0.293	0.420	0.537	0.855	0.824	0.870	0.859	0.599	0.704	0.698	0.701	0.803
20	78	0	-0.640	-0.250	-0.186	-0.497	-0.632	-0.867	-0.731	-0.346	0.634	-0.046	-0.111	-0.415	0.206	-0.649
21	81	1	1.339	0.573	0.027	-0.254	-0.590	-0.421	-0.320	-0.113	0.073	0.026	-0.040	-0.872	0.045	-0.392
22	82	0	-0.582	-0.719	0.713	1.047	0.781	0.637	-0.084	-0.330	0.502	0.029	0.000	0.640	0.445	0.171
23	84	0	1.798	0.148	0.247	0.691	0.028	-0.749	-0.973	-0.335	0.796	0.036	-0.177	0.648	0.814	-0.752
24	88	0	-0.200	0.040	-0.129	0.085	0.278	0.276	0.275	0.226	-0.476	-0.220	0.093	0.042	0.005	0.221
25	91	0	-0.376	-0.171	0.287	0.460	0.669	0.111	0.030	0.351	-0.605	0.250	0.321	0.247	0.463	0.076

Supplementary Table 13: PLS-DA score data for the longitudinal analysis of sphingolipid dynamics

Patient	Outcome	Comp1	Comp2
P 1	NonResponder	-1.78208	-1.01977
P 2	Responder	1.789021	0.24182
P 3	NonResponder	-1.47993	1.3344
P 4	NonResponder	-2.14659	0.529044
P 5	Responder	0.209066	0.152065
P 6	Responder	3.313324	1.490849
P 7	Responder	2.314084	-0.37204
P 8	NonResponder	-3.93513	-1.03413
P 9	NonResponder	-3.24906	-1.12757
P 10	Responder	0.338542	-0.00253
P 11	Responder	1.236138	1.216635
P 12	Responder	2.921662	-0.07915
P 13	NonResponder	0.835329	-7.66621
P 14	NonResponder	-1.17851	0.924503
P 15	Responder	-2.5826	4.277216
P 16	Responder	1.442342	0.81834
P 17	Responder	-0.24743	1.239949
P 18	Responder	0.456763	0.91212
P 19	Responder	2.51668	-0.45142
P 20	Responder	-0.47712	1.376103
P 21	NonResponder	-1.83493	-1.46425
P 22	Responder	1.35183	0.072073
P 23	Responder	-1.65076	-2.06602
P 24	Responder	0.606548	0.427597
P 25	Responder	1.23281	0.27037

Supplementary Table 14: Variable Importance in Projection (VIP) scores from the PLS-DA model

Lipid	VIP Score
CER(d18:1/26:0)	1.45792
SPH	1.408646
S1P	1.375921
CER(d18:1/24:0)	1.172296
Total CER(d18:1)	1.121335
CER(d18:1/22:0)	1.013501
CER(d18:1/16:0)	0.849414
CER(d18:1/22:1)	0.834315
CER(d18:1/20:0)	0.831788
CER(d18:1/24:1)	0.805425
CER(d18:1/18:0)	0.736174
CER(d18:1/26:1)	0.663893
CER(d18:1/20:1)	0.599732
CER(d18:1/18:1)	0.487467

Supplementary Table 15: Statistical data for post-radiotherapy fold changes of key sphingolipids between responders and non-responders

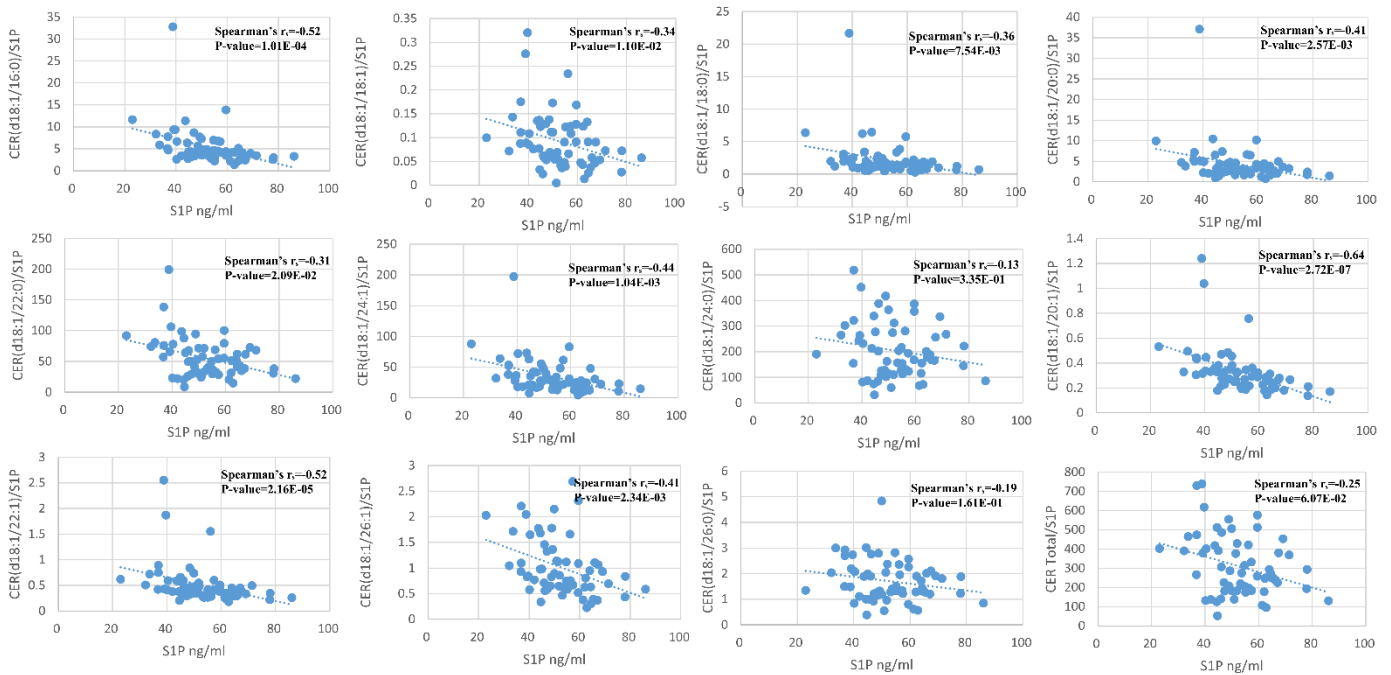
Lipid	n(Responder)	n(Non-Responder)	statistic	df	p	FDR-adjusted P value	significant
CER(d18:1/22:0)	17	8	1.535	11.085	0.153	0.153	ns
CER(d18:1/24:0)	17	8	2.492	13.147	0.027	0.051	ns
CER(d18:1/26:0)	17	8	3.755	15.18	0.002	0.011	*
S1P	17	8	-2.742	14.124	0.016	0.047	*
SPH	17	8	-2.430	10.757	0.034	0.051	ns
Total CER(d18:1)	17	8	2.1291	11.937	0.055	0.066	ns

*, FDR-adjusted P value < 0.05; ns, not significant.

Supplementary Table 16: Univariable Analysis of Plasma Sphingolipids and Clinical Variables: Original and FDR-Adjusted P Values

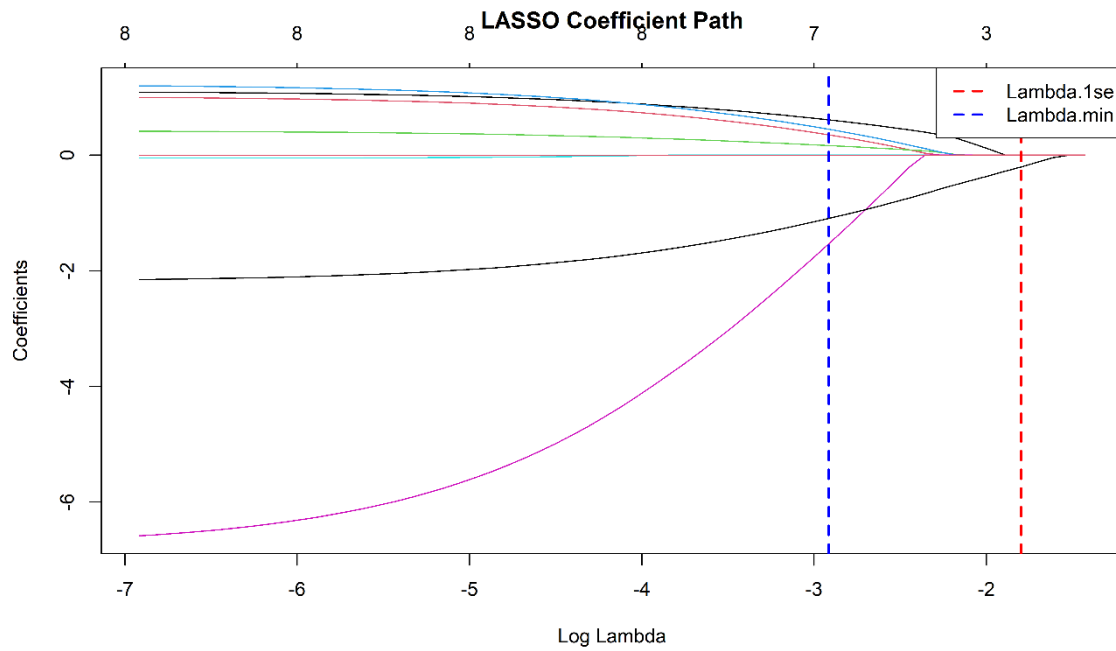
Plasma Sphingolipids/ Clinical Variables	P value	FDR-Adjusted P Values
SPH	0.336	0.607
S1P	8.61E-07	3.70E-05
CER(d18:1/16:0)	0.118	0.461
CER(d18:1/18:0)	0.052	0.279
CER(d18:1/20:0)	0.024	0.206
CER(d18:1/22:0)	0.062	0.296
CER(d18:1/24:0)	0.339	0.607
CER(d18:1/26:0)	0.524	0.669
CER(d18:1/18:1)	0.265	0.607
CER(d18:1/20:1)	0.385	0.637
CER(d18:1/22:1)	0.311	0.607
CER(d18:1/24:1)	0.029	0.208
CER(d18:1/26:1)	0.108	0.461
Total CERs(d18:1)	0.144	0.516
Age(years)	0.597	0.713
Gender	0.192	0.516
HbsAg	0.506	0.669
AFP(ng/ml)	0.009	0.129
Max Tumor size(cm)	0.384	0.637
Child Pugh grade	0.008	0.129
BCLC stage	0.465	0.669
Lesions with prior intervention	0.841	0.865
ALBI score	0.525	0.669
Prior targeted /immuno-therapy	0.297	0.607
ALT(U/L)	0.409	0.651
AST(U/L)	0.627	0.729
TBIL(μ mol/L)	0.024	0.206
ALB(g/L)	0.297	0.607
ALP(U/L)	0.037	0.227
WBC($\times 10^9$)	0.179	0.516
LYM($\times 10^9$)	0.548	0.673
NEU($\times 10^9$)	0.490	0.669
MONO($\times 10^9$)	0.191	0.516
HB(g/L)	0.529	0.669
PLT($\times 10^9$)	0.239	0.605
Radiation Target Sites	0.682	0.772

BED(Gy)	0.845	0.865
Fractionation Schedule	0.301	0.607
Hypertension	0.171	0.516
Diabetes mellitus	0.522	0.669
BMI (kg/m ²)	0.935	0.935
PIV	0.781	0.840
SII	0.732	0.807



Supplementary Figure 1: Scatter plots of plasma sphingosine-1-phosphate levels versus individual ceramide-to-S1P ratios.

Each panel displays the relationship between plasma S1P concentration (ng/ml) and the ratio of a specific ceramide (CER) species to S1P. Spearman's rank correlation coefficient (r_s) is calculated and displayed for each pair.



Supplementary Figure 2: Coefficient paths from LASSO regression analysis for variable selection, with cross-validation criteria.

The plot illustrates the change in coefficient magnitude (y-axis) for all candidate sphingolipid ratio variables across a range of the penalty parameter (Lambda) values (x-axis, log scale). Two vertical dashed lines are displayed: one positioned at the λ value that gives the minimum mean cross-validated error (Lambda.min), and another at the largest λ value within one standard error of the minimum (Lambda.1se).